Jon Kobashigawa
Editor

Clinical Guide to Heart Transplantation

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Introduction

Since the first successful human heart transplant surgery in 1967 by Christiaan Barnard, the field of heart transplantation has evolved from a novel investigational pursuit to an established therapy for the treatment of end-stage heart failure. With the advent of improved surgical techniques, the development of immunosuppressive drugs and the utilization of more sophisticated monitoring strategies and treatments for graft rejection, heart transplantation now offers patients an avenue to both improved survival and quality of life.

In the early years of thoracic transplantation, allograft rejection had been the main challenge limiting survival. Acceptable survival rates only evolved with the introduction of effective immunosuppressive agents. Rejection rates sharply declined as did infection rates as host responses to bacterial and fungal infection were relatively preserved with the new immunosuppressive regimens. The improvements in morbidity and mortality led to a remarkable expansion in heart transplantation. Currently, around 4100 heart transplants per year are being performed globally with a half-life of 11 years, with 1-year survival approaching 90%.

Equally important, great strides have been made to provide an equitable system of organ allocation and to improve organ procurement and preservation strategies, with a view toward increasing the volume and viability of donor hearts for transplantation. Yet, there remains a large disparity between the number of available donor hearts and the number of patients on the waitlist, which has resulted in high waitlist mortality. In the current era, patients referred for transplant evaluation often have a complex pathophysiology, multiple comorbidities, and other risk factors such as sensitization or mechanical support. It can be difficult to objectively prioritize these ill patients given the overwhelming demand for transplantation. Efforts have been made to develop risk scores to aid in assessing transplant candidacy, but clinical judgment continues to be the primary determinant of patient selection and management. The prevalence of heart failure continues to increase, ensuring that donor selection and allocation policy will remain at the forefront of cardiac transplantation for decades to come.

Despite advances in the field of immunosuppression and rejection surveillance, we cannot take our progress thus far for granted. Cardiac allograft vasculopathy, an immune-mediated process, remains the largest barrier to long-term survival. From novel medications, to bio-engineered hearts and modulation of the immune system to achieve complete tolerance, there are many glimpses from preclinical research of what may eventually be possible,

with the ultimate goal of completely eliminating the possibility of rejection and thus vastly increasing long-term survival. Transplantation medicine is truly the frontier for translational research.

As practitioners in this field, we are charged with making critical determinations in the management of patients, donor organs, and the transplant process itself in order to achieve the greatest benefit in the utilization of a scarce resource. This handbook is designed to be an easy reference for those on the front lines. While this compilation of best practices cannot address the complexity of the individual patients we care for on a daily basis, it is my hope that it will serve to help us ask the right questions, access the best evidence, and ultimately make the best decisions for the patients we are privileged to serve.

Los Angeles, CA, USA Jon Kobashigawa, MD

Author Biography

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He received his undergraduate degree at Stanford University, earned his medical degree at Mount Sinai School of Medicine in New York and completed his medical residency and cardiology fellowship at the UCLA Medical Center. He is a past president of the International Society of Heart and Lung Transplantation, past chair of the American College of Cardiology Committee on Heart Failure and Transplantation, and past member of the United Network of Organ Sharing National Thoracic Committee.

Kobashigawa is recognized nationally and internationally as a leader in heart transplantation. He has published more than 300 peer-reviewed articles, chapters, and monographs in the field of heart failure and transplantation and has chaired several multicenter clinical studies. He has organized and chaired several International Consensus Conferences to discuss pertinent questions regarding heart failure and heart transplant. He lectures at universities around the world and has mentored several young physicians who have ascended to important academic positions throughout the country.

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1 Medical and Device Options for Patients with End-Stage Heart Failure

Michele Hamilton, Michelle Kittleson, and Jon Kobashigawa

Clinical Pearls

- Heart failure prevalence (1.5% in the US) will continue to increase for the foreseeable future given the aging population, and is a major cause of death and hospitalization in patients over 65 year of age.
- The new heart failure medication, sacubitril/valsartan is now indicated as first line therapy for patients with class II/III heart failure together with beta-blockers, diuretics (if volume overloaded) and aldosterone antagonists; digoxin and hydralazine/isosorbide dinitrate may additionally be warranted in certain situations.
- Angiotensin converting enzyme inhibitors are indicated as second line therapy for patients with class II/III heart failure.
- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and ARNIs are first-line options for patients displaying chronic reduced left ventricular systolic function (LVEF ≤35–40%) who remain largely asymptomatic and are classified as NYHA class I.
- Ivabradine is indicated to reduce HF hospitalization in patients with symptomatic (NYHA class II-III) stable chronic heart failure with reduced systolic function (LVEF ≤35%) receiving guideline-directed evaluation and management, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.
- Inotropic therapy including adrenergic agonists and phosphodiesterase inhibitors are indicated for Stage D heart failure if previous pharmacological therapies have been exhausted.
- Cardiac resynchronization therapy is a suitable option for symptomatic heart failure patients (NYHA class II-IV, LVEF ≤35%) who demonstrate substantial

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prolongation of the QRS interval on ECG (≥150 msec) and are in sinus rhythm.
- The implantable cardioverter-defibrillator is a suitable option for primary prevention in patients with LVEF ≤30% at least 40 days after myocardial infarction, and in patients with ischemic and non-ischemic heart failure (NYHA class II-III) with LVEF ≤35%, to reduce mortality.

Introduction

In modern times, heart failure has increasingly become a major public health issue, with a prevalence of approximately 5.1 million in North America [1]. Furthermore, one in 7 Americans are age 65 or greater, with this proportion set to rise to one in 5 by 2050 [2]. Given the age-dependent increase in incidence and prevalence of heart failure, the proportion of heart failure will only continue to increase; already, it is one of the main causes of death and hospitalization in this age group. Combined with demographic improvements in life expectancies and recent improvements in the treatment of heart-failure, the proportion of patients that develop advanced heart failure has also increased substantially. The majority of patients with so-called "end-stage" heart failure are characterized by advanced structural heart disease and profound symptoms of heart failure at rest or upon minimal exertion despite maximal guideline-directed medical treatment, and typically fall into stage D of the ABCD classification of the American College of Cardiology (ACC)/American Heart Association (AHA), and class III–IV of the New York Heart Association (NYHA) functional classification (see Table 1.2 for a full explanation of heart failure classifications). There are varying etiologies of such severe heart failure, which can broadly be divided into ischemic and non-ischemic; these may include unstable arrhythmias, idiopathic cardiomyopathies and many others. Regardless of the etiology, the subgroup of stage D heart failure demonstrates a particularly high 5-year mortality rate of 80% [1], and thus requires special therapeutic interventions. This chapter will assume background knowledge in the principles of heart failure and its early management, and will cover current medical and device strategies for the management of end-stage heart failure, with acknowledgement to the options of mechanical circulatory support and cardiac transplantation which will be covered in detail in upcoming chapters.

Table 1.1 Comparison of ACCF/AHA stages and NYHA functional classifications of heart failure

ACCF/AHA stages of HF		NYHA functional classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

Reused with permission from Yancy et al. [1]

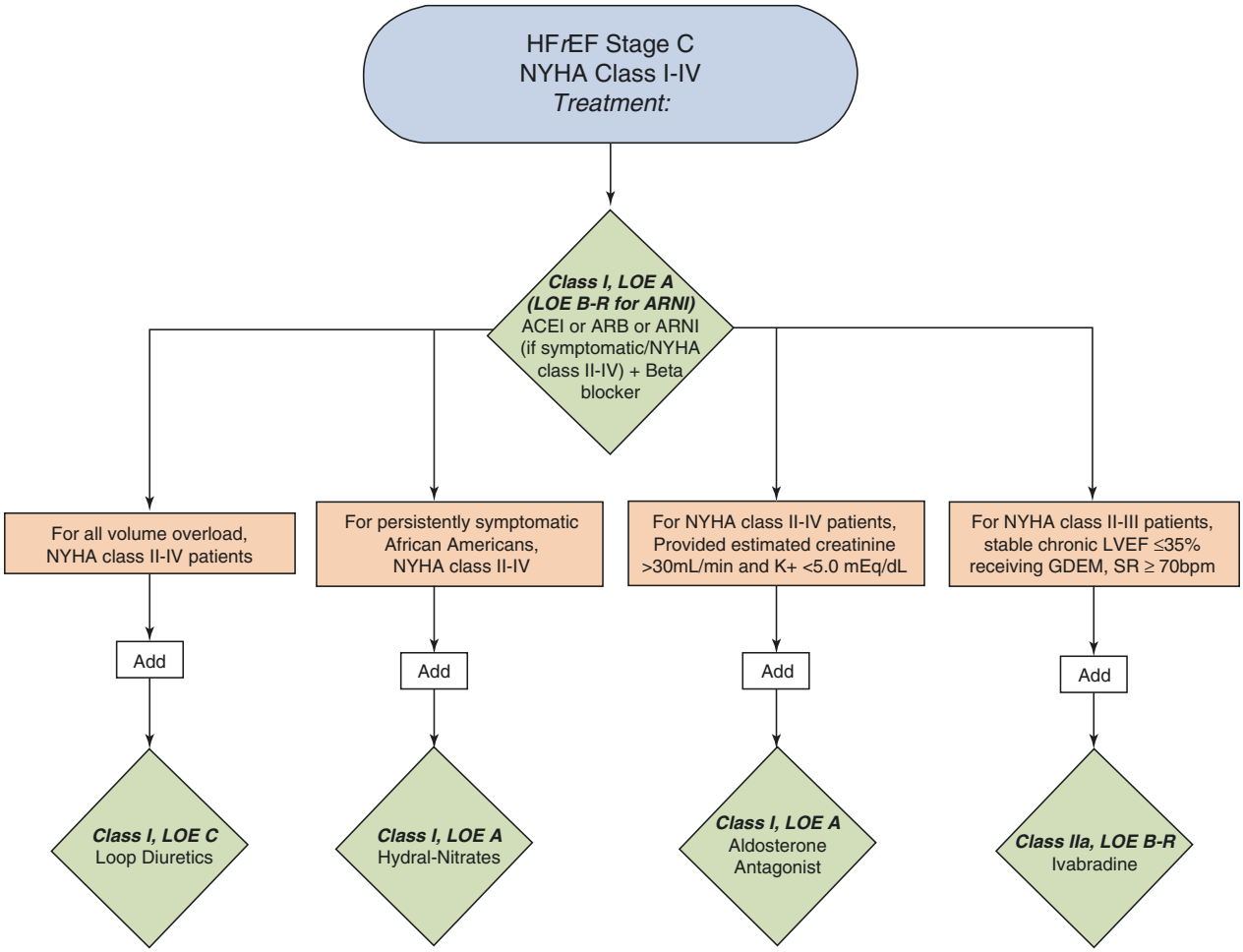

Fig. 1.1 Summary of ACC/AHA algorithm for recommended pharmacological management of Stage C heart failure. *Abbreviations*: *HFrEF* Heart failure with reduced ejection fraction, *NYHA* New York Heart Association, *LOE* level of evidence, *ARNI* angiotensin receptor-neprilysin inhibitor, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *GDEM* guideline directed evaluation and management, *LVEF* left ventricular ejection fraction, *SR* sinus rhythm, *bpm* beats per minute

Medical and Pharmacological Management of End-Stage Heart Failure

By definition, patients classified as stage D according to the ACC/AHA stages of heart failure will demonstrate persistent heart failure refractory to guideline-directed medical treatment, with a functional classification of class III-IV NYHA heart failure (Table 1.1); patients classified as such will also demonstrate marked limitation or complete inability to perform physical activity, with symptoms of HF either at rest or upon minimal exertion. While most of the pharmacological therapies below are generally initiated for patients in the earlier stages of heart failure, it is prudent to note that these same strategies may slow or even reverse the progression towards the point of severe heart failure. The current recommendations for the pharmacological treatment of heart failure patients with NYHA class I–IV are summarized in Fig. 1.1.

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)

Until recently, angiotensin-converting enzyme (ACE) inhibitors were considered the definitive first line treatment for chronic symptomatic heart failure with reduced ejection fraction (NYHA class II/III) [1]. However, the development of novel drugs in heart failure, including the angio-

tensin receptor-neprilysin inhibitors (ARNIs), has recently changed this paradigm. Sacubitril/valsartan is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an established angiotensin-receptor blocker. Sacubitril increases vasoactive peptide levels through inhibition of neprilysin, which is normally responsible for degradation of these peptides. In turn, blood volume is lowered, relieving the patient's diseased heart. The PARADIGM-HF study, a randomized trial of sacubitril/valsartan compared to the established ACE-inhibitor enalapril in heart failure, was stopped early at 27 months due to overwhelming evidence of benefit in the sacubitril/valsartan study arm [3]. Specifically, patients in the sacubitril/valsartan arm demonstrated significantly less mortality and hospitalizations for heart failure. In 2015, sacubitril/valsartan was FDA approved for use in patients with chronic NYHA class II-IV heart failure, and in 2016 was officially designated by the ACC/AHA guidelines as the first-line therapy for patients with chronic symptomatic heart failure with reduced ejection fraction (NYHA class II/III), replacing ACE-inhibitors due to the increased survival benefit [4]. Notably, sacubitril/valsartan is contraindicated in patients taking ACE-inhibitors, and should be avoided in patients with a history of angioedema or other adverse reactions to ACE-inhibitors [3].

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) remain a first-line option for patients displaying chronic reduced left ventricular systolic function (LVEF ⩽35–40%) who remain largely asymptomatic and are classified as NYHA class I. However, in cases of chronic symptomatic patients with reduced ejection fraction who meet the criteria for NYHA class II/III, patients on an ACE-inhibitor should be switched to sacubitril/valsartan, unless sacubitril/valsartan is contraindicated or unable to be tolerated [4]. Additionally, it is important that ARNIs should never be administered concurrently with ACE-inhibitors or ARBs [4].

There is strong evidence from several large multicenter trials worldwide that ACE inhibitors are able to improve symptoms and functional capacity, while simultaneously decreasing the rate of hospitalizations and mortality [5]. In patients who develop heart failure following an acute myocardial infarct, ACE inhibitors have been demonstrated to improve survival and reduce re-infarction rates [1]. Importantly, dosages should be up-titrated to the target dosages shown to be effective in clinical trials, with intermediate doses unlikely to have significant effect [1]. Monitoring should comprise of regular assessment of blood pressure (both supine and standing), renal function, and serum electrolytes (especially potassium) at regular intervals. For those who are unable to tolerate or are contraindicated against ACE inhibitors, angiotensin receptor blockers (ARBs) are a viable alternative that have been demonstrated to improve both morbidity and mortality [6, 7]. In persistently symptomatic patients already on ACE inhibitors and other optimal medical treatment including beta-blockers, ARBs on top of ACE inhibitors may also be considered [1].

Diuretics

Diuretics, including either loop or thiazide diuretics, are recommended in all heart failure patients with signs or a history of fluid retention. In general, they should be combined with an ARNI or ACE inhibitor/ARB and beta-blocker. Multiple intermediate-term studies have shown that diuretics can improve symptoms and exercise tolerance in heart failure patients [8–10]. Due to the principal potential adverse effects of electrolyte (in particular magnesium and potassium) and fluid depletion, serum electrolytes and renal function should be monitored at regular intervals. Loop diuretics may be effectively used in combination with thiazides in cases of treatment-refractory fluid overload [11].

Beta-Blockers

In combination with ARNIs or ACE inhibitors, beta blockers should be prescribed to all patients

with stable heart failure (NYHA II–IV) with reduced ejection fraction. Large, international multicenter clinical trials demonstrate that carvedilol, bisoprolol and metoprolol succinate are most effective in reducing the risk of death and combined risk of death or hospitalizations [1, 12]. Initiation of beta-blockers should be at a very low dose, incrementally increasing to the higher doses proven to be effective in clinical trials [1]. In patients with fluid retention, beta blockers must be prescribed with diuretics in order to avoid the exacerbation of fluid retention. Patients taking beta-blockers should be closely monitored for signs of hypotension, heart failure symptoms, fluid retention, and bradycardia.

Ivabradine

Ivabradine is a new selective inhibitor of the cardiac pacemaker "funny"current I_f that lowers heart rate without reducing contractility; in a European 6558-patient multicenter study [13], it was found that among patients already on maximally tolerated beta-blocker dosages, ivabradine reduces the risk of HF hospitalization. Recently, the US Food and Drug Administration (FDA) granted approval for use of ivabradine, and a 2016 update to ACC/AHA recommends the use of ivabradine in chronic heart failure patients to reduce the risk of hospitalization in patients with EF ≤35%, who are in sinus rhythm with a resting heart rate of ≥70 bpm, and on maximally tolerated doses of beta-blockers or contraindicated to beta-blocker use [4].

Aldosterone-Receptor Antagonists

Aldosterone-receptor antagonists, which include the agents spironolactone and eplerenone, are generally recommended in patients with advanced heart failure (NYHA II–IV) who demonstrate LVEF of 35% or lower, in addition to ARNIs or ACE inhibitors, β-adrenergic receptor blockers, and diuretics [1]. However, they must be avoided in patients with severe renal failure (creatinine 2.5 mg/dl or greater in men, 2.0 mg/dl in women) and hyperkalemia (>5.0 mEq/l), as they may cause life-threatening harm in this subgroup. In patients with a history of diabetes or recent MI, the threshold for LVEF for which aldosterone-receptor antagonists are acceptable is slightly higher at 40%. Nevertheless, the multicenter RALES (Randomized Aldactone Evaluation Study) trial demonstrated that these agents are able to reduce all-cause mortality as well as confer a reduced risk of sudden cardiac death and heart failure hospitalizations [14]; the subsequent follow-up multicenter studies, the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) and EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms) trials, have confirmed their benefit [15, 16]. Patients on these agents should be monitored by regular assessment of serum potassium values, renal function, and fluid status, as well as examined for potential gynecomastia in the case of spironolactone.

Hydralazine and Isosorbide Dinitrate

The combination of hydralazine and isosorbide dinitrate, two vasodilators, is recommended for African-Americans with heart failure and reduced ejection fraction that is refractory to treatment with ARNIs or ACE inhibitors, beta-blockers, and aldosterone receptor antagonists, having demonstrated improved mortality [1, 17, 18]. Currently, benefit in non-African Americans is unclear [1]. Furthermore, there is some evidence to suggest that they may be useful in reducing morbidity and mortality in symptomatic heart failure patients who are unable to tolerate ACE inhibitors or ARBs [1, 19]. Patients should be monitored for adherence (found to be difficult due to the large number of tablets required) and checked for adverse reactions, which may include headache, GI distress and dizziness.

Digoxin

Digoxin, a cardiac glycoside that increases myocardial contractility via inhibition of the Na+/K+ATPase, has demonstrated that it can be beneficial in heart failure patients with reduced ejection fraction, with regard to decreasing frequency of related hospitalizations [1, 20, 21]. It is considered

a viable option in those with persistent symptoms despite administration of ARNIs/ACE-inhibitors/ARBs, beta-blockers, diuretics and aldosterone antagonists. Importantly, patients should not be administered digoxin if they display significant sinus or atrioventricular block. While well tolerated by the majority of patients, adverse effects can include arrhythmias, GI distress and visual disturbances. Concomitant use of certain antibiotics or immunosuppressants may also increase the risk of digoxin toxicity [22]. Patients on digoxin should be monitored by assessing heart rate, atrioventricular conduction, serum potassium and digoxin levels, as well as renal function.

Anticoagulation

Due to the stasis of blood in dilated hypokinetic cardiac chambers and the peripheral vessels, patients with end-stage heart failure are especially at increased risk of thromboembolic events. However, anticoagulation is only recommended in patients with chronic heart failure combined with atrial fibrillation (AF) [1]. In heart failure patients without AF, a prior thromboembolic event, or a cardioembolic source (e.g. mobile LV thrombus), there has been demonstrated to be no benefit to anticoagulation. The choice of anticoagulant is generally one of warfarin, dabigatran, or apixaban, and is initiated on the basis of the nature of the patient's AF (as well as cost, potential for drug interactions, and other individual clinical considerations).

Fluid Restriction

In stage D heart failure, fluid restriction to 1.5–2 L per day is recommended, especially in patients with hyponatremia or congestive symptom [1].

Inotropic Agents

While the drugs mentioned above will have been initiated while that patient was still in the relatively early stages of heart failure (stage A, B or C, NYHA class I-III), a deterioration to Stage D/NYHA class III-IV almost always implies a severe heart failure refractory to guideline-directed medical therapy as detailed above. At this point, inotropes must be considered to support the failing heart [1]. Favored agents include adrenergic agonists, such as dopamine and dobutamine, and phosphodiesterase inhibitors, such as milrinone (see Table 1.2 for an overview, including dosing instructions).

Importantly, inotropes are not a definitive therapy, and are intended to be a temporary solution to maintain systemic perfusion and preserve end-

Table 1.2 Overview of intravenous inotropic agents used in management of heart failure.

Inotropic agent	Dose (mcg/kg)		Drug kinetics and metabolism	Effects				Adverse effects	Special considerations
	Bolus	Infusion (/min)		CO	HR	SVR	PVR		
Adrenergic agonists									
Dopamine	N/A	5–10	$t_{1/2}$: 2–20 min	↑	↑	↔	↔	T, HA, N, tissue necrosis	Caution: MAO-I
	N/A	10–15	R,H,P	↑	↑	↑	↔		
Dobutamine	N/A	2.5–5	$t_{1/2}$: 2–3 min H	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; CI: sulfite allergy
	N/A	5–20		↑	↑	↔	↔		
PDE inhibitor									
Milrinone	N/R	0.125–0.75	$t_{1/2}$: 2.5 h H	↑	↑	↓	↓	T, ↓BP	Renal dosing, monitor LFTs

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BP indicates blood pressure, *CI* contraindication, *CO* cardiac output, *F* fever, *H* hepatic, *HA* headache, *HF* heart failure, *HR* heart rate, *LFT* liver function test, *MAO-I* monoamine oxidase inhibitor, *N* nausea, *N/A* not applicable, *N/R* not recommended, *P* plasma, *PDE* phosphodiesterase, *PVR* pulmonary vascular resistance, *R* renal, *SVR* systemic vascular resistance, *T* tachyarrhythmias, $t_{1/2}$ elimination half-life

organ performance [1]. In patients with cardiogenic shock or with severe systolic dysfunction and/or severe low blood pressure, inotropes are only recommended as a bridge to coronary revascularization, insertion of mechanical circulatory support (MCS) or heart transplantation; in more stable patients but with stage D heart failure, continuous inotropic support is only recommended as bridge therapy until MCS or heart transplantation. Indeed, there is evidence that long-term use of continuous or intermittent inotropes in patients in scenarios without severe systolic dysfunction/low blood pressure causes greater mortality, mostly due to arrhythmias [1]. The exception to this rule is in palliative cases, where further special interventions may not be deemed appropriate (e.g. extremely elderly, comorbid patients); continuous inotropic support for symptomatic relief is acceptable in these scenarios [1].

Device Management of End-Stage Heart Failure

While insertion of mechanical circulatory support and heart transplantation are the two main special interventions for stage D severe heart failure, and are covered in Chaps. 2 and 3 respectively, there are other device-based strategies that may be employed prior to the onset of stage D, and thus warrant mention. In certain clinical scenarios, both the implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) are recommended by the ACC/AHA guidelines for patients with stage B or C heart failure with reduced ejection fraction [1].

Cardiac Resynchronization Therapy

Approximately one-third of heart failure patients demonstrate substantial prolongation of the QRS interval on ECG, which is associated with worse outcomes [1, 23]. In these patients, multisite ventricular pacing (termed cardiac resynchronization therapy (CRT) or biventricular pacing) can improve ventricular contractile function, diminish secondary mitral regurgitation, reverse ventricular remodeling, and sustain improvement in LVEF [1].

Thus, in patients with reduced LV function (EF ≤35%), sinus rhythm, left bundle branch block and a QRS width ≥150 ms, who display NYHA class II, III or ambulatory IV symptoms despite optimal medical treatment, cardiac resynchronization therapy (CRT) is recommended to improve symptoms and exercise capacity while decreasing hospitalizations and mortality [1, 24]. For those patients who meet all the aforementioned categories except for a shorter QRS width within the 120–149 ms range, CRT may also be considered, although evidence for a benefit is less clear [1]. Importantly, for patients who are functionally stage IV and who are refractory (i.e. not ambulatory), CRT is not recommended; it is not a "rescue" therapy for severe heart failure, and instead the patient should be considered for special interventions (detailed below). In cases where the patient is not expected to survive more than 1 year due to comorbidities and/or frailty, CRT should also not be considered.

Implantable Cardioverter-Defibrillator (ICD)

Patients who exhibit systolic dysfunction remain at risk of sudden cardiac death (SCD) due to ventricular tachyarrhythmias. For secondary prevention of SCD, ICD implantation has been demonstrated to reduce mortality in cardiac arrest survivors and in patients with sustained symptomatic ventricular tachyarrhythmias [1, 25]. For primary prevention of SCD in heart failure patients with optimal pharmacological treatment, ACC guidelines specify ICD therapy to be indicated in selected patients with LVEF ≤30% at least 40 days after myocardial infarction and in patients with ischemic and non-ischemic heart failure (NYHA class II–III) with LVEF ≤35% to reduce mortality [1, 26, 27].

Importantly, the effectiveness of ICD therapy has been observed to be time-dependent; no survival benefit is seen until after the first year in various clinical trials [26, 27]. The decision for ICD implantation in stage D patients is therefore particularly difficult given the poor expected prognosis yet high frequency of tachyarrhythmias seen in this subgroup.

Further Options

While heart failure medications, and in certain cases, cardiac resynchronization therapy or implantable cardiac defibrillators have improved quality of life and survival in heart failure patients, overall morbidity and mortality is still high [28]; refractory end-stage heart failure patients ultimately require either short or long-term mechanical circulatory support (MCS) or heart transplantation. The use of MCS, including an overview of devices and their indications/contraindications, are covered in Chap. 2; evaluation for cardiac transplantation is covered in Chap. 3.

Palliative Approaches to Heart Failure

In stage D heart failure scenarios where mechanical circulatory support and transplantation are strongly contraindicated due to multiple co-morbidities/frailty, a palliative path may be the most viable approach. Emphasizing communication, caregiver support, symptom management, comfort measures and coordinated care, palliative care offers an integrated approach to supporting patients and families with serious chronic illnesses in which prognosis cannot be reliably predicted. Indeed, the value of palliative care in heart failure has only recently reached national recognition, and was first included in the ACC/AHA guidelines for heart failure in 2005 [1].

Once a poor prognosis becomes clear, it is important to consult with patients and their families at the earliest opportunity in order to educate them regarding options for formulating advance directives, palliative and hospice care, as well as the option of re-evaluation according to clinical status. In particular, this may include a preference (or otherwise) for resuscitation in the event of a cardiac arrest, and indication of which supportive care measures and interventions should be initiated.

For palliation of end-stage heart failure symptoms, continuous inotropic support is acceptable [1]. In addition to guideline-directed medical treatment, nitrates may improve angina and dyspnea, and calcium antagonists may be used to treat refractory arterial hypertension and angina. Furthermore, anxiolytics and opioids may be used to relieve symptoms in end-of-life situations where no further therapeutic options are available.

Continuity of care between inpatient and outpatient settings is a crucial concept of palliative care; hospice care may provide continued options to relieve suffering from symptoms in an outpatient setting. In the setting of the final days of end-stage heart failure, it can be particularly difficult to decide when the priorities change from improving survival to maintaining comfort and quality of life in order to allow for a peaceful, pain-free death.

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2 Mechanical and Surgical Options for Patients with End-Stage Heart Failure

Jaime Moriguchi

Clinical Pearls

- General indications for referral for MCS include stage D patients who demonstrate LVEF <25% and NYHA class III-IV functional status in spite of guideline-directed medical therapy, with either high predicted 1–2 year mortality or continuous dependence on parenteral inotropic support.
- Relative contraindications to LVAD insertion include acute cardiogenic shock with uncertain neurological status, active severe bleeding, uncontrolled systemic infection, severe right ventricular dysfunction, severe uncorrected aortic insufficiency or mechanical aortic valve.
- Patient selection for MCS should be a multidisciplinary decision involving advanced heart failure/transplant cardiologists, cardiothoracic surgeons, nurses, social workers, and palliative care clinicians.
- Ventricular assist devices may be used as bridge-to-transplant, bridge-to-candidacy or as destination therapy; the destination therapy option is increasingly being utilized.
- The INTERMACS scale is useful for perioperative risk assessment and stratification for future outcomes post-implant, including mortality and complications.
- Mechanical circulatory support device-related complications such as driveline infection, stroke, and gastrointestinal bleeding are common and may result in reduced survival post-transplant.
- Short-term mechanical circulatory support methods are indicated in the setting of acute refractory cardiogenic shock, including intra-aortic balloon pump and veno-arterial extra-corporeal membrane oxygenation support.
- The total artificial heart is an option for patients with end-stage heart failure with biventricular dysfunction.

Introduction

While heart failure medications, and in certain cases, cardiac resynchronization therapy or implantable cardiac defibrillators have improved quality of life and survival in heart failure patients, overall morbidity and mortality is still high [1]; refractory end-stage heart failure patients ultimately require either short or long-term mechanical circulatory support (MCS) or heart transplantation. While transplantation is

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the current gold standard and only definitive solution, the lack of available donor hearts and prevalence of significant comorbidities as contraindication to transplantation has led to growing use of MCS devices. Indeed, in patients with end-stage heart failure considered too unstable to await a suitable donor organ, biventricular or left ventricular assist devices (LVADs) as well as total artificial hearts (TAHs) can be employed as bridge-to-transplantation therapy and have been shown to improve quality of life, survival-to-transplantation rates, and post-transplant survival [2, 3].

ACC/AHA guidelines state that general indications for referral for MCS include stage D patients who demonstrate LVEF <25% and NYHA class III-IV functional status in spite of guideline-directed medical therapy, with either high predicted 1–2 year mortality (based on reduced peak oxygen consumption or clinical prognostic scores) or continuous dependence on parenteral inotropic support [2]. Generally, patient selection should be a multidisciplinary decision involving advanced heart failure/transplant cardiologists, cardiothoracic surgeons, nurses, social workers, and palliative care clinicians.

Mechanical circulatory support consists primarily of ventricular assist devices (VADs) and the newer Total Artificial Heart (TAH), of which the latter will be discussed in detail in Chap. 17. Overall, the optimal strategy should include implanting the ideal MCS device with the best durability and lowest incidence of adverse events and that provides satisfactory cardiac output for either one or both failing ventricles. This chapter aims to provide an overview of mechanical circulatory support devices and indications for their usage in end-stage heart failure patients.

Ventricular Assist Device Categories: A Generational History

Fifty years ago, the first ventricular assist device (VAD) was implanted by DeBakey, with the aim of acting as a bridge to recovery. VADs are mechanical circulatory pumps which partially or completely take over ventricular function in order to assist systemic circulation and improve end-organ perfusion. A VAD may be used as a left ventricular (LVAD), right ventricular (RVAD), or as a biventricular assist device (BiVAD).

Initially introduced in the 1980s, the first generation LVADs were large paracorporeal devices such as the Thoratec PVAD and Abiomed BVS 5000 (and subsequently the AB 5000). Intracorporeal devices included the HeartMate I IP/VE (Thoratec Inc., Pleasanton, California, USA) (Fig. 2.1) and the Novacor N100 (WorldHeart Inc., Salt Lake City, Utah, USA). All of these functioned on the basis of pulsatile systemic perfusion, otherwise known as "pulsatile-flow" devices. However, their bulkiness, lack of durability, and proclivity to malfunction and complications meant that patients were often bedridden and had less than optimal outcomes, including high stroke rates [4]. Subsequent miniaturization of the control and power-supply components resulted in smaller versions of these first-generation pulsatile VADs that could be implanted intra-abdominally [5, 6]. While these enabled patients to mobilize, devices still remained restricted to patients with a large body surface area; device failure rates remained high, infections continued to be problematic, and durability remained poor [7].

The second generation of LVADs consist of smaller continuous axial flow pump systems that allow considerably less extensive surgery (thus reducing the risk of complications, see Fig. 2.2), and confer improved durability, ability to use in a wider range of patients due to smaller size, and reduced thrombogenicity. The increase in durability arises in part from the fact that there is only one moving part. The prototypic device of this class is the HeartMate II (HM II; Thoratec Inc., Pleasanton, California, USA) (Fig. 2.1), which is the most commonly used LVAD with over 20,000 implants worldwide. Introduction of these devices has proved successful, with demonstrated superior survival and less organ failure in patients on continuous-flow VADs compared to patients on pulsatile VADs. 1-year survival for these more modern devices has been reported at 81% for bridge-to-transplantation and 73% for destination therapy [8, 9], which while not as impressive as the 90% seen in heart transplantation, is

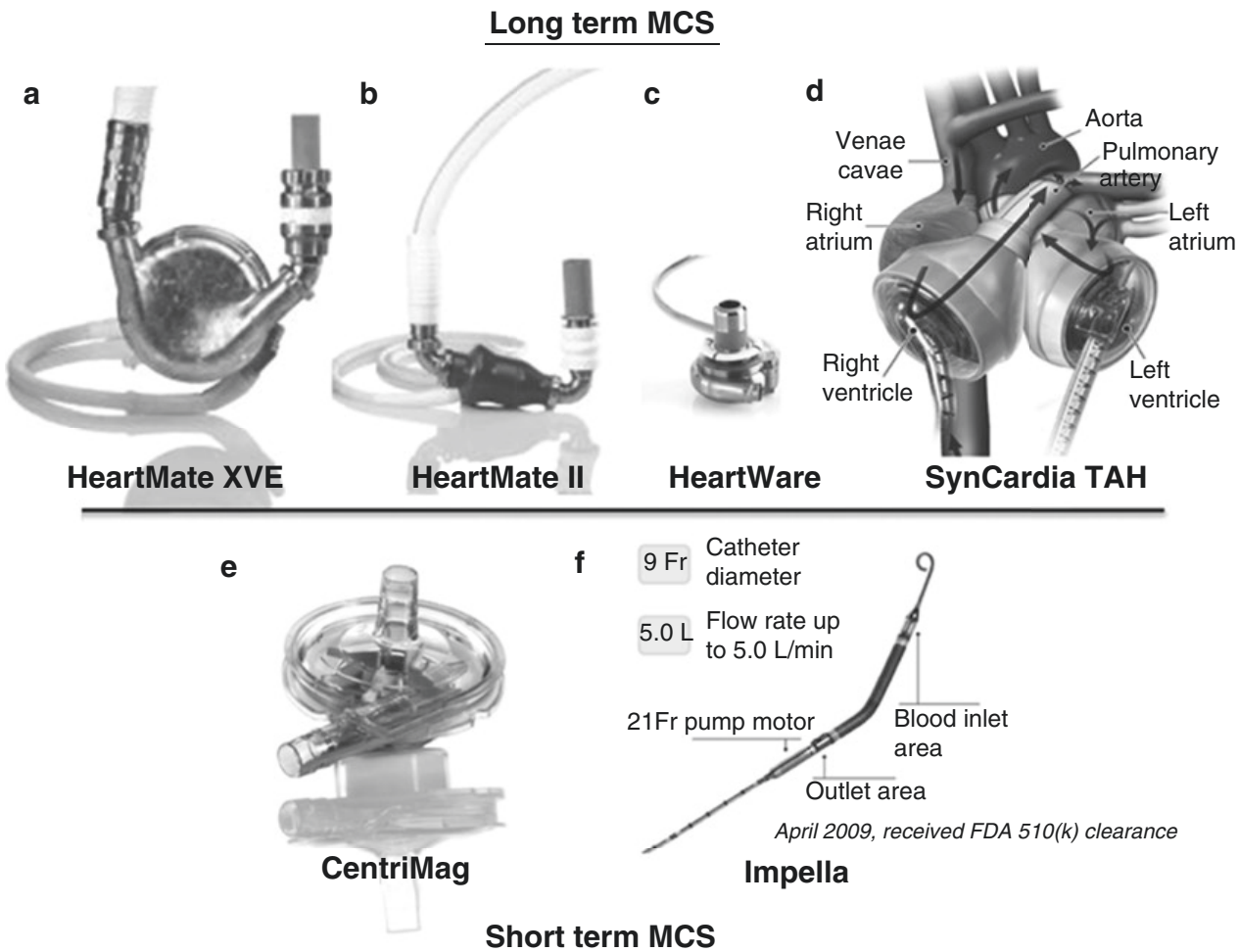

Fig. 2.1 Overview of commonly used mechanical circulatory support devices. First-generation device (**a**) Thoratec HeartMate XVE: pulsatile flow LVAD (left ventricular assist device) (Reprinted with the permission of Thoratec Incorporated). Second-generation LVAD (**b**) Thoratec HeartMate II (Reprinted with the permission of Thoratec Incorporated). Third-generation LVAD (**c**) HeartWare HVAD (Reprinted with the permission of HeartWare). Approved TAH (**d**) SynCardia CardioWest TAH (Courtesy: SynCardia.com). Short-term MCS devices with (**e**) Levitronix CentriMag extracorporeal RVAD (Reprinted with the permission of Thoratec Incorporated), and the (**f**) AbioMed Impella 5.0 (Reprinted with the permission of Abiomed). *RVAD* right ventricular assist device, *TAH* total artificial heart (Reused with permission from Toeg et al. [7])

certainly much improved from the first-generation of LVADs. Furthermore, in continuous flow devices, quality of life, general well-being and ability to perform self-care are significantly improved post-LVAD implantation [9, 10]. This improvement means that LVAD patients are now able to engage in daily life as outpatients relatively unperturbed.

The subsequent third-generation LVADs have sought to further refine the continuous-flow concept, minimizing contact between the pump and the axial rotor by using magnetic levitation technology, thus reducing friction and mechanical wear of the device. Given the small size, the pumps can be implanted within the pericardium, thus further reducing postoperative complications. Examples of third-generation LVADs include the DuraHeart (Terumo Heart Inc., Ann Arbor, Michigan, USA), VentrAssist LVAD (Ventracor Ltd., Chatswood, New South Wales, Australia), Incor (Berlin Heart Inc., Berlin, Germany), and the HeartWare HVAD centrifugal pump (HeartWare International Inc., Framingham, Massachusetts, USA) (Fig. 2.1).

The ADVANCE (Evaluation of the HeartWare Ventricular Assist Device for the Treatment of Advanced Heart Failure) Trial (and continued access enrollment) included 332 pts. implanted

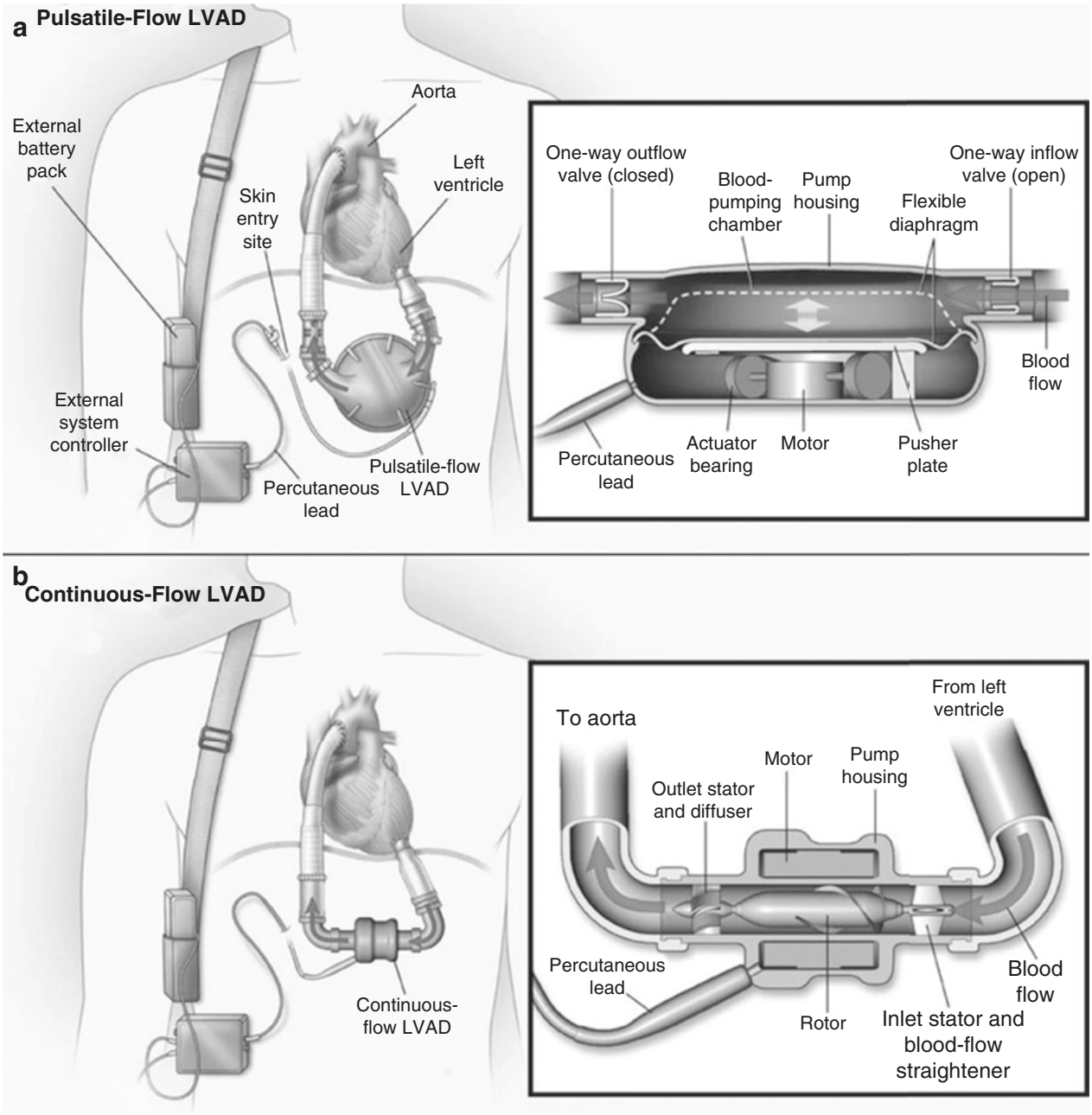

Fig. 2.2 A visual overview of left ventricular assist devices (LVAD). *Panel A* shows a first-generation pulsatile flow left ventricular assist device (LVAD). *Panel B* shows a second-generation continuous flow LVAD. Both mechanical pumps are placed in the abdominal wall. The inflow cannula of the LVAD is placed in the apex of the left ventricle. The outflow cannula is subsequently anastamosed with the ascending aorta. A percutaneous lead connects the LVAD pump with an external system controller and the battery pack (Reused with permission from Slaughter et al. [30])

with the HeartWare HVAD with 91% survival at 180 days and 84% at 1 year [11]. Currently, over 5000 HeartWare HVADs have been implanted worldwide and has CE approval in Europe. In the U.S. along with the HM II LVAD, it is the only FDA approved LVAD for bridge-to-transplant candidates. With respect to destination therapy (see below), the HM II LVAD is the only FDA approved device at the current time. However, the ENDURANCE (Clinical Trial to Evaluate the HeartWare® Ventricular Assist System) Trial for destination therapy comparing the HVAD to HM II is ongoing [12]. Another multicenter trial of the VentrAssist LVAD in 33 patients demonstrated a favorable efficacy and safety profile for the use of this device as bridge-to-transplant [13], with 82% of the patients surviving at 5 months post-implant. However, this device is no longer

available. The DuraHeart, a LVAD used primarily in Europe, has also shown comparable survival as bridge-to-transplant, with 77% at 1 year and 61% at 2 years [14]. However, longer follow-up and data is required before firm conclusions can be drawn.

Total Artificial Heart

An emerging alternative to VADs in patients with biventricular failure, TAHs will be covered in more detail in Chap. 17.

Trends in Ventricular Assist Device Use: Strategies and Outcomes

Ventricular assist devices are typically used in one of 3 ways: to stabilize the waitlist patient until a donor heart becomes available, otherwise known as bridge-to-transplant; to stabilize the patient with an anticipated possibility of future listing for transplant, known as bridge-to-candidacy; and as "destination" therapy, which means that the patient is not a transplant candidate and thus the VAD is the terminal treatment. In patients who eventually end up with VAD as destination therapy, LVADs are often implanted with the intention of bridging to transplant (with the exception of those contraindicated to transplant). However, in recent years destination therapy survival has improved [15]; furthermore, as the waiting list for a heart becomes longer, the duration of MCS becomes longer, and some patients may remove themselves from the waiting list.

In rare cases (<5% of implants), LVADs have acted as a bridge to recovery, the theory being that unloading of the ventricle leads to reverse ventricular remodeling and subsequent functional improvement [16]; while this appears more likely to occur in myocarditis and other recoverable etiologies of heart failure, there are no reliable parameters to predict which patients will demonstrate this.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) represents the largest registry of MCS device utilization in the world, with 166 participating hospitals across the US and Canada. Its purpose is to collect MCS-related data and assess trends in survival, device strategy and risk factors for poor outcomes. The most recent seventh INTERMACS annual report presents MCS data from 23 June 2006 to 31 December 2014. Of the 15,745 patients who received an MCS device, 13,286 received an LVAD. Not surprisingly, given the survival benefits, over 90% (12030) of these patients received a continuous flow LVAD, with 955 receiving a pulsatile device and a further 301 receiving a TAH. Survival for continuous-flow devices implanted since 2008 remains at 80%, with 2-year survival at 70% [15]. Freedom from device exchange or death related to device malfunction has been demonstrated to be similar for pulsatile and continuous flow devices for the first 8 months (96%). However, there is a significant linear decrease in the freedom from device malfunction in the pulsatile device from 8 months until 24 months post-implant (40% at 24 months), compared to the relatively steady freedom from malfunction at 24 months in the continuous flow LVAD (94% at 24 months) [10].

In recent years, stimulated by the 2010 approval of the continuous-flow HeartMate II for destination therapy, the proportion of VADs implanted as destination therapy (DT) has increased considerably. DT plateaued in 2014, with 46% of implants designated as DT, 23% as bridge-to-candidacy, and 30% as bridge-to-transplant. This is in contrast to the previous trend from 2008 to 2011, which had only 29% of implants listed as DT, 38% listed as bridge-to-candidacy, and 32% listed as bridge-to-transplant. With the advancement of LVAD technology and improved perioperative care and patient selection, these trends look likely to continue. However, survival by implant strategy has remained constant over the years; specifically, bridge-to-transplant patients tend to fare significantly better post-implant than destination therapy. Survival with DT therapy at 1 and 3 years is 76% and 57%, respectively; with bridge-to transplant, it is 86% and 76% [15].

Table 2.1 INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) scale for classifying patients with Advanced Heart Failure

Profiles	Definition	Description
INTERMACS 1	*"Crash and burn"*	Hemodynamic instability in spite of increasing doses of catecholamines and/or mechanical circulatory support with critical hypoperfusion of target organs (severe cardiogenic shock)
INTERMACS 2	*"Sliding on inotropes"*	Intravenous inotropic support with acceptable blood pressure but rapid deterioration of kidney function, nutritional state, or signs of congestion
INTERMACS 3	*"Dependent stability"*	Hemodynamic stability with low or intermediate, but necessary due to hypotension, doses of inotropics, worsening of symptoms, or progressive kidney failure
INTERMACS 4	*"Frequent flyer"*	Temporary cessation of inotropic treatment is possible, but the patient presents frequent symptom recurrences and typically with fluid overload
INTERMACS 5	*"Housebound"*	Complete cessation of physical activity, stable at rest, but frequently with moderate water retention and some level of kidney dysfunction
INTERMACS 6	*"Walking wounded"*	Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity
INTERMACS 7	*"Placeholder"*	Patient in NYHA functional class II or III with no current or recent unstable water balance

Reused with permission from Stevenson et al. [18]

Contraindications to LVAD Insertion

Relative, but not absolute contraindications to LVAD insertion include acute cardiogenic shock with uncertain neurological status, active severe bleeding (as patients on VAD require anticoagulation), active uncontrolled systemic infection, severe right ventricular dysfunction, severe uncorrected aortic insufficiency or mechanical aortic valve that will not be converted to a bioprosthesis [7]. Furthermore, patients who would be unable to physically operate their pump and would not respond to device alarms are also considered unsuitable [17]. Management guidelines for LVAD patients are continually being updated and assessed, with increasing numbers of centers reporting their data [10, 17]; as such it is anticipated that these contraindications will change with improvements in LVAD technology, surgical methods and postoperative management.

INTERMACS Scale and Risk Factors for Mortality Post-implant

The INTERMACS scale [18] assigns patients with advanced heart failure into seven different classifications according to clinical status, hemodynamic profile and level of end-organ damage (see Table 2.1). The lower the number, the more gravely ill the patient; for example, an INTERMACS 1 patient will demonstrate hemodynamic instability and cardiogenic shock despite increased inotropic doses and/or mechanical circulatory support; in contrast, an INTERMACS 7 patient is a functional, ambulatory NYHA class IIIa patient with no fluid overload. Such a scale was designed for the purposes of perioperative risk prediction and stratification for future outcomes post-implant, including mortality and complications.

The major risk factors for mortality following continuous-flow device implantation include patients on hemodialysis, patients INTERMACS 1 and 2 levels, female age, history of stroke, previous ICD placement, increased bilirubin and requirement for RVAD implant in the same operation [15].

Potential Complications of Left Ventricular Assist Devices

The most common complications from VADs include stroke, bleeding, infection, device malfunction, arrhythmia and renal dysfunction.

Unfortunately, complications are frequent, and one of the main reasons, along with reduced survival, as to why LVAD is not yet superior to transplantation; the freedom from any major adverse event is low, with 30% at 1 year and 19% at 2 years, regardless of age or INTERMACS level [10]. Notably, the rate of adverse events is significantly higher in pulsatile devices, which show increased complication rates in all categories: bleeding, infection (most frequently with Staphylococci, most commonly at the driveline site) and device malfunction [10, 19]. Device malfunction is often a measure of durability, may derive from either a mechanical issue (motor failure) or a biochemical issue (device thrombosis or hemolysis). Pump failure is typically followed by stroke, bleeding and/or infection and necessitates redo-surgery for pump exchange.

Despite the improved rates of complications in continuous-flow devices compared to pulsatile devices, readmission rates still remain high, with one study demonstrating an average of 1.64 ± 1.97 admissions per patient-year follow up [20]. The most common reasons for readmission are infection and gastrointestinal bleeding resulting from anticoagulation.

Importantly, LVAD patients on the heart transplant waiting list are noted to have significantly worse waitlist mortality once a serious complication occurs [21]. Furthermore, there is evidence to suggest that in continuous-flow LVAD patients who are successfully bridged to transplant, device-related complications prior to transplant negatively affects survival at 1 year and 3 years post-transplant [22].

Left Ventricular Assist Device Selection

Ventricular assist device selection is generally tailored according to the patient's expectations and clinical status, using a multidisciplinary approach. Hemodynamically stable patients who are typically classified as INTERMACS 3 or greater may be considered for bridge-to-transplant or destination therapy using a durable, long-term continuous flow device such as those already mentioned. However, in the hemodynamically unstable or deteriorating patient, (i.e. INTERMACS 1 or 2), short-term MCS therapy should be immediately considered (see next section). Such a measure provides the patient with essential circulation and allows the medical team more time to optimize clinical status, perform neurologic assessment and decide on further management (LVAD, transplant, etc.). Pertinently, in regard to the timing of assist device therapy, reports have shown that survival of patients undergoing bridge-to-transplantation therapy is improved when assist devices are implanted electively, as compared to implantations for urgent or emergency indications [23].

Short Term Options for Mechanical Circulatory Support

Intra-aortic Balloon Pump

The intra-aortic balloon pump is a mechanical device that increases myocardial oxygen perfusion while simultaneously increasing cardiac output. Inserted via the femoral artery, it consists of a cylindrical polyethylene balloon that sits in the aorta, approximately 2 cm (0.79 in) from the left subclavian artery and counterpulsates. This method is often used as the first mechanical support treatment in efforts to improve coronary perfusion in the setting of refractory cardiogenic shock. Absolute contraindications include severe aortic valve insufficiency and ongoing aortic dissection, while relative contraindications include aortic aneurysm and presence of any aortic vascular grafts. Possible complications include ischemic leg, cerebral embolism, aortic dissection and mediastinal bleeding.

Extracorporeal Membrane Oxygenation

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a rapid mode of emergency biventricular support typically used as a last resort salvage therapy in the setting of cardiogenic shock, where implanting a IABP/VAD or other durable

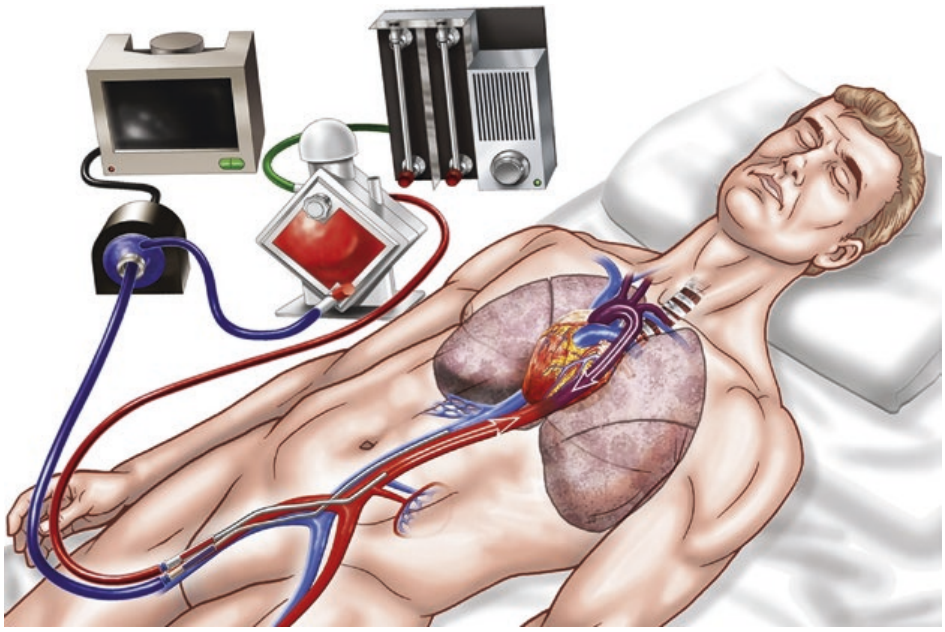

Fig. 2.3 Functional diagram of femoral venoarterial ECMO in a patient (Reused with permission from Abrams et al. [31])

device is not possible (see Fig. 2.3). Essentially a form of cardiopulmonary bypass, ECMO provides excellent hemodynamic support via a nonpulsatile (often centrifugal) pump connected in-line to a membrane oxygenator that receives blood via inflow venous cannulas, commonly inserted into the femoral vein, and returns oxygenated blood via an outflow arterial cannula, commonly inserted into the femoral artery. Survival rates in refractory cardiogenic shock patients with ECMO vary regarding clinical indication, with survival to discharge varying from 39 to 80% [24, 25]. The main disadvantages of ECMO are the relative lack of durability (mean of 4 days), inability to unload the left ventricle and the potential bleeding issues with regard to vascular access [24, 25]. Patients that survive are typically subsequently transitioned to a VAD, or rarely, transplant.

Percutaneous Mechanical Circulatory Support

Recent advances in MCS technology have uncovered new devices such as the Impella CP 4.0 and 5.0 (Abiomed) (Fig. 2.1); the Impella is an essentially miniaturized percutaneous LVAD catheter that is able to be inserted via the femoral artery and placed retrograde across the aortic valve to provide adequate perfusion in hemodynamically unstable patients. Their original use was supportive during high risk percutaneous coronary interventions in settings of cardiogenic shock post-MI. Such devices are not durable, and are recommended for use for up to only 7 days; however, some centers have maintained use of Impella for up to 27 days [26–28], by means of a right axillary approach. The TandemHeart® (Cardiac Assist, Inc., Pittsburgh, Pennsylvania, USA) is another percutaneous LVAD that requires a trans-septal puncture [29].

Cardiac Transplantation

Heart transplantation is considered the gold standard for the treatment of refractory end-stage heart failure. Indications and evaluation criteria will be detailed in Chap. 3.

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Evaluation for Heart Transplant Candidacy

3

Jon Kobashigawa, Minh Luu, and Christine Sumbi

Clinical Pearls

- The purpose of heart transplant evaluation is to identify the patients with the greatest need and highest potential for favorable outcome with transplantation.
- General indications for evaluation for transplant listing include cardiogenic shock requiring continuous intravenous inotropic support or mechanical support, refractory NYHA class III-IV/AHA stage D heart failure, recurrent ventricular arrhythmias with the risk of hemodynamic compromise, severe untreatable angina and end-stage congenital heart disease.
- Cardiopulmonary exercise testing provides an objective measure of cardiac impairment and prognosis via measurement of oxygen consumption at peak exercise (V_{O2}max).
- Heart failure patients on beta-blockers with a V_{O2}max ≤12 ml/kg/min or younger patients with less than 50% of predicted V_{O2}max, considered in conjunction with other evidence of functional impairment, may be appropriate for transplant.
- Hemodynamic assessment with right heart catheterization also is useful to assess the level of cardiac impairment and confirm there is no evidence of irreversible pulmonary hypertension.
- The Heart Failure Survival Score (HFSS) and Seattle Heart Failure Model (SHFM) are multifactorial scores that are helpful in guiding decisions on listing for heart transplantation.
- Potential relative contraindications include age >70 yrs., obesity (BMI >35 kg/m^2), pulmonary hypertension, primary pulmonary disease, poorly controlled diabetes (HbA_{1C} >7.5%) or diabetes with end-organ damage, renal dysfunction (eGFR<30 ml/min/1.73m^2), and any active infection excluding LVAD-related infections.
- Absolute contraindications include severe or multiple of the above relative contraindication factors, active or metastatic malignancy, severe cerebrovascular disease, strong indicators for non-compliance and a lack of social/caregiver support.

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Ultimately, the decision to list a patient for transplantation is not based on any one test or factor but acknowledges multiple factors, including indicators for poor prognosis without transplant as well as potential contraindications that may cause suboptimal outcomes post-transplant.

Introduction

Despite advances in pharmacological and device treatment of chronic heart failure, long-term morbidity and mortality remain unacceptably high; the 5-year mortality rate for patients with symptomatic heart failure approaches 50% and may be as high as 80% at 1 year for end-stage patients [1]. For those patients in whom these therapies (as detailed in Chaps. 1 and 2) have been attempted without success, heart transplantation may be a suitable option, and is considered the gold standard for the treatment of refractory end-stage heart failure. Evaluation for transplant candidacy is a multidisciplinary endeavor. This chapter aims to summarize the medical and psychosocial criteria for transplant listing including indications and contraindications, the methods by which these criteria are measured, and other extraneous considerations regarding suitability for transplantation.

Indications for Cardiac Transplantation

Select patients with refractory AHA Stage D or NYHA class III-IV heart failure and poor prognosis are usually referred to a cardiac transplantation center for evaluation and transplant consideration. Patients should be referred to an advanced heart disease center that can provide individualized care, considering all advanced therapies including transplantation, mechanical support devices, and new innovative treatments. The evaluation process is summarized in Fig. 3.1. Due in part to the current shortage in available donor hearts, careful evaluation for candidacy is warranted. Generally speaking, patients must be sick enough to warrant transplant, but not so sick that there is no reasonable expectation of long-term post-transplant survival in order to maximize the utility of donor hearts given their scarcity. Simultaneously, the potential survival benefit (as compared to without transplantation) to the patient must be considered, including factors such as life expectancy and potential quality of life after transplantation. Finding a balance between maximal individual survival benefit and maximal utility will always remain a complex issue requiring frequent reassessment by a multidisciplinary team.

The fundamental indication for cardiac transplantation is a poor quality of life and/or expected survival, despite maximal medical therapy, that has a high likelihood of being improved with transplant. This essentially means patients with Class III/IV symptoms or a 1-year expected cardiac-related survival significantly lower than the 1-year post-transplant survival, with no other life-limiting medical problems. The most common indications for evaluation for transplantation include refractory cardiogenic shock requiring continuous intravenous inotropic support or mechanical support, refractory NYHA class III-IV/AHA stage D heart failure, reduced exercise capacity (as defined by peak V_{O2} below a certain threshold), recurrent arrhythmias with the risk of hemodynamic compromise, and severe untreatable angina and end-stage congenital heart disease [2]. Current heart transplant patients who develop significant cardiac allograft vasculopathy with refractory cardiac dysfunction may also be considered for redo-transplant. A full list of indications is summarized in Table 3.1. Once a patient is euvolemic with optimal medical management, physicians are able to assess whether the patient is limited enough to merit transplantation. Of note, the inability to achieve optimal medical therapy because of progressive renal dysfunction or hypotension indicates poor reserve and is also an indication for transplantation [3] as are frequent episodes of decompensation despite medical compliance.

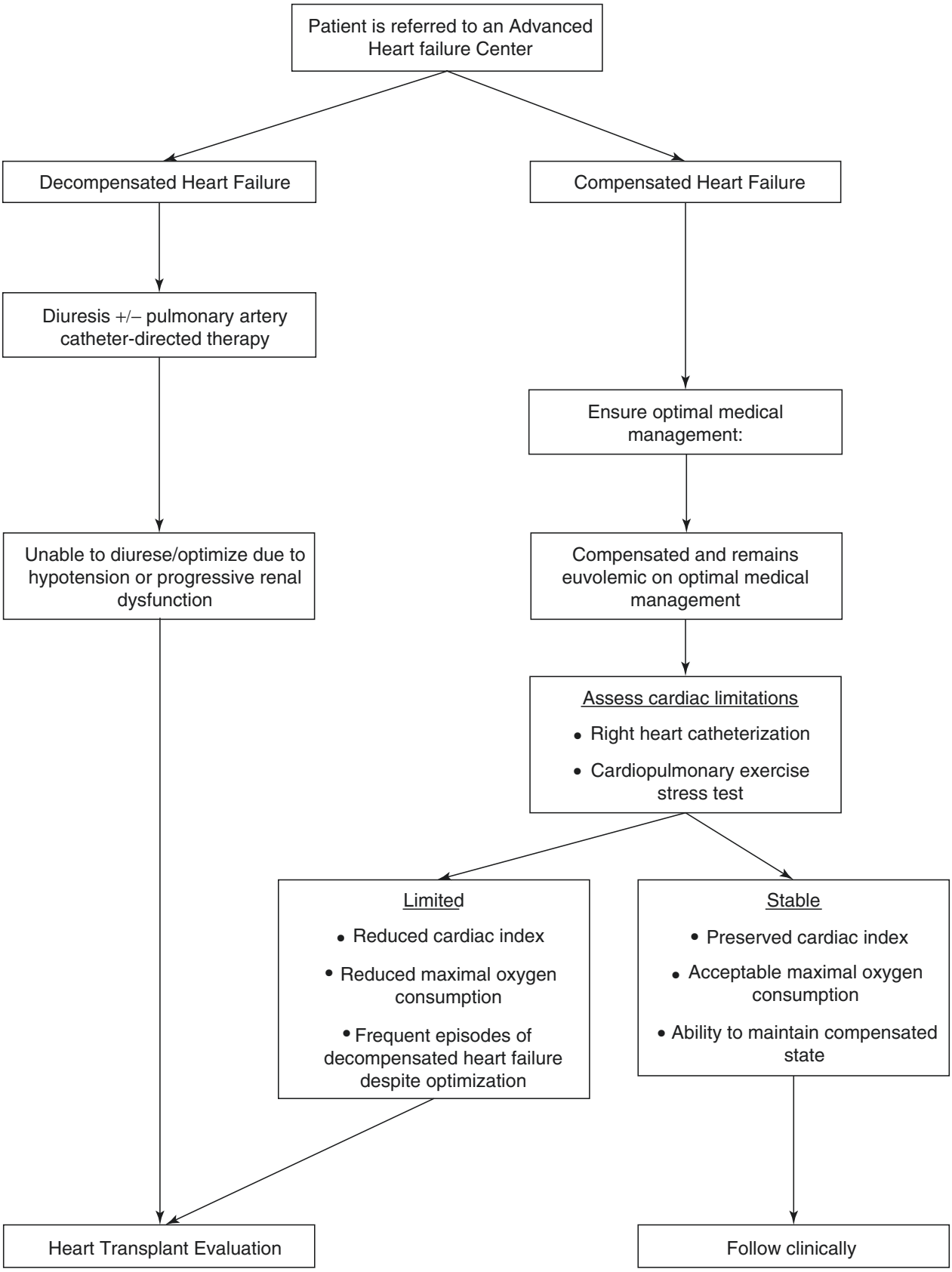

Fig. 3.1 The heart transplant evaluation process (Reused with permission from Kittleson et al. [14])

Table 3.1 Recommended tests for initial evaluation of heart transplant candidacy

Recommended tests
Weight/body mass index
Immuno-compatibility
ABO typing
Human leukocyte antigen tissue typing
Panel reactive antibodies and flow cytometry
Assessment of severity of heart failure
Cardiopulmonary exercise test
Echocardiogram
Right heart catheterization
Evaluation of multi-organ function
Routine laboratory work (basic metabolic profile, complete blood count, liver function tests)
Urinalysis with toxicology screen
24-h urine collection for protein and creatinine
Pulmonary function tests
Chest radiograph
Abdominal ultrasonography
Carotid Doppler (if >50 years or with ischemic heart disease)
Ankle-brachial indices (if >50 years or with ischemic heart disease)
Dental examination
Ophthalmologic examination (if diabetic)
Chest and abdomen/pelvic CT scans (if indicated)
Infectious serology and vaccination
Hepatitis B surface, core, envelope antigen, antibody (IgG/IgM)
Hepatitis C antibody
Human immunodeficiency virus (HIV)
Rapid plasma reagin
Immunoglobulin G for herpes simplex virus
cytomegalovirus, toxoplasmosis, Epstein-Barr virus, varicella
Purified protein derivative
If from Latin American: Chagas screen
Immunizations: influenza, pneumovax, hepatitis B
Preventive and malignancy
Stool for occult blood x 3
Colonoscopy (if indicated or if >50 years)
Mammography (if indicated or if >40 years)
Papanicolaou smear test
Prostate-specific antigen and digital rectal examination (men >50 years)
General consultations
Social assessment
Psychiatry
Financial
As indicated: pulmonology, nephrology, infectious disease, endocrinology, hematology

Reused with permission from Mehra et al. [32]
Abbreviations: *IgG* immunoglobulin G, *IgM* immunoglobulin M

Evaluation Testing

The first goal of cardiac transplant evaluation is to objectively determine whether or not a patient has sufficiently poor functional capacity and prognosis in order to be listed. Risk stratification of heart failure patients is important, in order that patients with a high probability of survival benefit are selected for transplant, and that appropriate priority criteria can be developed. It is important that the criteria to define eligibility are as objective as possible; however, many of the accepted criteria used to define eligibility for heart transplant are somewhat unreliable, including resting hemodynamic data and NYHA classification. Firstly, NYHA classification as a measure of functional capacity is highly subjective and often inaccurate, and can vary on a day-to-day basis. Furthermore, while hemodynamic measurements accurately reflect the state of cardiac performance at rest, they may not always predict functional capacity and measures such as resting cardiac output may be poorly predictive of outcome after hemodynamic optimization. Cardiopulmonary exercise testing is considered one of the most objective methods of assessment of both functional capacity and prognosis. Ultimately, combinations of several methods are typically employed to objectively estimate clinical status and the likelihood of adverse prognosis with medical/device therapy alone. Scoring tools to improve risk stratification of HF patients have also been developed, and are also frequently used in combination with testing to inform a decision on listing for transplantation; however, even these scoring tools should not be used as the sole determinant of listing [4], and the decision to list/not list should be based on multiple factors.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET), a bicycle or treadmill based exercise test with gas exchange measurements via a mouthpiece, is considered a gold standard for objectively establishing a severity of functional cardiac impairment that would merit listing for transplantation [4]. The key measurement in CPET that provides prognostic information is the oxygen consumption at peak exercise, or V_{O2}max. This is particularly relevant because the very basis of heart failure is the lack of ability to provide oxygen to peripheral tissues at a sufficient rate for aerobic respiration. Testing is performed in an incremental fashion in order to identify the point at which the patient reaches their maximal aerobic capacity.

Maximal Oxygen Consumption

The ISHLT guidelines state that a cut-off for V_{O2}max of ≤14 ml/kg/min in heart failure patients not on beta-blockers should be used to decide which patients are sufficiently impaired for transplantation [4]. In the presence of a beta-blocker, a cutoff of ≤12 ml/kg/min should be used. Studies that have demonstrated that patients with preserved exercise capacity (V_{O2}max> 14 mL/kg/min) despite severe resting hemodynamic impairment, have survival and functional capacity equal to those afforded by cardiac transplantation [5, 6]. Because beta-blocker therapy has improved survival rates in patients with systolic HF including patients with very low V_{O2}max to as low as 10 mL/kg per min [6], the threshold is lower in patients on beta-blockers. In younger patients (below 50 years old) and women, it is reasonable to use additional variables such as percentage of predicted V_{O2}max; below 50% of predicted is considered sufficiently impaired for transplantation [7–9]. In obese patients, adjusting V_{O2}max to lean body mass should be considered; a lean body mass-adjusted V_{O2}max of less than 19 ml/kg/min serves as the threshold to decide which patients are sufficiently impaired [4]. Of note, the presence of a cardiac resynchronization therapy device does not alter the V_{O2} cut-off recommendations. It must be emphasized that the decision to list must not be made on V_{O2}max on CPET alone; many other factors, including risk scores and potential contraindications, must be considered.

Reaching anaerobic threshold defines a maximal CPET test, and is necessary to accurately measure V_{O2}max. The anaerobic threshold is defined as the point during exercise when oxygen delivery (and hence cardiac output) to exercising muscles is insufficient to sustain aerobic respiration, at which point anaerobic pathways are predominantly utilized. It occurs at approximately 60–70% of V_{O2}max in heart failure patients. When carbon dioxide production is greater than consumable oxygen (respiratory exchange ratio (RER) >1.05) and lactate levels sharply rise, this indicates the anaerobic threshold has been met, and helps differentiate true cardiac limitation from poor effort or potentially confounding pulmonary or musculoskeletal problems. The index of ventilatory efficiency (V_E/V_{CO2}) on CPET testing, defined as the ratio of minute ventilation (V_E) to the rate of carbon dioxide production (V_{CO2}), may also be used as a measure for determining whether listing for transplant should be considered, and may be especially useful for patients who do not achieve their anaerobic threshold. Specifically, patients with a V_E/V_{CO2} slope of greater than 35 have a worse prognosis and should be considered for transplantation [4]. Recent studies have suggested that ventilatory efficiency may be a more powerful prognostic factor than V_{O2}max [10, 11]. Ventilatory efficiency has also been shown to maintain prognostic value regardless of body mass index, another potential confounding factor that can limit interpretation of V_{O2}max [12].

CPET testing may also be a useful tool for identifying patients who have demonstrated clinical stability while on the waiting list and are being considered for delisting.

Hemodynamic Performance Assessment

Initial assessment of resting hemodynamics in heart failure patients typically includes assessment of left and right ventricular function by echocardiogram. Assessment of left ventricular systolic ejection fraction provides a useful initial

rapid assessment of the severity of impairment in left ventricular function and therefore likelihood of requiring transplantation; it is also used to assess response to medical or surgical therapies. A left ventricular ejection fraction of less than 25% has been shown to be associated with increased mortality and morbidity compared to an ejection fraction of over 35% [13]. However, low ejection fractions alone within a cohort of patients with advanced heart failure have been shown to be poorly predictive of short-term or medium-term mortality- information needed to make a decision regarding listing. Indeed, there is a wide range of functional capacities associated with a low ejection fraction; some are able to freely ambulate, while some are bedridden and require ventricular assist device support. There are also problems inherent in the technique-to-technique, inter-observer and intra-observer variability of ejection fraction measurement that make it unsuitable as a lone guide to listing for transplantation [4].

Right heart catheterization (RHC) assessment of hemodynamic performance remains an important test for ongoing assessment and maintenance of heart transplant candidacy [4]. It is recommended that right heart catheterization be performed on all adult candidates in preparation for listing for cardiac transplantation, as well as periodically prior to transplantation [4]. Indicators for more frequent assessment would include the presence of reversible pulmonary hypertension or worsening of heart failure symptoms. Of measurements obtained via RHC, higher right atrial pressure, higher pulmonary capillary wedge pressures, lower mean arterial pressure, higher pulmonary artery pressure (>50 mmHg) and lower cardiac index (<2.5 L/min/m^2) have all been variably associated with increased mortality [4, 14–17]. However on their own they remain poor prognostic indicators for heart failure patients [4]. In clinical practice, hemodynamic measurements are most useful as a method to gauge response to medical therapy, and to make sure a patient does not have irreversible pulmonary hypertension (see below).

Overall, resting hemodynamic assessment remains an important part of the evaluation process. Combined with CPET data resting hemodynamic measurements have proved highly prognostic [17], and are therefore useful for the purposes of listing.

Heart Failure Survival Score (HFSS)

While certain measurements such as ejection fraction are poor prognostic indicators by themselves, the combination of multiple measures of cardiac function into a survival score has provided greater prognostic value. The Heart Failure Survival Score (HFSS) is one such score. It is derived from a multivariable analysis of 268 ambulatory patients referred for consideration of cardiac transplantation from 1986 to 1991 and was subsequently validated in a population of 199 similar patients from 1993 to 1995 [18]. The component predictors of survival in the HFSS include: Presence or absence of coronary artery disease; resting heart rate; left ventricular ejection fraction as per echocardiography; mean arterial blood pressure; presence or absence of an intraventricular conduction delay on electrocardiogram; serum sodium; and V_{O2}max as determined by CPET.

Scores are categorized into low-risk (score ≥8.1), medium-risk (score ≥7.2 and <8.1), and high-risk (<7.2). It was demonstrated that patients in medium and high-risk groups are most likely to die or require urgent transplant in the following year, with a 1-year survival of 72% and 43%, respectively [18]; consequently, the ISHLT guidelines recommend that these patients should be considered for cardiac transplantation if no contraindications are present [4]. The validation data show that transplantation can be safely deferred in patients in the low-risk group, with a 1-year survival of 93%. Compared to V_{O2}max alone, HFSS has been demonstrated to be superior for the purposes of heart transplant selection in patients supported with continuous-flow ventricular assist devices [6].

The Seattle Heart Failure Model (SHFM)

The Seattle Heart Failure Model (SHFM) is another scoring tool, derived from a cohort of 1125 heart failure patients and subsequently

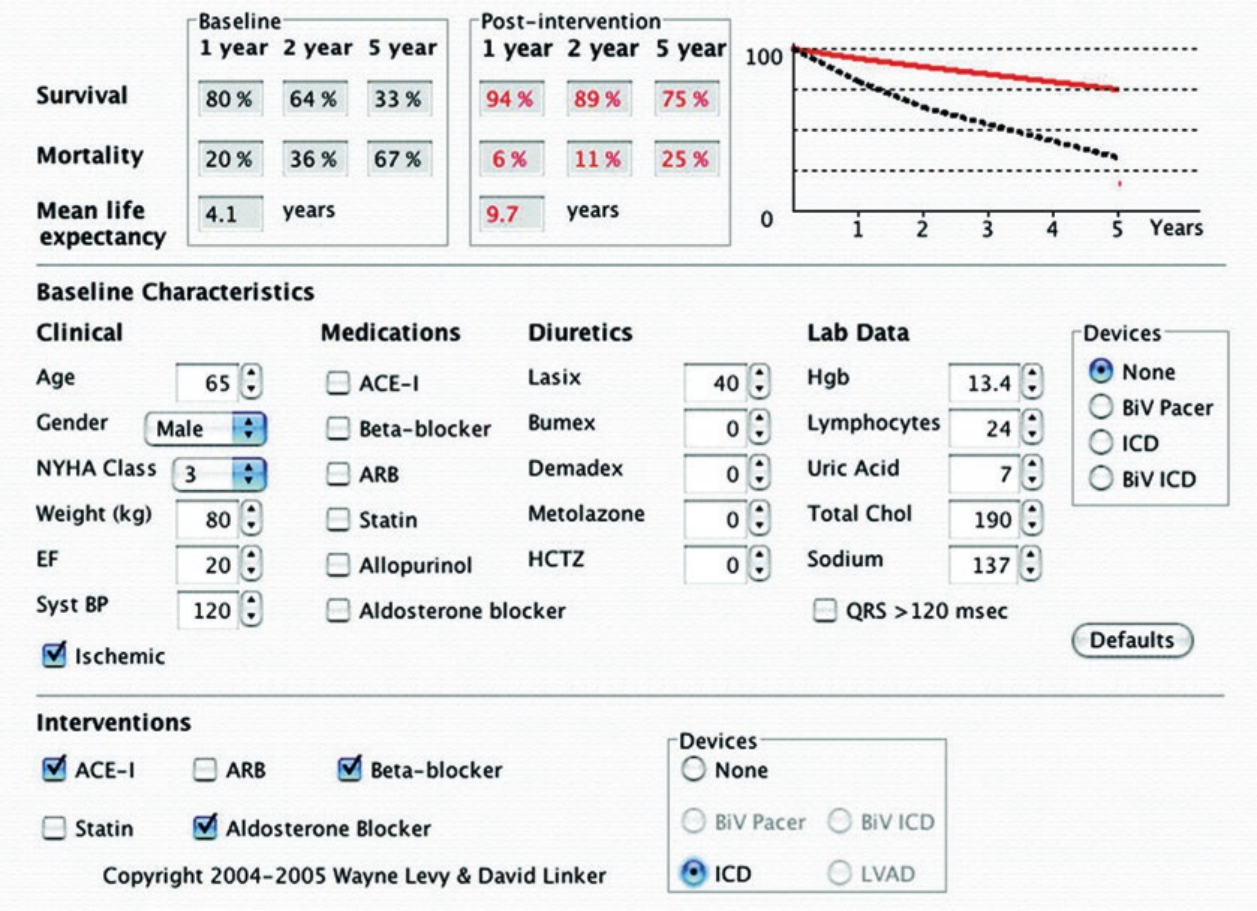

Fig. 3.2 An example of the use of the seattle heart failure model (Reused with permission from Levy et al. [16])

validated in 9942 patients [16]. It is most useful for estimating the prognosis for ambulatory patients with advanced heart failure. The SHFM incorporates the variables of age, sex, NYHA class, ischemic etiology, body mass index (BMI), ejection fraction, systolic blood pressure, diuretic dosages, laboratory values (serum sodium, cholesterol, hemoglobin, percent lymphocytes, creatinine, uric acid) and other clinical information (see Fig. 3.2). Most pertinently, the model is able to incorporate the impact of newer heart failure therapies on survival (including implantable cardioverter-defibrillators and cardiac resynchronization therapy), and allows evaluation of the estimated effect of interventions on an individual patient's prognosis. Validation data demonstrate that the model is able to provide an accurate estimate of 1-, 2-, and 3-year survival. The primary limitation of the SHFM is that it was derived from in an ambulatory HF population thus may overestimate survival in the overall advanced heart failure population [19, 20]. Nevertheless, it remains a useful method for estimating the chance of survival for the purposes of transplant listing; the ISHLT guidelines consider a less than 80% estimated chance of 1-year survival as per SHFM to be a reasonable cut-off for consideration of transplantation [4].

Other Factors

Besides the measurements and scoring systems covered, other factors that are typically considered include consideration of NYHA class (the inherent problems of such a subjective classification have been discussed above); assessment to ensure optimal medical and surgical (if applicable) management has been considered; and the duration of heart failure illness, as shorter durations of advanced heart failure have been associated with a greater likelihood of recovery.

Table 3.2 General indications for cardiac transplantation

Refractory cardiogenic shock requiring intra-aortic balloon pump counterpulsation or mechanical circulatory support (i.e. left ventricular assist device (LVAD), total artificial heart).
Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e. dobutamine, milrinone, etc.).
Cardiopulmonary exercise testing demonstrating V_{O2}max ≤14 mL/kg/min in patients not on beta-blockers, or V_{O2}max ≤12 mL/kg/min in patients on beta-blockers.
Persistant NYHA class of III or IV heart failure symptoms despite maximized medical, surgical and/or resynchronization therapy.
Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, maximal pharmacological antiarrhythmic therapy, or catheter-based ablation.
End-stage congenital HF with no evidence of pulmonary hypertension.
Refractory angina despite maximal medical therapy and not amenable to percutaneous or surgical revascularization.
Severe hypertrophic or restrictive cardiomyopathy, with NYHA Class IV symptoms.
Transplanted patients who develop significant cardiac allograft vasculopathy with refractory cardiac allograft dysfunction.

Adapted from Mancini and Lietz [2]
NYHA New York Heart Association

Potential Contraindications to Cardiac Transplantation

The 2 major categories of contraindications for heart transplantation are medical and social/psychological (Table 3.2). Many of these factors are not absolute on their own and need to be considered in the context of the severity of the patient's heart disease and associated comorbidities. Table 3.3 summarizes the screening investigations that should be performed during evaluation of a potential transplant candidate in order to assess indications and contraindications. A useful rule is that the presence of any non-cardiac condition that would substantially increase the peri- or postoperative risks of the transplant or itself shorten life expectancy would represent a medical contraindication. Similarly, any psychosocial issues that would increase the risk of death from rejection due to medical non-compliance would also place the patient at a prohibitively high risk for transplant.

Age

ISHLT guidelines state it is now reasonable to consider patients for heart transplantation up to the age of 70 years since advances in post-transplantation care have shown that survival in the older age groups up to 70 (50–70) is comparable to that of younger recipients [21]. However, being over 70 years is not an absolute contraindication; patients over 70 years of age have also been reported to have acceptable outcomes [22], but careful consideration of associated comorbidities is essential. Thus, carefully selected patients greater than 70 years of age may be considered for transplantation [4]. At some centers, such patients are offered non-standard donor hearts on an "alternate" list, including those with mild pre-existing coronary artery disease, mildly decreased left ventricular ejection fraction, left ventricular hypertrophy, or from donors aged greater than 55 years. The alternate list allows older end-stage patients with otherwise limited life expectancy to undergo heart transplantation with acceptable outcomes and thus gain a survival benefit without denying the scarce resource to younger potential recipients [23].

Obesity

It is known that obese patients (defined as BMI >30 kg/m^2) have a greater risk of poor wound healing, infections, and pulmonary complications after cardiac surgery [14]; previously, it was unclear whether this translated to poor transplant

Table 3.3 Summary of potential contraindications to cardiac transplantation

Potential contraindication	Comments
Age	>70 years old is a relative contraindication depending on associated comorbidities.
Obesity	BMI <35 kg/m^2 is recommended.
Malignancy	Active or metastatic neoplasms are an absolute contraindication.
Pulmonary Hypertension	TPG >15 mmHg, PVR >5 Wood units or pulmonary artery pressure > 60 mmHg with one of the above, or the inability to achieve PVR <2.5 Wood Units with vasodilator or inotropic therapy, are relative contraindications; such patients may benefit from long-term unloading with ventricular assist device followed by reassessment.
Primary Pulmonary Disease	In the presence of known primary lung disease, e.g. emphysema or fibrosis, in combination with impaired pulmonary function tests, defined as FEV_1 <40% of predicted, FVC <50% of normal, DL_{CO} <40%, is a relative contraindication. Recent pulmonary embolism (wthin 6 weeks) is also a contraindication.
Diabetes	Uncontrolled diabetes (HbA_{1C} >7.5% or 58 mmol/mol) or diabetes with significant end-organ damage is a relative contraindication.
Renal dysfunction	If due to diabetes, may be an absolute contraindication; eGFR <30 is a relative contraindication.
Hepatic dysfunction	Bilirubin >2.5 mg/dL if not due to reversible hepatic congestion, transaminases > 2 x normal, are relative contraindications.
Peripheral vascular disease	Severe disease not amenable to revascularization is an absolute contraindication.
Infection	Active infections except LVAD-related infections are contraindications; HIV, Hepatitis B and Hepatitis C are not contraindications if not active and well-controlled by treatment as defined by viral load/CD4 thresholds. Latent TB and Chagas are not contraindications.
Substance use	6 months of abstinence from smoking, alcohol and illicit drugs is required; in critically ill patients, consultation with psychiatry and social work is essential. Marijuana is a controversial topic.
Psychosocial issues	Non-compliance, lack of caregiver/social support, and dementia are absolute contraindications; mental retardation may be a relative contraindication.

Abbreviations: *BMI* body mass index, *TPG* transpulmonary gradient, *PVR* pulmonary vascular resistance, *FEV* forced expiratory volume, *FVC* forced vital capacity, *DL_{CO}* lung diffusion capacity, *HbA_{1C}* glycosylated hemoglobin, mmol millimoles, mol moles, *eGFR* estimated glomerular filtration rate, *mg* milligrams, *dl* deciliters, *HIV* human immunodeficiency virus, *TB* tuberculosis

outcomes, but there is now clear evidence that a BMI of >35 kg/m^2 results in worse outcomes following heart transplant [24–26]. Patients in the 30–35 BMI range have not been convincingly associated with worse outcomes [24–26]. It is currently recommended that patients achieve a body mass index less than 35 kg/m^2 before listing, as patients above the threshold have been demonstrated to have longer waiting times due to the difficult in finding a suitable donor as well as poorer outcomes. Obesity may not always be an absolute contraindication, and given that reduction in BMI to below threshold may be difficult to achieve in patients with poor functional status, some centers will still consider patients with BMI >35 kg/m^2.

Malignancy

Active neoplasms with the exception of non-melanoma skin cancer, are absolute contraindications to heart transplantation, on the basis that the course of the tumor may be accelerated by immunosuppression and the utility of the donor heart would not be maximized [4]. Metastatic disease is also an absolute contraindication. However, patients with pre-existing treatable low-grade neoplasms (such as prostate cancer) or neoplasms in remission may be considered for transplantation. Collaboration with oncology specialists is recommended in order to assess the risk of tumor recurrence [4], especially given that post-transplant immunosuppressive therapy is known

to be associated with malignancy. When tumor recurrence is deemed to be low based on tumor type and there is a good response to therapy and negative metastatic work-up, this patient may be considered for transplant if all other factors are favorable towards listing.

Pulmonary Hypertension

Pre-operative pulmonary hypertension assessed by RHC is a known risk factor for right sided heart failure post-transplant [27], which in turn contributes to overall morbidity and mortality after cardiac transplantation. Relative contraindications to transplantation include: (a) transpulmonary gradient greater than 15 mm Hg and calculated pulmonary vascular resistance greater than 5 Wood units, (b) pulmonary artery systolic pressure greater than 60 mm Hg in conjunction with 1 of the above findings, and (c) the inability to achieve pulmonary vascular resistance less than 2.5 Wood units with vasodilator or inotropic therapy. In these patients, long-term unloading with a ventricular assist device is suggested to achieve an acceptable pulmonary vascular resistance for transplantation, with reassessment by RHC every 3–6 months [4].

Primary Pulmonary Disease

Evaluation of pulmonary function during work-up for cardiac transplantation is important, because of the possibility of co-existent primary intrinsic lung disease (e.g. smoking-related emphysema, COPD). While pulmonary function tests (PFTs) are used to establish baselines, they are also confounded somewhat by the effect of heart failure, as most patients already have some degree of pulmonary dysfunction secondary to heart failure. A number of abnormalities (as compared to the healthy population) are usually noted on PFTs in regular heart failure patients with secondary pulmonary dysfunction, including reduced forced expiratory volume per second (FEV_1), forced vital capacity (FVC) and diffusion capacity (DL_{CO}) [28]. However, the presence of co-existing primary disease usually means that the impairment is even greater, particularly in the DL_{CO}, which is usually over 50% predicted in heart failure patients without primary disease, but is significantly decreased in patients with co-existent primary lung disease [29].

End-stage heart failure with co-existent severe intrinsic lung disease is generally considered to be a contraindication to transplantation, although these patients may be considered at some centers for combined heart-lung transplantation. While there is no clear threshold for what constitutes severe disease, transplantation may be unwise if the FEV_1 is less than 40% of predicted, FVC is less than 50% of normal and DL_{CO} is less than 40% in the presence of proven emphysema or pulmonary fibrosis [30]. However, it is unclear as to what level of impairment on PFTs in the absence of proven intrinsic lung disease would be required to preclude cardiac transplantation.

A recent pulmonary embolism within the last 6 weeks also serves as a contraindication to transplantation because of the fear of recurrent emboli from the original source and the potential for abscess formation at the embolism site. Such patients should be treated for 4–6 weeks with anticoagulants, and then re-evaluated for listing.

Diabetes Mellitus

Uncontrolled diabetes or diabetes with evidence of moderate or severe end-organ damage (i.e. proliferative retinopathy, severe neuropathy, nephropathy with proteinuria, peripheral vascular disease) is considered a relative contraindication to transplantation [4]. Poor glycemic control is defined as a glycosylated hemoglobin (HbA_{1C}) greater than 7.5% or 58 mmol/ml; patients should aim for an HbA_{1C} well below 7.5% to be considered for listing. Collaboration with an endocrinologist in order to achieve this goal is recommended [4].

Renal Dysfunction

Renal function is an important factor in consideration for listing, given the renal insult experi-

enced during transplantation and the toxicities of post-transplant medications, with well-documented negative impact of pre-transplant renal dysfunction on post-transplant outcomes [31]. In view of the prevalence of cardiorenal syndrome, reversibly worsening renal function in this population, renal function should be assessed after optimization of hemodynamic status, sometimes requiring intravenous vasodilator and/or inotropic support to achieve this goal. Patients in whom a low pre-transplant eGFR is primarily reflective of poor cardiac function, may have improvement in renal function post-transplant.

Renal dysfunction due primarily to diabetes is most concerning, because, in this situation, it is usually a sign of advanced diabetes with substantial end-organ damage. Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl), as well as renal ultrasonography and urine evaluation for proteinuria to exclude the presence of intrinsic renal disease. An irreversible eGFR of less than 30/ml/min/1.73m^2 is considered a strong contraindication for cardiac transplantation alone [4]; however, some of these patients may be considered for dual heart-kidney transplantation.

Peripheral Vascular Disease

There is relatively little data studying the impact of cerebrovascular and peripheral vascular disease on heart transplant outcomes. The ISHLT guidelines suggest that clinically severe symptomatic cerebrovascular disease may be considered a contraindication to transplantation [4]. Peripheral vascular disease may be considered a contraindication for transplantation when it is associated with poorly healing ulcers, has required amputation, or its presence limits rehabilitation.

Frailty

With increasing numbers of older patients undergoing cardiac transplantation, the role of frailty in heart failure patients and its impact on subsequent outcomes has been increasingly investigated [4]. Currently, the recommended assessment for frailty consists of a checklist of 5 possible symptoms, including unintentional weight loss of 10 pounds or greater within the last 1 year, muscle loss, fatigue, slow walking speed, and low levels of physical activity [4]. Those meeting the definition of "frail" are likely to meet at least 3 of these criteria; however there are no fixed recommendations with regard to listing frail patients due to the current difficulty at measuring frailty in an objective manner [4].

Infections

Active acute infections, with the exception of LVAD-related infections, are considered contraindications to cardiac transplantation and should be treated with appropriate antibiotic therapy before being reconsidered. Chronic infections such as HIV, Hepatitis B and C are no longer absolute contraindications, given recent advances in the treatment of these conditions.

HIV

Current guidelines suggest that selected HIV-positive patients may be considered for transplantation if they have had no active or prior opportunistic infections for 1 month, and are clinically stable and compliant with combination antiretroviral therapy [4] for at least 3 months. Laboratory thresholds of undetectable HIV RNA viral load, CD4 counts greater than 200 cells/microliter for at least 3 months must also be met. Within the HIV-positive population, the guidelines regarding past neoplasms such as squamous cell carcinoma apply: if in remission and upon consultation with oncology, the patient may still be considered for transplantation. However, candidates with a history of primary CNS lymphoma and visceral Kaposi's sarcoma should not be considered for listing [4]. In general, the management of HIV-positive transplant candidates requires a multidisciplinary approach to cope with the complex drug interactions during the perioperative period.

Hepatitis B

While acute or fulminant Hepatitis B (HBV) infection is an absolute contraindication to transplant, patients with either chronic or previously resolved infections may still be considered for transplantation.

All patients should undergo complete HBV viral evaluation at 3-month intervals while on the waitlist prior to transplantation, in order to distinguish active from chronic and previously resolved infections. This includes Hepatitis B core antigen (HBcAg), Hepatitis B surface antigen (HBsAg), Hepatitis B envelope antigen (HBeAg), and IgG/IgM antibodies against Hepatitis B core antigen (anti-HBc), antibody against Hepatitis B surface antigen (anti-HBs) and antibody against Hepatitis B envelope antigen (anti-HBe). Prior HBV infection is defined by positive anti-HBc or anti-HBs with negative HBsAg, while chronic infection is defined by HBsAg positivity or the presence of an antiviral drug regimen.

It is also recommended that patients with chronic HBV infection undergo liver biopsy in order to exclude severe disease before listing for transplantation. Any clinical, radiologic or biochemical (including alpha-fetoprotein levels) signs of cirrhosis, portal hypertension or hepatocellular carcinoma are contraindications to transplantation [4].

Hepatitis C

The recent advances in treatment for Hepatitis C (HCV) with pegylated interferon-alfa and ribavirin have meant that many centers are now more comfortable transplanting these patients. As such, HCV infection (unless active) is no longer an absolute contraindication to transplant, and transplant may be considered in patients with chronic, resolved or prior inactive HCV infection [4].

HCV antibody testing and HCV ribonucleic acid polymerase chain reaction (RNA PCR) testing should be performed at 3-month intervals after initial screening until the time of transplantation to monitor viral loads and identify the status of infection. Resolved HCV infection is defined by the HCV-antibody positivity, negative HCV RNA PCR and normal synthetic liver function; chronic infection is defined by HCV RNA PCR positivity, and/or the use of HCV antiviral drugs [4]. It is also recommended that patients with chronic HCV infection have their viral genotype determined, due to differing responses to treatment [4].

As with HBV, HCV patients require thorough liver workup, including biopsy; any clinical, radiologic or biochemical (including alpha-fetoprotein levels) signs of cirrhosis, portal hypertension or hepatocellular carcinoma are contraindications to transplantation [4].

Tuberculosis

While active tuberculosis is a contraindication to transplant, latent TB should not be a contraindication to transplantation, as treatment is effective. All transplant candidates should be screened for latent tuberculosis infection (using tuberculin skin test or interferon-gamma release assay), and if positive, undergo sputum or bronchoalveolar lavage testing to exclude active TB. Subsequent treatment should not interfere with the timing of transplantation; treatment can commence prior to and continue after transplantation.

Chagas Disease

All patients born or who spent significant time in Latin America should undergo serologic testing for *Trypanosoma cruzi*, the parasite that leads to Chagas cardiomyopathy. If positive, treatment with benznidazole or nifurtimox should be administered [4]. Heart transplantation is the treatment of choice for these candidates and is therefore not contraindicated in this population, although there is the risk of reactivation of disease. Collaboration with an infectious disease specialist in these cases is recommended [4].

Substance Use

Active cigarette smoking is a relative contraindication to heart transplantation, mainly due to the fact that smoking during the previous 6 months before transplantation is a risk factor for poor outcomes [4]. At most centers, patients must display abstinence from smoking for 6 months, documented by urine cotinine screens, before they

are listed for transplantation. Continuing addiction to alcohol or illicit drugs is an absolute contraindication, because these patients are more likely to demonstrate poor compliance after transplantation. For these patients, at least 6 months of abstinence with participation in counseling programs and contractual commitment to long-term abstinence is required. In the critically ill patient who urgently needs transplantation, this assessment may be difficult to make; consultation with social workers and psychiatrists would be essential in this scenario in order to gauge the patient's potential for abstinence.

Regarding the use of marijuana in transplant candidates, there is scant data, and it is a controversial topic. The policy on marijuana use and listing for transplantation currently varies from center to center [4]. Generally, caution in listing is urged in those patients unable to give up cannabis or those with such heavy use that cognitive ability is impaired [4] or commitment to compliance with a complex medical regimen is of concern.

Other Systemic Diseases

Active diseases that may or may not contribute to the etiology of heart failure but have systemic involvement should be evaluated on a case-by-case basis with regard to potential impact on post-transplant survival and quality of life, preferably in collaboration with an specialist in the relevant field. Evaluation of the potential effects of immunosuppression on the disease itself as well as potential interactions with existing medications should also be considered.

Psychosocial Evaluation

Psychosocial assessment should be performed prior to listing for transplantation. This includes assessments to determine the patient's ability to comprehend and comply with care instructions, as well as the patient's ability to give informed consent. Neurocognitive testing may be considered as part of this process. Poor compliance with drug regimens is a risk factor for graft rejection and mortality. Patients who have demonstrated consistent inability to comply with drug therapy on multiple occasions should not receive transplantation. The ability to demonstrate social support with a dedicated caregiver after transplantation is also extremely important: patients have been denied transplantation because of a lack of social support. Mental retardation and dementia are also relative contraindications to heart transplantation, the former because of concerns about compliance and the latter owing to its progressive nature and overall poor prognosis. For these patients with stable cognitive dysfunction (i.e. congenital or prior stroke) who do qualify for transplant, dedicated social support is key to acceptable outcome.

Psychiatric evaluation should also be incorporated into the overall evaluation process for heart transplant listing. This includes a determination of any active psychiatric disease which may have a negative association with adherence to care regimens both pre and post heart transplantation. Transplantation can be an emotionally and psychologically taxing experience for candidates and recipients, who may contend with significant challenges related to the evaluation, listing and waiting period for a suitable donor, as well as adjustment to life with a transplanted organ.

Financial Considerations

Heart transplantation requires a significant financial commitment. The costs for pre-transplant testing, transplant surgery, hospitalization during recovery, follow-up care, including immunosuppressive medications and monitoring for graft rejection, can be substantive, even with insurance benefits. It is important that patients understand the terms and conditions of their insurance plans and other benefits and have the resources necessary to manage the financial aspects of transplantation without undue stress.

Heart transplantation is a covered expense for most insurance companies, but coverage varies

on a case by case basis. Accordingly, a financial coordinator or counselor should review all coverage benefits as part of the evaluation process. This review should include prescription drug coverage, co-pays and deductibles, and requirements for prior authorizations. This information should be reviewed with patients prior to listing and include an estimate of out-of-pocket costs for the surgery and post-transplant care as well as an overview of fees associated with transplantation. The financial commitment involved is important to consider in the decision to move forward with heart transplantation.

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4 Listing, Donor Allocation and Optimization of the Pre-transplant Patient

Michelle Kittleson, Jon Kobashigawa, and Minh Luu

Clinical Pearls

- Following rigorous medical and psychosocial evaluation, the listing decision is made by a final multi-disciplinary review involving heart failure cardiologists, transplant surgeons, other physicians involved with the patient's care, transplant coordinators, and social workers.
- The heart transplant list is a national computerized list managed by the United Network for Organ Sharing and contains relevant recipient patient variables, including patient name, weight, weight range of acceptable donors, blood group, unacceptable antigens, and immunological virtual crossmatch data.
- The Final Rule mandates that organ allocation within the US is fair and equitable; balancing maximal utility of the donor heart with clinical urgency of the recipient is required.
- Each patient is assigned a status code according to clinical urgency for transplant; there is a 3-tier system consisting of Status 1A (most urgent), Status 1B, and Status 2 (least urgent).
- Organ procurement organizations (OPOs) are responsible for coordination of the donation process within a defined geographic area.
- Patients should be frequently evaluated while on the waitlist to determine if they have developed potential contraindications to transplantation or become too well to merit transplantation; this evaluation will focus on heart failure symptoms, hemodynamic stability (including pulmonary hypertension), exercise capacity and renal function.

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Immediate pre-operative care includes a final immunological and sizing compatibility check, reversing of anticoagulation, and planned immunosuppression and antibiotic administration.

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Introduction

Once evaluation as a potential transplant candidate is complete, there are still many processes that a patient must undergo before receiving a donor heart. All transplant candidates spend time on the waitlist after listing; the current donor heart shortage means that unfortunately, waitlist mortality remains a significant problem [1]. This chapter aims to provide an overview of the listing process, the current US system of heart allocation as well as current controversies and potential changes; finally, optimization of the patient prior to transplant will also be covered.

Listing Process

As described in Chap. 3, patients undergo rigorous medical and psychosocial evaluation for transplant suitability. In most institutions, the culmination of this process is a final review of relevant information at regularly scheduled multi-disciplinary meetings including the transplant and heart failure cardiologists, transplant surgeons, other physicians involved with the patient's care, psychiatrist, social workers, transplant coordinators, pharmacist, and dietician. At these meetings, a final decision regarding suitability for transplant is made, and the patient, if suitable, is listed for transplant.

The heart transplant waiting list is a national, computerized list that is managed and maintained by the United Network of Organ Sharing (UNOS). Listing includes relevant recipient patient variables, including patient name, weight, weight range of acceptable donors, blood group, unacceptable antigens, immunological virtual crossmatch data (see Chap. 6 for more details), and whether a prospective crossmatch will be required (for highly sensitized patients) at the time of donor selection.

Each patient is also assigned an urgency status code according to priority level on the list (see below for more details). Within a status code level, candidates are ordered by time spent on the waiting list. As a donor becomes available, the donor heart is offered to the highest recipient on the list that matches in terms of sizing, weight, blood group and immunological criteria; if declined, the heart is offered to the next candidate on the list.

Allocation Criteria

A Brief History

The National Organ Transplant Act, which was enacted by Congress in 1984, was responsible for the formation of the Organ Procurement and Transplantation Network (OPTN), a unified transplant network that governs organ transplantation in the United States. UNOS, based in Richmond, Virginia, serves as the OPTN under contract with the Health Resources and Services Administration of the US Department of Health and Human Services and is charged with developing allocation policy. Since the inception of the OPTN, allocation policy has undergone several iterations. A formal urgency-based system was first adopted in 1988 by the Department of Health and Human Services (DHHS). Initially, there were only two status levels: Status 1 and Status 2, with the sickest patients in Status 1, and others in Status 2. Further major revisions occurred in 1999, with the introduction of a higher priority level for sicker Status 1 patients, dividing the Status 1 classification into Status 1A and 1B. The Final Rule, issued by the DHHS in 2000, dictates that policy must attempt to balance the difficult combination of equitable organ allocation (including across regions) while prioritizing according to severity of illness. Unfortunately, unlike kidneys, explanted hearts are currently only viable for a maximum of 4–5 h, so allocation needs to be delineated within geographic regions, further affecting distribution equity.

Current System

Organ Procurement Organizations

There are 58 organ procurement organizations (OPOs) in the United States. The primary function of OPOs is to coordinate the donation process when donors become available, along with outreach to increase the number of currently registered organ donors. When a donor heart becomes available, OPOs evaluate the potential donors, check the deceased's state donor registry, discuss donation with family members, contact the OPTN

and run a match list, and arrange for the recovery and transport of donated organs [2]. While OPOs were initially developed in the 1970s from individual transplant programs, modern OPOs are a product of the National Organ Transplant Act of 1984 and generally serve a number of transplant centers within a certain pre-defined geographic area. The OPOs are an important concept in understanding geographic considerations in organ sharing, as will be detailed below.

Urgency-Based Tiers

There are currently 3 urgency-based tiers within the UNOS system for donor heart allocation: Status 1A, Status 1B and Status 2. Generally speaking, the most severely ill meet the criteria for Status 1A, and the most stable patients are in Status 2. There is also a Status 7, for patients who are temporarily unsuitable for heart transplant, often due to acute deterioration. For patients that do not fit neatly into the predefined urgency criteria but are deemed clinically urgent, an exception may be applied for by the transplant physician; these cases are retrospectively reviewed by a Regional Review Board (RRB) who may uphold or reject the decision. A full description of the clinical criteria for heart allocation status is detailed in Table 4.1 [3].

While the principles of a three-tiered status system have stayed constant since 1999, current policy is the result of a 2006 revision, which aimed to improve equitability by involving broader regional sharing of donor hearts to Status 1A and 1B candidates to a neighboring OPO

Table 4.1 UNOS status codes for medical urgency

Status 1A			A patient listed as Status 1A is an admitted inpatient at the listing transplant center hospital or an affiliated VA hospital and has at least one of the following devices or therapies in place:
	(a)		Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:
		(i)	Left and/or right ventricular assist device implanted for 30 days or less (the 30 days do not have to be consecutive);
		(ii)	Total artificial heart (TAH);
		(iii)	Intra-aortic balloon pump (IABP); or
		(iv)	Extra-corporeal membrane oxygenator (ECMO).
	(b)		Mechanical circulatory support for more than 30 days with objective medical evidence of significant device related complications such as thromboembolism, device infection, mechanical failure, and/or life-threatening ventricular arrhythmias. Sensitization is not an acceptable device-related complication; any complications not listed here will be reviewed by the Regional Review Board.
	(c)		Requiring continuous mechanical ventilation.
	(d)		Continuous infusion of a single high-dose intravenous inotrope (e.g. dobutamine ≥ 7.5 μg/kg/min, or milrinone ≥ 0.50 μg/kg/min), or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of left ventricular filling pressures. OPTN-approved definitions for qualifying inotropes and doses are maintained by the OPTN Contractor. Qualification for Status 1A under this criterion is valid for 7 days with a one-time 7-day renewal for each occurrence of a Status 1A listing for the same patient.
	(Exception)		A patient who does not meet the criteria specified in (a), (b), (c) or (d) may be listed as Status 1A if the patient is admitted to the listing transplant center hospital and has documented need for urgent listing, for example a life expectancy without a heart transplant of less than 7 days. A patient listed as Status 1A under this criterion shall be retrospectively reviewed by the applicable UNOS Regional Review Board and the UNOS Thoracic Organ Transplantation Committee.

(continued)

Table 4.1 (continued)

Status 1B			A patient listed as Status 1B has at least one of the following devices or therapies in place:
	(a)		Left and/or right ventricular assist device implanted for more than 30 days; or
	(b)		Continuous infusion of intravenous inotropes.
	(Exception)		A patient who does not meet the criteria specified in (a) or (b) may be listed as Status 1B if the patient has documented need for more urgent listing. A patient listed as Status 1B under this criterion shall be retrospectively reviewed by the applicable UNOS Regional Review Board and the UNOS Thoracic Organ Transplantation Committee.
Status 2			A patient who does not meet the criteria for Status 1A or 1B is listed as Status 2.
Status 7			A patient listed as Status 7 is considered temporarily unsuitable to receive a thoracic organ transplant.

Adapted from Organ Procurement and Transplantation Network: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf

For all adult patients listed as Status 1A, a completed Heart Status 1A Justification Form must be received by the UNOS Organ Center within 24 h of a patient's listing as Status 1A or continuance as Status 1A in accordance with the criteria in (d) or (e). If a completed Heart Status 1A justification form is not received by the UNOS Organ Center within 24 h of a Status 1A listing, the patient will be reassigned to their previous status. Recertification for Status 1A is required every 7 days for Status 1A(d) patients and every 14 days for Status 1A(a)(ii), 1A(a)(iii), 1A(a)(iv), 1A(b), 1A(c), 1A(exception) patients. Patients within a status (1A) are differentiated by time spent at that status, not 1A(a), (b) or (c) etc.

(Zone A) before allocating to local Status 2 candidates; prior to 2006, an organ was offered to local Status 1A, 1B and 2 candidates before being offered to Status 1A/1B candidates in a neighboring region, or zone. This revised policy demonstrated efficacy in decreasing waitlist mortality for Status 1A/1B candidates while maintaining their post-transplant survival rate [4]. Generally, organ preservation considerations (see Chap. 7) limit the geographic distance that a donor organ may be transported to a recipient. The national allocation algorithm by geographic region is detailed in Table 4.2.

Table 4.2 Current (as of 2006) National Heart Allocation Algorithm by Geography: United States

Area	In order of priority
Local	Status 1A candidates
	Status 1B candidates
Zone A	Status 1A candidates
	Status 1B candidates
Local	Status 2 candidates
Zone B	Status 1A candidates
	Status 1B candidates
Zone A	Status 2 candidates
Zone B	Status 2 candidates
Zone C	Status 1A candidates
	Status 1B candidates
	Status 2 candidates
Zone D	Status 1A candidates
	Status 1B candidates
	Status 2 candidates
Zone E	Status 1A candidates
	Status 1B candidates
	Status 2 candidates

Adapted from Organ Procurement and Transplantation Network: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf

Zones are determined by distance from donor hospital to transplant hospital: Zone A ≤ 500 nautical miles, Zone B = 500–1000 nautical miles, Zone C = 1000–1500 nautical miles, Zone D = 1500–2500 nautical miles, Zone E > 2500 nautical miles

Current Controversies in Heart Allocation

As per the Final Rule, ensuring fair and equitable allocation of organs in the US is the charge of the OPTN/UNOS, in order to allow access to organs to the patients most in need and those that would benefit most from transplant. However, these principles can present a difficult conundrum. The concept of fairness is difficult to apply to the waitlist population. Ideally, it would mean that all patients with end-stage heart disease of equiva-

lent severity would have an equal chance of obtaining a transplant, regardless of geographic location, although this is unrealistic to measure. While waiting time has also been proposed as a measure of fairness, the argument is clouded by the expectation by many that sicker patients should wait less time for a transplant (because they are more likely to die). Further complicating the issue is the fact that there is no uniform set of rules when it comes to initiating inotropic and other invasive therapy that might elevate a patient's priority status. Furthermore, the currently proven regional variation in waitlist time [5] certainly undercuts the concept of fairness in heart allocation. The current disparity between various regions in waitlist time impacts both waitlist and post-transplant morbidity and mortality between regions, especially if hearts are only allocated to gravely ill patients as a result.

The concept of utility is also important in heart allocation. Given the donor heart shortage, and the known poor post-transplant outcomes in critically ill patients (e.g. those on extra-corporeal membrane oxygenation support), it could be considered ethically irresponsible to "waste" precious donor hearts by simply transplanting the sickest patients first. Thus, it is generally accepted that donor hearts should only be allocated to candidates in whom there is a reasonable expectation of post-transplant survival and in whom transplantation is the only reasonable option (compared to an LVAD, which might in certain circumstances provide a similar duration and quality of life to transplantation). Defining survival benefit can also be troublesome: is it better to transplant a heart that will produce a 30% to 70% improvement in life expectancy rather than a 70% to 90% improvement?

These concepts, and how they can be best applied, define the current controversies within heart allocation today. While Status 2 candidates on the waiting list now display 1-year survival comparable to heart transplant recipients [6], Status 1A waitlist mortality remains high compared to Status 1B patients [5]. Compounding the problem is the continued shortage of donors in the face of an increasing prevalence of end-stage heart failure [7].

In the years since the 2006 revision, the landscape of the heart transplant waitlist has changed considerably. There have been recent significant advances in the management of heart failure patients, notably in the field of mechanical circulatory support (MCS) as a bridge to transplantation. The advent of the continuous-flow non-pulsatile ventricular assist device (VAD) has resulted in vastly improved survival rates in MCS patients, and has contributed to reduced waitlist mortality [8, 9]. This raises the question as to how these increased numbers of waitlist patients should be prioritized.

Recent research has demonstrated that there are several patient subgroups with higher waitlist mortality, and thus are disadvantaged by the current system. These subgroups involve those with restrictive cardiac physiology and preserved systolic function such as hypertrophic cardiomyopathy and amyloid patients [4, 10]. These patients generally do not benefit from LVAD therapy, and generally do not meet Status 1A criteria despite sometimes having significant diastolic dysfunction. Patients with high levels of anti-HLA circulating antibodies (sensitized patients) may also be at a disadvantage [11], as a result of a smaller compatible donor pool, resulting in increased waitlist time. Patients with a life threatening arrhythmia [12] and congenital heart disease [13] have also been demonstrated to be disadvantaged, due to difficulties qualifying for Status 1A.

The Future of Heart Allocation: A Further-Tiered System?

Due to the factors mentioned above, the OPTN/UNOS Thoracic Committee was commissioned by the OPTN/UNOS Board to assess opportunities for broader, more equitable sharing of donor hearts [1]. The ensuing result was a vote to explore a further-tiered system, which is currently undergoing evaluation. While a scoring system for the purposes of heart allocation has been proposed in the past, it is felt that there is currently not enough data to create a reliable tool for this purpose. Hence, part of the potential

proposals also includes prospective data collection that will identify the variables necessary to eventually develop a heart allocation score in the future. It is worth noting that other organ priority systems, such as kidney and lung, use an allocation score.

Optimization of the Pre-transplant Patient

Medical Surveillance on the Waitlist

Medical treatment of heart failure and the evaluation criteria for heart transplant candidacy have already been covered in the first two chapters. However, even once listed, patients should be frequently clinically reevaluated and managed accordingly, taking into account heart failure symptoms, hemodynamic stability (including blood pressure and EF by echocardiography), and exercise capacity. Serum electrolytes and renal function should also be reviewed. The general aim is to maintain or even improve the level of function at listing until transplantation, essentially to make sure each patient remains an optimal candidate and is appropriately risk-stratified. UNOS requires formal reevaluation on a yearly basis to reassess each patient's ongoing candidacy for transplant. A significant number of patients initially listed for transplantation may have clinical improvement, no longer requiring active transplant listing; In these cases, the patient should still undergo exercise testing, clinical evaluation and hemodynamic assessment every few months. A detailed list of criteria for inactivation of heart transplant candidates due to clinical improvement is given in Table 4.3. Alternatively, some patients may have further clinical deterioration, requiring the difficult task of delisting them. Ideally, palliative care teams should be involved with all patients evaluated and undergoing transplant to assist with the complex issues involved.

UNOS outcomes data suggest that 5.9% of adult patients listed for heart transplant die within 90 days, and that 10.4% die within 1 year of listing without undergoing transplantation [4]. Thus, vigilance for indications of worsening heart failure or complications related to heart failure is crucial in both the inpatient and outpatient waitlist candidates. In the outpatient waitlist candidate, such a scenario should necessitate immediate admission for evaluation and appropriate treatment. Likewise, inpatients should be monitored daily for the above. Ultimately, the aim is to prevent conditions which may subsequently negatively affect perioperative outcome, as well as death on the waitlist. A full list of indications for readmission is summarized in Table 4.4.

Risk factors noted to predispose to early pre-transplant waiting list mortality in the first 90 days post-listing include patients aged 70 or greater, Status 1A patients, Status 1B patients, those on temporary MCS, those on mechanical ventilation, and those with renal failure (defined as GFR <30 ml/min or requiring hemodialysis) [4]. These patients should therefore be monitored especially closely.

Table 4.3 Guidelines for consideration of inactivation of heart transplant waitlist candidates due to clinical improvement

Clinical criteria	Exercise criteria (assuming initial peak oxygen consumption of <14 ml/kg/min)
Stable fluid balance without orthopnea, elevated jugular venous pressures or other evidence of congestion Stable blood pressure with systolic ≥ 80 mmHg Stable serum sodium (≥133 mEq/L) Stable renal function (BUN <50 mg/dl, Creatinine <2 mg/dl) Absence of symptomatic ventricular arrhythmia Absence of frequent angina Absence of severe drug side effects Stable or improving activity level without dyspnea during self-care or 1-block exertion. Increasing ejection fraction by echocardiogram	Improvement in peak oxygen consumption of ≥2 mg/kg/min Peak oxygen consumption of ≥14 ml/kg/min

Reused with permission from Kirklin et al. [16]

Table 4.4 General indications for admission of waitlist candidates

Unstable angina
Syncope
Frequent implantable cardioverter-defibrillator discharges
Suspected embolic event
Refractory congestive symptoms despite compliance with increased diuretics, which may:
Render patients bedridden
Cause increased hepatic congestion
Worsen pre-existing pulmonary hypertension
Persistently low blood pressure <80 mmHg
Pulse pressure <12 mm Hg with cool extremities
Chronic renal failure, creatinine >2 mg/dl
Clinical evidence of severe or progressive low cardiac output
Clinical or catheterization evidence of severe pulmonary hypertension (systolic PA pressure >60 mmHg)

Reused with permission from Kirklin et al. [16]

Should a patient deteriorate and consequently display a relative contraindication to transplantation, the patient is placed on the inactive list (Status 7) and medical or device therapy is administered as appropriate. Once the patient has improved, the patient is reevaluated for transplanted suitability, and is able to return to the transplant list without penalty (i.e. the time previously spent on the waitlist is counted) (See Table 4.4).

Immunological Optimization

While this topic will only be touched upon briefly here (it is covered in greater detail in Chap. 6), a notable proportion of waitlist patients display elevated levels of circulating anti-HLA antibodies as well as donor-specific anti-HLA antibodies. These anti-HLA antibodies may develop from events such as previous pregnancy, prior blood transfusions or implantation of a mechanical circulatory support device. Patients with high levels of circulating anti-HLA antibodies are considered "sensitized" and as a cohort demonstrate poorer outcomes post-transplant [14], including increased rejection (acute and chronic) and increased mortality. Furthermore, the chances of an immunologically compatible donor are much lower. Therefore, any events such as blood transfusions need to be documented and preformed antibody levels rechecked, with leukocyte filtered blood administered whenever possible to reduce the risk of further sensitization.

Desensitization therapy is an option for end-stage heart failure waitlist patients who are highly sensitized and would otherwise have a low chance of finding an acceptable donor organ [15]. Desensitization may be carried out by a number of methods, including the administration of agents such as intravenous immunoglobulin, rituximab and bortezomib; it may also be carried out by procedures such as plasmapheresis [15]. Desensitization is not always successful; however, in those patients whose circulating antibodies reduce in type and number, there is an increased chance of finding an immunologically acceptable donor.

In highly sensitized patients for whom a donor becomes available, a prospective crossmatch will also be performed shortly before transplant. The purpose is to definitively identify donor hearts which would be at risk of exposure to the specific circulating cytotoxic antibodies of the potential recipient. The need to physically transport the recipient's blood to the donor location reflects a geographical limitation of transplant in these highly sensitized patients. In recent years, the virtual crossmatch has largely eliminated this problem [11]; however, for the most highly sensitized patients, many centers prefer a prospective crossmatch to be certain.

Other Considerations for the Wait-Listed Patient

Patients on anticoagulation with one of the novel oral anticoagulants or on antiplatelet agents such as clopidogrel or plasugrel need to have them changed to more easily reversible options, since there may be little time from notification to the surgical procedure. Patients with histories of recent cigarette or other drug use should have periodic toxicology screening while waiting. All patients should be monitored for compliance with visits and the medical regimen, and

instructed to notify the team of any change in their medical condition or residence, to reinforce the importance of these factors post-transplant.

Pre-operative Preparation of the Patient for Transplantation

Once a donor heart is made available, the patient is typically contacted by the on-call transplant coordinator and if an outpatient, promptly admitted. The patient is told to refrain from eating or drinking. A brief re-evaluation of the potential recipient is performed to ensure that they have not developed any contraindications that may compromise the goals of early management post-transplant. The pre-transplant evaluation summaries should be reviewed for any additional comorbidities or conditions which may require specialized care during and after the transplant operation. For example, patients with pre-existing arrhythmias who are on amiodarone must be carefully watched, as this medication can slow the donor heart rate post-transplantation. A final compatibility check is run, including checking whether the blood type matches appropriately and whether the donor is of an appropriate size for the patient's height and weight.

Pre-operative management includes special considerations for those with a history of pulmonary hypertension, as well as those with a predilection for increased bleeding. In those with pre-existing pulmonary hypertension, placement of a pulmonary artery catheter and measurement of pulmonary artery pressure is recommended prior to transplantation. If necessary, pharmacological adjustment through selective vasodilation to reduce pulmonary artery pressure should be performed, in order to prevent acute right heart failure of the donor heart. Information based on this may also be used to make a final decision regarding whether to accept the donor heart, especially where the donor heart is undersized. For those recipients at risk of increased intra-operative bleeding (usually due to previous sternotomy, MCS device, long-term right heart failure, or chronic warfarin therapy), vitamin K (10 mg subcutaneously) and fresh frozen plasma may be administered prophylactically prior to the operation.

Standard pre-operative measures also include immunosuppression, such as administration of pre-operative corticosteroids at some centers (500 mg IV 4 h before transplantation; 250 mg IV 1 h before), as they are thought to help reduce the damaging inflammatory processes that are the result of cardiopulmonary bypass. At some centers, pre-operative administration of anti-proliferatives and calcineurin inhibitors occurs, whereas other centers prefer to initiate these agents peri-operatively or shortly after transplant. Pre-operative broad-spectrum antibiotic prophylaxis is also administered to protect against gram-positive and gram-negative organisms. For more details on peri-operative immunosuppressive and antibiotic regimens, see Chaps. 9, 10 and 11.

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Overview of Transplantation Immunobiology

5

Xiaohai Zhang, Nancy Reinsmoen, and Jon Kobashigawa

Clinical Pearls

- Both the innate and adaptive immune systems normally collaborate to mount a response to external pathogens, but the same mechanisms also play a role in allograft rejection and injury.
- Mismatched HLA alloantigens on the donor graft are targeted by the recipient's immune system.
- Donor graft alloantigens are presented to the recipient's T-cells through the indirect, direct or semi-direct pathway, ultimately leading to CD8+ T-cell-mediated cytotoxic response; various effector T-cell subsets are implicated in the cellular rejection process.
- Alloantibodies to the donor graft, originating from plasma cells, damage the graft through complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity through natural killer cell recruitment, and endothelial activation.
- Antibody production can be stimulated by sensitizing events, such as pregnancy, transfusion and previous transplant.
- CD20 is expressed on surfaces of B-cells and can be targeted by anti-CD20 monoclonal antibodies such as rituximab to reduce alloantibody production and thus subsequent antibody-mediated rejection. Bortezomib is a proteasome inhibitor used to inhibit antibody production.
- Tolerance may theoretically be induced by induction of chimerism, depletion of specific lymphoid tissues, costimulatory blockade and regulation through B-cell mechanisms.

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Innate Versus Adaptive Immunity

The immune system protects us from infection by recognizing pathogens, and destroying or containing them. The immune system can be categorized into two branches: the innate immune system and adaptive immune system. The innate immune system and adaptive immune system are not completely independent systems.

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Instead, there is crosstalk at multiple levels and collaboration with each other to mount immune response to pathogens. The processes that initiate transplant-directed alloimmune responses are mediated by components unrelated to organ transplantation but rather are developed from a system that maintains the integrity against various pathogens. Exposure to pathogens such as viruses, bacteria, fungi and protozoa first countered by the innate immune system composed of inflammatory cells, usually granulocytes, which include neutrophils, eosinophils, basophils, and mast cells. A second important cellular component of the innate immune response includes the monocytes, macrophages, and dendritic cells, which can take up and process exogenous materials. Also included in the cellular innate immune response are the γδ and natural killer (NK) cells, which can kill virally infected cells without prior sensitization [1]. These same cells survey the periphery including transplanted organs with usually a slower response than that observed in innate immune responses against pathogens.

The cellular components of the adaptive immune response include T and B cells which express unique and polymorphic antigen receptors, T cell receptor (TCR) and B cell receptor (BCR). The process that generates the antigen-detecting region of these receptors provides the ability to recognize and potentiate a response to specific antigens which may include pathogens but also may be self-antigens. During this process, the T and B cell undergo a selective maturation process which removes strongly binding, autoreactive cells. When an organ transplant occurs between genetically disparate individuals, there is a T cell mediated adaptive immune response which must be addressed with immune modulation. The cells of the innate immune component may also play a role in presenting the alloantigen to these effector T cells. These activated T cells can in turn help B cells produce alloantibodies as part of the humoral response thereby damaging the graft. Further details of these cells that participate in the transplant immune response are included later in this chapter.

Overview and Polymorphism of HLA

The difference between proteins expressed by the recipient and donor is actively surveyed by the recipient's immune system. The most polymorphic proteins in humans are the human leukocyte antigens (HLA). The number of HLA alleles identified increases constantly as more people are HLA typed and new technology is used. Nearly 14,000 HLA alleles have been identified as of the time of writing. The high degree of polymorphism is necessary for HLA antigens to present various peptides to the immune system; however, this degree of polymorphism creates a substantial barrier to transplant between individuals. It is very common that the donor and recipient do not share exactly the same HLA molecules. The mismatched HLA molecules are often targeted by the recipient's immune system. The HLA gene cluster, localized on chromosome 6, includes genes encoding HLA class I (HLA-A, HLA-B, and HLA-C) and HLA class II (HLA-DR, HLA-DQ and HLA-DP). Non-classic genes Major Histocompatibility Complex Class I Chain-Related Gene A (MICA) and Major Histocompatibility Complex Class I Chain-Related Gene B (MICB) are also located in this region (Fig. 5.1).

HLA class I polypeptides (HLA-A, HLA-B, or HLA-C) function as a dimer when noncovalently bound to a non-polymorphic polypeptide called β2 microglobulin. This dimer presents peptides to the T cell receptor present on T cells. The HLA class I polypeptide is organized as α1, α2, α3, transmembrane and cytoplasmic domains. The α1 and α2 domains of the HLA class I polypeptide are highly polymorphic and form the antigen recognition site. HLA class II polypeptide (HLA-DR, DQ or DP) also forms a dimer: α chain and β chain. The HLA class II α chain is encoded by genes HLA-DRA1, DQA1 or DPA1. The β chain is encoded by genes HLA-DRB1, DQB1 or DPB1. Both α chain and β chain can be polymorphic for HLA-DQ and DP. For HLA-DR, only HLA-DRB1 is polymorphic. The HLA class II polypeptide is organized as α1 and α2, transmembrane, and cytoplasmic domains. The antigen recognition site of HLA class II peptides is contributed by α1 domains of

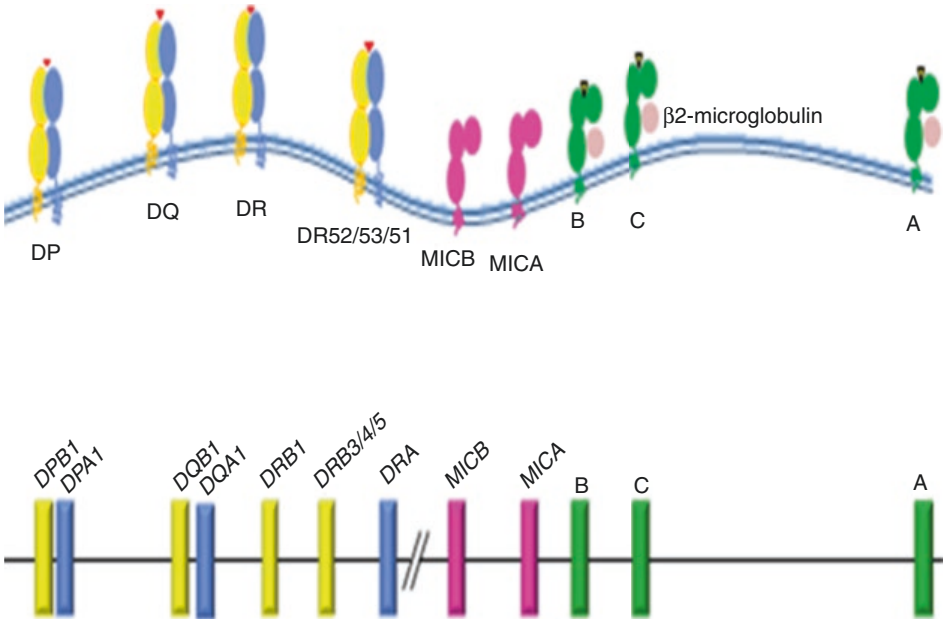

Fig. 5.1 The HLA gene cluster is localized on chromosome 6. HLA class I genes (HLA-A, B, C) encode HLA class I heavy chain which pairs with non-polymorphic protein β2-microglobulin on the cell membrane. HLA class II (HLA-DP, DQ and DR) are also dimers comprised of α chains and β chains. Some individuals may also express antigen DR52, DR53 and DR51, of which the β chain is encoded by gene DRB3, DRB4 and DRB5, respectively. MICA and MICB genes are also localized in this region

both α chains and β chains. HLA class I molecules predominantly present endogenous peptides derived from defective folded proteins or virus proteins synthesized inside the cell, while HLA class II molecules present peptides derived from protein/pathogens in extracellular compartments to T cells. The non-classic HLA gene, including MICA, is also localized in this region. MICA can be stress induced and bind to and activate NK cells against stressed or damaged cells. MICA has limited polymorphism and is not associated with β2 microglobulin. Although MICA cannot present peptides to the immune system, it can be recognized by the recipient's adaptive immune system. The presence of MICA antibodies has been shown to be associated with transplant coronary artery disease in heart transplantation.

These HLA genes are localized in a 4 Megabase region in chromosome 6 and tend to transfer together from parents to their offspring. Each individual carries one copy of genes at each HLA locus on each of two chromosome 6, and these two chromosomes segregate during meiosis. Therefore, there is ¼ chance that two siblings share the same HLA gene content. It isn't always easy to find a matched donor carrying compatible HLA alleles, especially for highly sensitized patients. The frequency of HLA alleles varies among different ethnic groups. For example, HLA-B46 has a high frequency in East Asian populations, such as in Thai populations where the frequency is as high as 14%, while it may hardly be detected in other ethnic groups [2]. Because some HLA alleles exist at much higher frequencies in certain populations, it would likely be easier to find a donor carrying these alleles in that particular population than others.

Alloantigen Presentation/Cell Mediated Rejection

In order for the recipient's adaptive immune system to recognize mismatched alloantigens, they need to be presented as peptides by the HLA antigens on the recipient's antigen presenting cells which are recognized by the recipient's CD4+ T helper cells. Activation of the recipient's CD4+ T helper cells is prerequisite to initiate CD8+ T cell mediated cytotoxic response, and B cell mediated humoral response against alloantigens. Alloantigens can be presented to the recipient's T cells through three pathways: the indirect, direct,

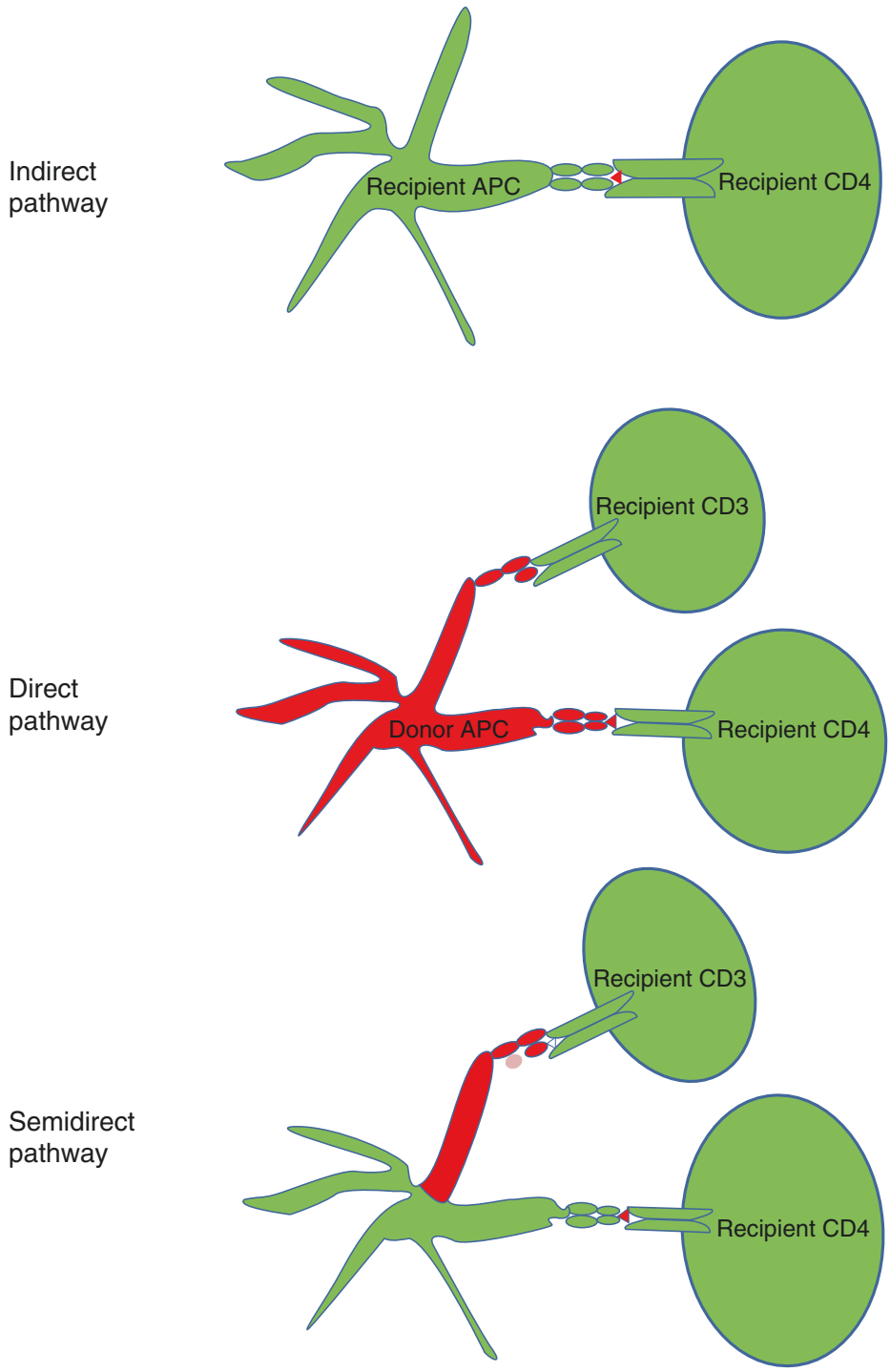

Fig. 5.2 In the indirect pathway, recipient antigen presenting cells (APC) present donor-derived peptides on the context of recipient HLA class II to recipient CD4+ T helper cells. This pathway is important for initiating antibody mediated rejection. In the direct pathway, donor derived APC present allopeptides restricted on donor HLA class II to recipient CD4+ T helper cells, and allopeptides restricted on donor HLA class I recipient CD8+ cytotoxicity cells. This pathway is usually responsible for acute cellular mediated immune responses to intact donor HLA class I antigens. In the semidirect pathway, recipient APC capture membrane fragments bearing intact HLA class I antigens from donor cells, and present intact class I antigens to recipient CD8+ T cells. Allopeptide restricted on recipient HLA class II are also presented to recipient CD4+ T helper cells by the same APC

and semi-direct pathways (Fig. 5.2). In the indirect pathway, alloantigens are presented in a similar way as antigens derived from pathogens. The recipient's antigen presenting cells capture alloantigens which are shed from the graft, and present these antigens on the context of the recipient HLA class II to the recipient CD4+ T helper cells. Alloantigens targeted by de novo donor specific antibody usually are mainly presented through the indirect pathway [3]. Because in the indirect pathway, alloantigens have to be captured and processed first by the recipient's antigen presenting cells before being presented to CD4+ T helper cells, it takes longer, compared to the direct pathway of recognition to alloantigens. The recipient immune system usually takes more than 2 weeks to develop do novo donor specific antibodies.

Compared to the indirect pathway, alloantigens are presented directly by donor-derived antigen presenting cells to the recipient's CD4+ T helper cells in the direct pathway. These passenger antigen presenting cells in the allograft are

transplanted into the recipient along with the graft. These passenger cells can interact with the recipient's CD4+ T helper cells directly and present alloantigens restricted by the donor HLA molecules to CD4+ T helper cells to initiate adaptive immune response. In this pathway, antigen presenting cells don't need to process new antigens, and immune response is activated relatively fast. This pathway usually is responsible for the acute cellular mediated immune response [4].

Immune response to alloantigens can also be initiated by the third pathway, the semi-direct pathway. In this pathway, the recipient antigen presenting cells, mainly dendritic cells obtain donor HLA: peptide complexes by capturing the membrane from the donor passenger antigen presenting cells or endothelial cells. These recipient dendritic cells then can present HLA alloantigens to both CD8+ cytotoxic T cells as an intact protein and to CD4+ T helper cells as processed allopeptide simultaneously. This semi-direct pathway explains how CD8+ cytotoxic T cells can target HLA alloantigens expressed on the graft. This semi-direct pathway may be critical for the CD8+ T cell mediated cytotoxic response for mismatched HLA antigens between the donor and recipient [5].

T Cell Mediated Response: Effector T Cells and the Memory Response

Murine models have shown that rejection of different organs may depend on certain T cell subsets. Studies in heart have shown that rejection can occur in the absence of CD8+ T cells but not in the absence of CD4+ T cells, suggesting that class II expression on the graft is sufficient to mediate rejection [6]. Distinct effector phenotypes, Th1, Th2, and Th17 have been described; however, cytokines are pleotropic and their role in the clinical rejection process remains somewhat controversial. Naïve T cells may be polarized into distinct helper T cell subsets based on cytokine signatures, the signature signal transducer and activator of transcription (STAT) molecules which sense the extracellular cytokine environment. Briefly, the Th1 cells secrete IL-2, IFN-γ, and TNF; Th2 cells secrete IL-4, IL-5, IL-10 and IL-13; Th17 cells secrete IL-17. Subsets of T cells, which can be either CD4+ or CD8+, can inhibit the immune response of other T cells and are termed regulatory T cells (Tregs). Although these various Th subsets were thought to be stable, more recent reports indicate these subsets may be flexible in their T cell phenotypes [7].

Naïve T cells proliferate through the autocrine growth factor IL-2 and can differentiate into various types based their encounters with different cytokines. The CD4+ cells are often termed T helper cells and CD8+ cells are frequently termed cytotoxic cells. However, cells of both phenotypes can be helper or cytotoxic based on their MHC antigen specificity toward class I versus class II. That is, CD4+ cells can be helper or cytotoxic. When exposed to IL-12, activated T cells can differentiate into a predominantly IFN-γ producing phenotype and are designated in the Th1 category. Activated T cells that are exposed to IL-4 predominantly differentiate into the Th2 cells that produce IL-4, IL-5, IL-10 and IL-13. Upon exposure to TGF-β and IL-6, they can differentiation into Th17 cells producing IL-17 (A and F) and IL-22 [8, 9]. The Th1 and Th17 cells have been associated with autoimmunity while the Th2 cells are often associated with asthma and allergies. The Th1 IFN-γ producing cells are often associated with acute allograft rejection along with the presence of IL-17. The Th2 cells have also been associated with the rejection process.

After an initial antigenic challenge, a second stimulation by the same foreign antigen triggers a memory response characterized by a faster kinetics of lymphocyte activation for both the T and B cell compartments. After an initial response where the antigen is cleared, the number of effector cells peaks at about 1 week, after which about 90% of the effector cells die. The remaining population is long-lived memory T cells with distinct phenotype and function. These memory T cells have a lower activation threshold allowing them to respond quickly upon restimulation. These effector memory T cells express homing receptors that allow for migration to non-lymphoid sites of inflammation [1].

B cells go through an affinity maturation process which depends on the interactions with the APC and the activated T cells environment. Some of the B cells differentiate into antibody secreting

plasma cells while others become memory B cells which persist for long periods of time. The secondary response for the memory B cells is also shorter (3–5 days) compared to the primary response (7–10 days). The antibodies produced by a B cell memory response have higher affinity and are usually characterized by subgroups such as IgG, IgA and IgE versus IgM. Important to transplantation is the varied effectiveness of specific immunosuppressive drugs for removing antibody producing cells depending on their characteristics.

Antibody Production and Biology

Despite the improvement of immune suppressing regimens, antibody mediated rejection remains a major obstacle to long term graft survival. With the help from CD4+ T helper cells, naïve B cells with an alloantigen bound on their B-cell antigen receptor are primed and differentiate to plasma cells secreting antibodies against the antigen that is bound to the B cell antigen receptor. Naïve B cells can also differentiate to memory B cells which can rapidly differentiate into plasma cells upon recurrent exposure to the initial antigens. Plasma cells can survive in niches mainly in bone marrow for long periods of time. Both memory B cells and long lived plasma cells provide long-term humoral immunity [10].

CD20 protein is widely expressed on the surface of B cells during B-cell ontogeny, and is necessary for B-cell activation [11]. Anti-CD20 antibodies, Rituximab or Obinutuzumab, are used to treat lymphoma and autoimmune disorders by depleting B cells through antibody dependent cell cytotoxicity. CD20 antibodies are also used for desensitization or antibody mediated rejection for solid organ transplant. However, the expression of CD20 is lost after the B cells differentiate into plasma cells. Therefore CD20 antibody therapy would be ineffective to remove antibodies after B cells differentiate to antibody-secreting plasma cells. This may be the reason why CD20 antibody treatments are not always effective to desensitize or treat antibody-mediated rejection. Another drug used for desensitization or treatment of antibody mediated rejection is Bortezomib. Bortezomib is a proteasome inhibitor originally used to treat myeloma. Bortezomib is used to inhibit antibody production on the premise that plasma cells which synthesize a large amount of antibodies, and need to degrade incorrectly folded proteins, might be more sensitive to the inhibition of proteasome.

Antibody production can be stimulated by sensitizing events, such as pregnancy, transfusion and previous transplant. Alloantibodies damage the graft mainly through three ways. The first is complement dependent cytotoxicity. Upon binding to antigens on cells of the graft, alloantibodies recruit C1q, the first complement component activated in the classic complement pathway, through the Fc fraction of IgG [12]. There are 4 isotypes of IgG antibodies: IgG1, IgG2, IgG3 and IgG4. The affinity of these IgG to C1q is IgG3> IgG1> IgG2> IgG4. IgG3 and IgG1 alloantibodies may be more potent than IgG2 and IgG4 to activate the classic complement pathway. The presence of donor specific IgG3 antibodies against HLA is associated with high risk of antibody mediated rejection in renal transplant [13]. C1q binding to alloantibodies sequentially activates complement components C4, C3 and then C5, which in turn can lead to the formation of membrane attack complex. Membrane complex composes a pore in the cell membrane and causes cell death. Unintended activation of complement is detrimental to the tissue and organ; the activation of complement is tightly controlled by many negative regulators [14]. Even if alloantibodies are produced, complement may not necessarily be activated on the graft due to these negative regulations.

C4d, a split product of complement C4, produced after the activation of the classic complement pathway, is covalently linked to the cell membrane. Its half-life is 12–31 days in vivo [15]. These characteristics make positive C4d staining on the biopsy a useful marker for diagnosis of antibody mediated rejection in kidney and heart transplant. In the classic complement activation pathway, activation of complement C1 stimulates complement C4 to transform into active form C4b through proteolytic cleavage. The activity of C4b is negatively regulated by complement 4-bindig protein (C4BP). C4BP prevent C4b from activating the downstream

complement cascade by degrading C4b through proteolytic cleavage. One of the cleavage products is C4d [14]. Thus C4d deposition on the graft is dependent on both the activation of complement C1 and the presence of negative regulator of C4BP. When C4BP negative regulator is missing, or its activity is low, C4d will not be generated and detected even if the complement is fully activated, which might be one of the reasons why a biopsy diagnosed with antibody mediated rejection is stained C4d negative.

Activation of the complement pathway can also produce anaphylatoxin C3a and C5a which are cleavage products of the complement components C3 and C5. Due to the expression of multiple complement negative regulators on the cell surface of the graft, formation of membrane attack complexes and cell killing do not always happen in antibody mediated rejection. Formation of C3a and C5a may be the major culprit for graft damage caused by complement activation. C5a is a pivotal chemoattractant for macrophages and neutrophils. Receptors for C3a and C5a are expressed on granulocytes and monocytes. Signaling activated by C3a and C5a triggers histamine release, oxidative burst and chemotaxis. Stimulation of C5a signaling can also un-regulate the expression of activating FcγR receptor on macrophages, which further enhances antibody dependent cell cytotoxicity. Eculizumab, a humanized monoclonal antibody against complement C5, is used to prevent/treat acute antibody mediated rejection in solid organ transplant. Eculizumab binds to complement C5, and can inhibit C5a production in addition to the blockade of membrane attack complex formation.

Antibodies against the allograft can also cause damage through antibody dependent cell cytotoxicity by recruitment of natural killer (NK) cells. NK cell transcripts have been found enriched in kidney biopsies with antibody mediated rejection [16]. Antibodies engage the innate immune system through the Fc fragment by interacting with the Fc receptor FcγRIIIa and/or FcγRIIc on NK cells. The signals activated through Fc receptors by antibodies cause NK cells to release cytokines, such as IFN-γ, which up-regulate HLA expression on the cell surface. Increased expression of allo-HLA molecules on the graft enhance the potential for cytotoxic T cell recognition of alloantigen HLA antigens and thus promotes the induction of cell-mediated immunity to recruit adaptive immune cells. NK cells can also recognize antibody-coated cells through the Fc receptor and induce rapid apoptosis in target cells via the release of granzyme [17]. The requirement of NK cells in transplant vasculopathy has been demonstrated in a mouse model with cardiac allografts in which depletion of NK cells abolished donor MHC class I induced transplant vasculopathy [18].

Endothelial Cell Activation by Antibodies

Transplant vasculopathy is characterized by concentric hyperplasia with intimal proliferation of the vessels of the allograft. Endothelial cells lining the blood vessels of allograft are directly targeted by the recipient immune system. HLA antibodies can stimulate proliferation and survival of endothelial cells and smooth muscle cells [19]. HLA molecules do not have intrinsic kinase activity. Instead, HLA class I molecules, upon ligation with antibodies, partner with integrin β4 to transduce intracellular signals [20]. Integrin β4 is a cell adhesion protein which regulates cell adhesion, migration, survival and proliferation. Depletion of integrin β4 dampens proliferation of endothelial cells stimulated by HLA class I antibodies. HLA class II molecules can also transduce signal into the cell, but the protein that partners with HLA class II is not known yet. The mammalian target of rapamycin (mTOR) is at the center of the HLA signaling pathway. Ligation of HLA molecules with antibodies activates mTOR signaling through the SRC/FAK-PI3K-AKT pathway in endothelial cells. mTOR exists in two structurally and functionally distinct protein complexes: mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). TORC1 is pivotal in the regulation of mRNA translation, cell growth, and proliferation, while TORC2 stimulates actin cytoskeletal rearrangement and cell survival [21, 22].

The degree of HLA molecule crosslinking with antibodies may determine which mTOR complex is preferentially activated. Ligation of HLA class I and class II molecules with high titers of antibodies activates TORC1 which promotes endothelial cell proliferation. Activation of TORC1 stimulates phosphorylation of p70 ribosomal protein S6 kinase (S6 K), which then phosphorylates S6 ribosomal protein (S6RP) and 4E–BP1 proteins. S6RP is essential for protein synthesis, and cell growth and proliferation. Using a murine heart allograft model, increased phosphorylation of these proteins was observed in the endothelium after MHC-I (HLA class I in mouse) antibody injection. It is suggested that staining for phosphorylated S6 K and phosphorylated S6RP can be useful markers for the diagnosis of antibody mediated rejection since expression of phosphorylated S6 K and phosphorylated S6RP is significantly increased in capillary endothelial cells in endomyocardial biopsies with evidence of pathological antibody mediated rejection. On the other hand, ligation of HLA class I with low titers of antibodies predominantly stimulates the TORC2 pathway with upregulation of cell survival proteins on the endothelium. Pretreatment with HLA class I antibodies at lower concentration protects the endothelium from complement-mediated and cytotoxic T cell–mediated injury in a mouse model. However, extended exposure of the endothelium to HLA class I antibodies even with low titers may ultimately cause graft injury via activation of complement and recruitment of NK cells or monocytes. Rapamycin, used as an immunosuppressive agent for solid organ transplant, can block mTOR signaling. TORC1 is highly sensitive to rapamycin, whereas TORC2 is relatively insensitive. However, prolonged treatment or high concentration of rapamycin can inhibit both TORC1 and TORC2 signaling.

The core changes of endothelial cell activation include upregulation of leukocyte adhesion molecules and cytokine release. It is suggested that alloantibodies can contribute to the pathogenesis of antibody mediated rejection by activating human endothelial cell exocytosis and leukocyte trafficking. Treatment of endothelial cells with alloantibody promotes leukocyte recruitment [19]. Antibodies eluted from acutely rejected allografts can upregulate VCAM-1 and ICAM-1 expression on the surface of endothelial cells, which leads to an increase in leukocyte adhesion. Treatment of endothelial cells with HLA class I antibodies can also stimulate the release of P-selectin and von Willebrand Factor (vWF) by triggering calcium-mediated exocytosis. The release of P-selectin in turn enhances platelet and leukocyte adherence. Fc fragment of IgG is not required for alloantibodies to stimulate exocytosis because only the bivalent F (‘ab’) 2 of HLA class I antibodies is effective in trigging exocytosis.

Tolerance

The seminal work of Billingham, Brent, and Medawar in 1953 established the groundwork for, and discipline of transplant immunology and neonatal tolerance [23]. Since then, tolerance or operational tolerance has been a goal of transplantation. There have been rare reports of allograft recipients, both kidney and liver, who have achieved successful immunosuppression withdrawal [24]. However, the ability to predict the feasibility, modes, or signatures of tolerance has been elusive. Tolerance appears to be achievable in experimental animal models but is rarely achieved in clinical transplantation. There are several mechanistic theories postulated for the development of tolerance including chimerism, depletion of specific lymphoid tissues, costimulatory blockade, and regulation through B cell mechanisms.

Chimerism, as defined by engraftment, can be achieved when all the bone marrow-derived cells of a recipient are replaced by donor cells, such as in bone marrow transplantation. In solid organ transplantation this approach is difficult since the donor needs to be HLA genetically identical or closely compatible with the recipient. With fully myeloablative condition requirements, there is a significant risk of infections and graft versus host disease-related morbidity. The feasibility of identifying a compatible donor for the marrow and concomitant solid organ transplant is slim.

Further, it is important to recognize that all transplant recipients are chimeric to a certain degree. Organs such as the liver, intestine, and lung contain massive amounts of donor cells capable of generating chimerism [25]. The increased degree of chimerism has been shown to be associated with lower incidences of chronic rejection. This type of phenomenon is not uncommon and has been shown with the detection of cells from the offspring in women who have given birth decades before. This phenomenon has given rise to the theory of improved graft outcome when non-inherited paternal antigens are expressed by the graft [26]. The use of non-myeloablative conditioning using hematopoietic stem cells to establish complete chimerism has been reported to induce tolerance in renal transplant recipients [27]. These studies enlighten us to the understanding of the mechanisms necessary to achieve tolerance and the need for addressing a combination of multiple mechanisms to achieve tolerance.

The approach of depletion has been achieved by total lymphoid irradiation [28], polyclonal and monoclonal antibodies to control the immune response. The depleting antibodies have been used as induction and as rescue therapy for acute rejection. These concepts are discussed in Chaps. 12 and 18. Although costimulation blockade has been proposed as a method to induce tolerance, there have been discrepancies between results in animal models and humans [29]. There appears to be mechanistic barriers in humans complicating the development of tolerance by this approach. More recent studies using belatacept, a high-affinity CTLA4-Ig for clinical use, may prove to be a component of future therapeutic intervention [30]. The initial studies of Medawar conceptualized that tolerance was probably reversible due to continued pressures by inflammation and pathogen exposures. Regulation through various therapies including T-regulatory cells is a challenge due to the low frequency of these cells and need for expansion. However, trials are underway to test the efficacy of expanding natural T regs in living donor kidney transplantation. B cell tolerance has been more difficult to achieve in human transplantation versus animal models. Various B cell targeted therapies have been used to treat AMR and to decrease antibody levels during desensitization but have failed to achieve tolerance. These various therapies are discussed in Chaps. 6 and 12.

In conclusion, clinical transplantation requires the need for chronic immunosuppression with only anecdotal reports of patients weaned off all immunosuppression. Long-term graft outcome is challenged by multiple factors including the effects of the immunosuppressive drugs used and the chronic rejection process. Better understanding of the multiple mechanistic processes involved may provide evidence of the feasibility for the best approach to achieve ultimate goal of donor specific tolerance.

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6 The Sensitized Patient Awaiting Heart Transplantation

Jignesh Patel and Jon Kobashigawa

Clinical Pearls

- Sensitization of a pre-transplant patient is characterized by the development of alloreactive antibodies against HLA molecules, which are designated into Class I (A, B, C) and II (DR, DP, DQ), and is associated with longer waitlist time and increased waitlist and post-transplant mortality.
- Risk factors for sensitization include blood transfusions, prior pregnancy, prior transplantation, prior use of homografts, and the use of ventricular assist devices.
- Sensitization is measured by the calculated panel reactive antibody (cPRA) blood test, which defines the proportion of the donor population to whom the recipient has preformed potentially cytotoxic anti-HLA antibodies.
- High resolution solid phase immunoassays offer increased sensitivity and specificity for HLA antibody detection, and allow determination of antibody specificity and binding strength; binding strength is measured by Mean Fluorescence Intensity (MFI).
- These immunoassays facilitate the use of the virtual crossmatch, in which potentially cytotoxic (based on binding strength) antibodies to donor HLA antigens are identified. The corresponding antigens to these antibodies are then avoided in any potential donor thus obviating the necessity of performing a prospective donor-specific crossmatch which expands the donor pool.
- C1q binding assays are able to distinguish complement-fixing from non-complement-fixing antibodies. The ability of an antibody to bind C1q may be a better marker of potential cytotoxicty than antibody strength. Using a C1q threshold to determine incompatible donors instead of an MFI threshold would result in fewer antigen avoids and thus expand the donor pool.
- The cPRA defines the proportion of the donor population to whom the transplant candidate has preformed potentially cytotoxic anti-HLA antibodies and thus is a marker of the degree of sensitization and the wait-time to transplant. In most

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programs, a threshold of cPRA >50% is used to perform desensitization.
- Therapeutic desensitization treatments may expand the donor pool and reduce waitlist time for sensitized patients: options include plasmapheresis and immunoadsorption, intravenous immunoglobulin, rituximab, and bortezomib routinely, and rarely, cyclophosphamide and splenectomy.
- Periodic monitoring of circulating antibodies in patients awaiting transplantation is warranted, even after desensitization, as antibodies may potentially rebound.

Introduction

The humoral theory of transplantation states that antibodies cause the rejection of allografts. This hypothesis was first proposed in the early twentieth century, when efforts were made to produce antibodies against tumors. However, it was soon realized that the antibodies were produced against transplant antigens present on transplantable tumors, not against the tumor-specific antigens. Development of inbred mouse subsequently allowed identification of the transplant antigens determined by the H-2 locus of mice [1]. The analogous human leukocyte antigen (HLA) system was established by discovery of antibodies against leukocytes in multiple transfused patients [2] and analysis of lymphocytotoxic alloantibodies made by pregnant women, directed against mismatched paternal antigens of the fetus [3, 4]. The HLA antibodies were then found to cause rejection of kidneys [5]. Antibodies appeared in almost all patients after rejection of kidneys.

Advances in antibody detection and understanding of humoral immunity would not have been possible without in vitro techniques developed initially by Pappenheimer and subsequently by Terasaki. The development of the dye exclusion test by Pappenheimer in 1917 [6] was a significant advance which allowed the in vitro assessment of the effect of antibodies on cells. Vital cells actively excluded the dye while cells destroyed by antibody and complement stained blue. This test still has important uses today.

A major advance in transplant immunobiology was made in 1964 with the development of the microlymphocytotoxic assay by Terasaki [7]. The test only requires 1 microliter – one lambda – of serum and a similarly small amount of lymphocytes. The importance of this was that as little as 1 ml of serum facilitated up to 1000 tests. This allowed efficient sharing of serum between different laboratories. By 1967, The Third Histocompatibility Workshop determined that all observed reactions fit into a single genetic locus. This was subsequently named "HLA" in 1968 by the World Health Organization.

Elucidation of the molecular structure of HLA antigens allowed synthesis of single HLA lines using recombinant technology. In early 2000s Terasaki's group developed single antigen Luminex beads with single HLA antigen on different colored beads, allowing accurate determination of antibody specificity and in particular, donor specific antibodies (DSA) [8].

HLA Antibodies

Sensitization is characterized primarily by the development of alloreactive antibodies against HLA molecules. HLA molecules are designated into Class I (A, B, C) and II (DR, DQ, DP) and are located in different regions of chromosome six. The genes encoding these molecules are highly polymorphic. Their expression on the cell surface is essential for antigen presentation to T cells and enables recognition of self from non-self. To date, more than 13,000 HLA alleles have been identified implicating a very low probability that two random individuals will express the same HLA. There is a variation in the distribution of HLA molecules. Class I HLA molecules are constitutively expressed on all nucleated cells. In contrast, class II HLA expression is restricted to B-cells, activated T-cells and antigen presenting cells (APC). Class II expression may be induced on certain cells such as endothelial cells under the influence of cytokine activation which occurs as a

result of ischemia-reperfusion injury. Differential HLA class I and II expression on allograft vascular endothelial cells will therefore account for hyperacute and delayed rejection occurring in the presence of class I and class II DSA respectively.

Antibody production begins with exposure of naïve B cells to antigen in the presence of APC or T-helper cells in secondary lymphoid tissues. These stimulated B cells become either plasmablasts secreting low-affinity antibody or activated B cells which interact with follicular dendritic and T helper cells to form germinal centers [9]. Within these germinal centers, B cells undergo proliferation, hypermutation and affinity maturation to become memory B cells or high-affinity antibody secreting terminally differentiated plasma cells. Plasma cells migrate back to the bone marrow and there, reticular cells and myeloid cells, principally eosinophils, interact with plasma cells to create a supportive niche in which they survive for long periods. Memory B cells circulate through secondary lymphoid organs and in the peripheral circulation. Memory B cells rapidly proliferate upon re-exposure to antigen and differentiate into plasma cells producing high-affinity antibodies. An important property of B cell maturation is that changes in cell surface marker expression characterize different stages of maturation and these markers may serve as important therapeutic targets. Therefore, expression of CD20 and CD19 is high on unstimulated B cells but low to absent on plasma cells, which instead express CD138 and CD38.

Allograft injury by antibodies occurs predominantly through complement activation. Binding of antibody to HLA antigen results in activation of C1 and triggering of the complement cascade. Complement products cause injury by recruitment of inflammatory cells (C3a, C4a, C5a), mast cell histamine release and up-regulation of endothelial adhesion molecules (C5a), tissue factor synthesis and thrombotic injury (C5a, C5b-9). However, the formation of the terminal C5b-9 membrane attack complex (MAC) is the most destructive, mediating endothelial cell lysis. Complement independent injury by DSA also occurs through Fc receptor recruitment of inflammatory cells and release of inflammatory mediators. The resulting cellular inflammation, thrombosis, hemorrhage and lysis cause allograft injury and dysfunction.

Risk Factors for Sensitization

Risk factors for sensitization include blood transfusions, prior transplantation [10], use of homografts with prior cardiac surgeries [11], and the use of ventricular assist devices (VADs) prior to transplantation [12]. Registry data show that 31% of African-Americans awaiting transplant have PRA >10% compared to 23% of Caucasians [13]. Twenty percent of patients receiving a transfusion exhibit an antibody response compared to 3% who do not [14]. Blood transfusion is likely to elicit an antibody response in women and African-Americans. Multiparous women are at risk of sensitization to paternal antigens [15]. VADs increase risk of sensitization due to the higher likelihood of needing blood transfusions, although biomaterials and textured surfaces have also been implicated in increasing immunologic risk through allosensitization. Sensitization after VAD implantation has been associated with an increased waiting time to transplant, increased risk of post-transplant acute rejection and increased risk of primary graft dysfunction [16, 17]. Half of all patients now undergoing heart transplant are now bridged with mechanical circulatory support. In early cohorts up to two-thirds of VAD patients were at risk of allosensitization [18, 19]. This risk has been particularly linked with older pulsatile devices and the use of newer axial flow devices have been associated with a much lower risk of allosensitization [20, 21]. In one study, the risk of allosensitization within 3 months of implant was 28% with the HeartMate I device compared to only 8% with the HeartMate II or DeBakey devices ($p = 0.02$) [21]. Even the risk of allosensitization from transfusions in VAD patients may be further mitigated by the use of leukocyte reduced, irradiated and ABO identical blood products. In a study [22] using this approach, de novo sensitization rates were maintained below 10% with no patient developing

broad sensitization (PRA >50%) despite each patient receiving a mean of 90 blood components.

Clinical Implication of HLA Antibodies

DSA present prior to cardiac transplantation have been demonstrated to be a risk factor for poor patient and allograft survival [23, 24]. In an early study of over 600 heart transplant recipients [24], the presence of a positive lymphocytotoxic crossmatch at transplant was associated with a 1 year survival of 56% compared to 73% for those with a negative crossmatch. In a study of 950 heart transplant recipients followed for 15 years after transplant, Ho [25] demonstrated that 15 year graft survival was greatest in those patients who never developed HLA antibodies (70%) or only had antibodies prior to transplant (71%). In contrast, patients who demonstrated antibodies both before and after transplant had a graft survival of only 56%. Lowest survival was noted in patients who developed de novo antibodies after transplant (47%). The development of de novo antibodies was preceded in 76% of these patients by cellular rejection ISHLT grade 3 or higher and the development of AMR had a significant negative impact on survival. In a more recent analysis of 105 pediatric transplant recipients, 43% were noted to have developed de novo DSA. Patients with DSA had significantly higher rates of rejection, allograft vasculopathy and mortality at 5 years [26]. While a significant portion of heart transplant recipients appear to develop HLA antibodies, it appears that increased mortality is only noted in those patients with persistent DSA [27]. Non-DSA and transient DSA do not appear to be associated with poor outcomes. In this study of a pediatric population, persistent DSA was characterized by Class II antibodies in 88% of the cases and the presence of antibodies to DQ was associated with the worst survival.

The challenge of the sensitized patient therefore, is that pre-transplant the presence of alloantibodies limits the donor pool. This results in a prolonged, often prohibitive time on the wait-list and a consequent increase in mortality while on the wait-list [28]. After transplant the patient remains at risk of rejection, graft loss, development of allograft vasculopathy and increased mortality.

Methods of Assessment for HLA and Non-HLA Antibodies

Panel Reactive Antibodies

Panel Reactive Antibody (PRA) has been traditionally performed on patients waiting for solid organ transplants and measures circulating anti-HLA antibodies. The PRA score is given as a percentage and represents the portion of the sample population that the anti-HLA antibody in the recipient's blood reacts with.

Techniques for measuring HLA antibodies have evolved significantly over the last 20 years [29, 30] (Fig. 6.1). Traditionally, complement-dependent cytotoxicity (CDC) assays have been performed to assess the ability of recipient serum to lyse a panel of T or B cells obtained from a panel of volunteers, representative of the population. Addition of anti-human globulin (AHG) increased the sensitivity of CDC assays and allowed for detection of cytotoxic-negative, absorption-positive HLA alloantibodies. However, as both IgG and IgM can bind complement, neither test is able to distinguish between the immunoglobulin classes. The CDC tests also cannot distinguish between major histocompatibility (MHC) Class I or Class II antibodies. The CDC assay also requires a large number of cell panels from multiple donors to provide adequate sampling for detecting the most common HLA antigens, and rare or unusual antigens may be omitted [31].

More recent techniques using flow cytometry or enzyme-linked immunosorbent assay (ELISA) [30] are much more sensitive for the detection of antibodies and generally provide more reproducible results. The Luminex® test allows for simultaneous detection of multiple antibodies, as up to 100 color-coded, antigen-coated microspheres can be detected in a single well [32]. The FlowPRA® test is a flow cytometry based technique which consists of a pool of microparticle beads coated

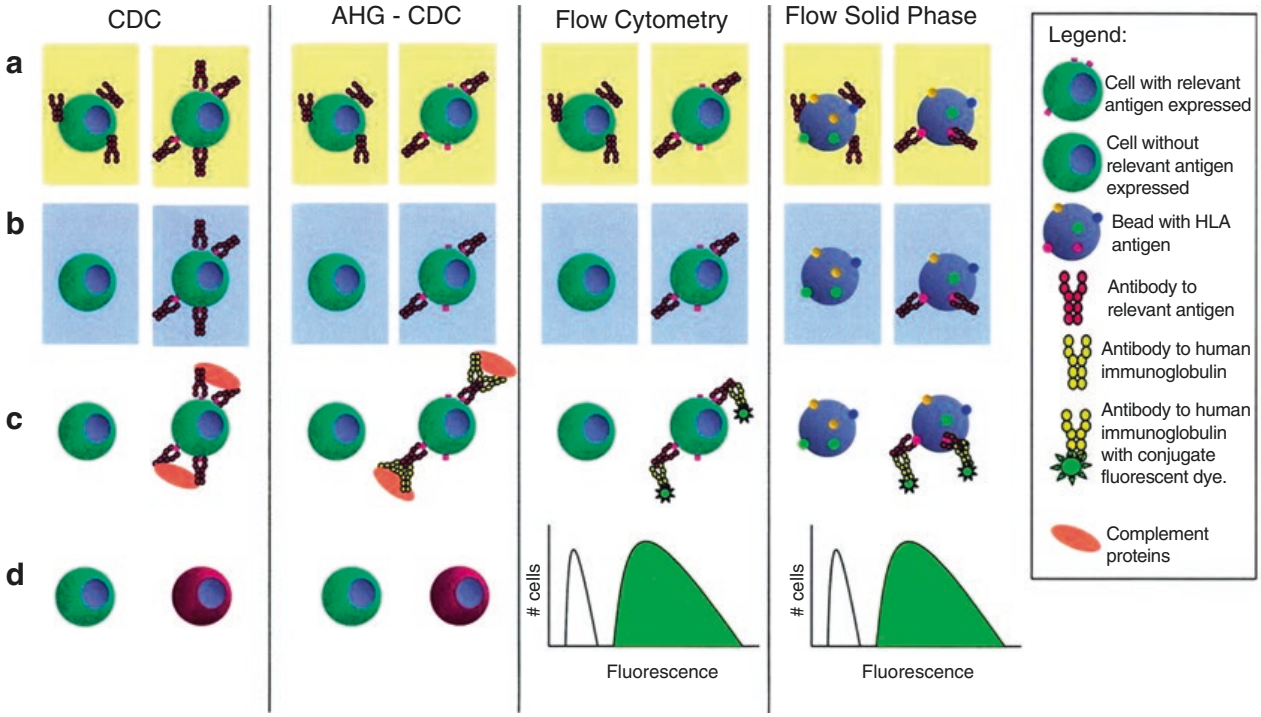

Fig. 6.1 CDC and flow methods for cross-matching and determination of circulating HLA alloantibodies *Abbreviations*: *CDC* Complement Dependent Cytotoxicity, *AHG* Anti-human Globulin (Reused with permission from Tinckam and Chandraker [29])

with full HLA Class I or Class II phenotype derived from purified HLA-bearing cell lines [33]. The percentage of PRAs can be determined by calculating the percentage of beads that react positively with patient sera. Due to variability in results between techniques, many laboratories will utilize multiple confirmatory tests.

While these assays are useful screening tools for determination of PRA, further tests are required to determine specificity and quantification of alloantibodies. The importance of the strength of circulating antibody is increasingly recognized as an important factor determining the risk of a cytotoxic response. For determination of multiple antibody specificities and quantification of antibodies, single-antigen bead (SAB) assays are now commonly deployed [34]. These assays contain beads individually coated with a specific purified recombinant HLA molecule that identifies antibody specificity.

The ability to detect and quantify the strength of specific antibodies has allowed estimation of which recipient circulating antibodies are present at a strength which may prove to be cytotoxic for a potential donor organ. Laboratories will typically perform validation studies to determine the relationship between antibody levels determined by single antigen beads and flow crossmatch. For this purpose, the strength of antibody binding on single antigen beads as represented by Mean Fluorescence Intensity (MFI) is compared to the degree of the flow crossmatch reported as median channel shift (MCS). However, it is important to note that MFI is a measure of antibody-antigen binding or HLA molecule bead saturation rather than a direct measure of antibody titer.

MFI is also affected by several technical and biologic factors. Antigen density on beads may vary depending on type of HLA molecule, between different assay manufacturers, assay batches, and antigen density on beads may not reflect the natural expression of HLA molecules on cells in vivo. Antibodies against public HLA epitopes (antigenic determinants produced by more than one gene) may be under-estimated and appear as a weak antibody due to a dilutional effect resulting from a single antibody being distributed across many beads. The presence of endogenous C1q inhibitors can also mask detection of HLA antibodies. This is known as the "prozone effect".

These C1q inhibitors may be diluted out or eliminated by heat inactivation or denaturing with dithiothreitol (DTT) or ethylenediaminetetraacetic acid (EDTA) [35–37]. The process of HLA molecule purification and coating on to the bead surface may also alter the natural conformation of antigens leading to exposure or loss of antigenic epitopes. Therefore, HLA antibodies may remain undetected if they are unable to bind to the distorted HLA molecule. Conversely, clinically irrelevant antibodies may be detected that bind to the denatured but not intact antigen. In one study, a fifth of patients awaiting a heart transplant had at least one antibody to cryptic epitopes that led to a false increase in calculated PRA (cPRA) by 5% [38]. Importantly, the technique allows detection of low level antibodies which may trigger a strong amnestic immune response upon re-exposure to the antigen.

Virtual Crossmatch

In the past, sensitized patients needed a prospective cross-match to ensure allograft compatibility before transplantation. A prospective crossmatch identifies donor hearts which may be at risk of exposure to circulating cytotoxic antibodies. This method however can be logistically challenging as recipient blood has to be available close the donor in order for the test to be performed in a timely manner. The test also requires local expertise and samples also need to be kept updated as clinical conditions change for the recipient who may be challenged with further potentially sensitizing events such as blood transfusions or ventricular assist device placement while awaiting transplantation. Recipient blood from sensitized patients has to be sent out to several locations where donors could potentially become available. The need for a prospective cross-match inherently limits the geographical area from which sensitized patients may qualify for organ donors and therefore substantially increases the waiting time to transplant.

The ability to perform high resolution antibody screening with solid phase assays has fortunately simplified appropriate donor selection by the use of a process termed “the virtual crossmatch.” In a virtual crossmatch, the recipient antibody profile is determined at the time of listing and potentially cytotoxic antibodies to HLA antigens identified. Cytotoxicity is presumed from the strength of the antibody following correlation studies with flow cytometry cross match as described above [39]. The corresponding antigens are then documented as unacceptable on the transplant list. The principle advantage of this strategy is that it obviates the need to send out recipient blood and therefore substantially increases the geographical region from which a donor may be accepted. This approach has been shown to substantially decrease the waiting time to transplant [40]. The virtual crossmatch also helps identify patients who are potentially at elevated risk of rejection in whom immunosuppression may need to be augmented after transplantation. The use of the virtual crossmatch has been validated in several studies. In pediatric heart transplant recipients the use of the virtual crossmatch was associated with a significantly decreased waiting time to transplant and improved survival compared to patients listed with a prospective crossmatch [41]. In another study the accuracy of virtual crossmatch was compared to prospective AHG-CDC crossmatch [42]. Based on analysis of 257 T-cell AHG-CDC crossmatch tests, the positive predictive value of virtual crossmatch (the likelihood of an incompatible virtual crossmatch resulting in an incompatible T-cell CDC-AHG crossmatch) was 79%, and the negative predictive value of virtual crossmatch (the likelihood of a compatible virtual crossmatch resulting in a compatible T-cell CDC-AHG crossmatch) was 92%. When used prospectively in a cohort of 28 sensitized patients awaiting heart transplantation, 14 received allografts based on a compatible virtual crossmatch alone from donors in geographically distant locations. Compared with the other 14 sensitized patients who underwent transplant after a compatible prospective serologic crossmatch, the rejection rates and survival were similar. About 65% of heart transplant centers now utilize the virtual crossmatch [43].

It is however unlikely that all classes and types of HLA antibodies have an equal impact on their ability to mount allograft rejection. The role of HLA-C and HLA-DP mismatches, for example, in allograft survival and their consideration in virtual crossmatch is still undetermined.

In contrast with CDC assays, conventional solid-phase assays do not discriminate between complement-fixing and non–complement-fixing antibodies. Avoidance of non-complement fixing and therefore non-cytotoxic antibodies in the virtual crossmatch may therefore unnecessarily restrict the donor pool. A novel C1q assay developed to detect the sub-set of immunoglobulin G (IgG) antibodies capable of fixing complement may allow further expansion of the donor pool by allowing exclusion of only complement fixing antibodies in the virtual crossmatch [44]. In this study the identification of complement fixing antibody in a standard virtual crossmatch correlated with a higher incidence of AMR compared to a virtual crossmatch with no complement fixing antibodies. Another important observation is that the ability of antibody to fix complement is independent of the strength of antibody and C1q fixation is independent of MFI values [45]. The C1q assay appears to be much more sensitive than the standard CDC at detecting complement fixing antibodies.

Given the variety of testing now available to evaluate the sensitized heart transplant candidate, an algorithm for assignment of unacceptable antigens for the virtual crossmatch has been used to allow transplantation of highly sensitized patients across the DSA barrier with survival rates comparable to DSA negative heart transplant recipients [46]. In this protocol, 4 antibody detection methods were used to prioritize unacceptable antigens: Luminex single antigen (LSA), LSA with 1:8 dilution, C1q LSA and CDC panel.

Non-HLA Antibodies

Antibody responses to non-human leukocyte antigens (HLA) have been reported in solid organ transplantation and may occur as alloantibodies or autoantibodies. In thoracic organ transplantation, several have been implicated in acute and chronic allograft rejection. The antibodies identified include those against major histocompatibility class I chain-related gene A (MICA) [47, 48], angiotensin II type 1 receptor (AT_1R) [49], endothelin-1 type A receptor (ETAR) [50], endothelial cell antigens [51], vimentin [52], K-alpha-1-Tubulin (KA1T) [53], and collagen-V [54] and other non-HLA IgM antibodies. In cardiac transplantation, anti-MICA and anti-endothelial antibodies have been associated with increased antibody mediated rejection [55] and development of cardiac allograft vasculopathy [47]. AT1R and ETAR have been implicated with development of ACR, AMR and early onset microvasculopathy [50].

The detection of these antibodies in the setting of acute and chronic rejection however at this time remains for investigational use and none of the assays used to detect these antibodies have been routinely used for clinical evaluation. The clinical significance and the role of these antibodies in mediating thoracic allograft injury currently remains chiefly undetermined.

Calculated PRA (cPRA)

Not all sensitized patients require treatment to decrease antibody burden. The need for therapy is dictated by the calculated PRA (cPRA). The cPRA value represents the percentage of donor hearts in a given population to which a heart transplant candidate will have cytotoxic anti-HLA antibodies.

The cPRA is determined based on the antibody strength threshold (MFI) for cytotoxicity determined by the individual center's laboratory. For example, if the laboratory determines that antibodies with MFI >5000 correlate with cytotoxicity, only those corresponding antigens will be entered into the calculator available online at the Organ Procurement and Transplantation Network website from the US Department of Health and Human Services. The current cPRA data is based upon HLA frequencies derived from the HLA

phenotypes of deceased kidney donors recovered over a 2 year period in 2003–04. Ethnic frequencies were derived from data in 2006–07.

As the cPRA is an estimation of the proportion of the donors not suitable for the sensitized patients, generally patients with a cPRA >50% may be considered for desensitization therapies as less than half the donor pool would be suitable for transplantation without treatment. The aim of desensitization therapy is to reduce antibody burden to facilitate a reduction in the cPRA and increase the chances of obtaining a suitable organ.

Therapeutic Options for the Sensitized Patient

The humoral response involves B cells, plasma cells, antibodies and complement. All of these have been commonly targeted as therapeutic options for desensitization (Table 6.1). Strategies for desensitization continue to evolve but published clinical data remain sparse and protocols in heart transplantation have been adapted from experience in renal transplantation. The general approach is to use multiple complementary therapies which are aimed at removing or neutralizing alloantibodies and suppress further production.

Table 6.1 Strategies to prevent antibody-mediated rejection

Approaches	Therapies
Antibody removal	Therapeutic plasma exchange, immunoadsorption
To alter antibody production	Rituximab, ATG, Bortezomib
B-cell modulation	
Plasma cell depletion	
Immunomodulation (Ab inactivation)	IVIG
Suppression of the T-cell response	Steroids, ATG, MMF, CNI, PSI
Complement blockade	Eculizumab

Abbreviations: *Ab* antibody, *ATG* anti-thymocyte globulin, *IVIG* intravenous immunoglobulin, *MMF.* mycophenolate mofetil, *CNI* calcineurin inhibitor, *PSI* proliferation signal inhibitor

Plasmapheresis and Immunoadsorption

Plasmapheresis allows physical removal of circulating antibodies. In one study, sensitized heart transplant candidates treated with preoperative plasmapheresis and intravenous immunoglobulin (IVIg) had similar rates of rejection and allograft survival compared to non-sensitized controls [56]. Antibody rebound due to rapid diffusion from the extravascular space and reflex stimulation of plasma cells leading to increased production can occur, and multiple treatments are usually needed to achieve low circulating antibody levels. Large bore intravenous access is required and filtration of clotting factors with plasmapheresis may require replacement with fresh frozen plasma instead of albumin to correct coagulopathy. Immunoadsorption allows targeted removal of allo-antiobodies and may be more effective than plasmapheresis [57].

Intravenous Immune Globulin (IVIg)

Intravenous immunoglobulin (IVIg) is a product of pooled IgG antibodies (immunoglobulin) extracted from the plasma of up to 100,000 blood donors. Originally developed for the treatment of primary immunodeficiency disorders, the product was found to have significant immunomodulatory effects. Its use was therefore expanded to treat autoimmune and inflammatory diseases and subsequently organ transplantation. IVIg has multiple immune effects including Fc receptor blockade, inhibition of complement deposition, enhancement of regulatory T cells, inhibition or neutralization of cytokines and B cell growth factors, accelerated clearance of autoantibodies, modulation of adhesion molecules and cell receptors, cross-linking B cell receptor and FcγRIIB, which reduce APC activity and induce B cell apoptosis and activation of regulatory macrophages [58, 59] (Fig. 6.2). A randomized placebo-controlled trial in sensitized patients awaiting renal transplantation revealed efficacy of high dose IVIg in reducing PRA leading to improved transplant rates but had no effect on rejection or

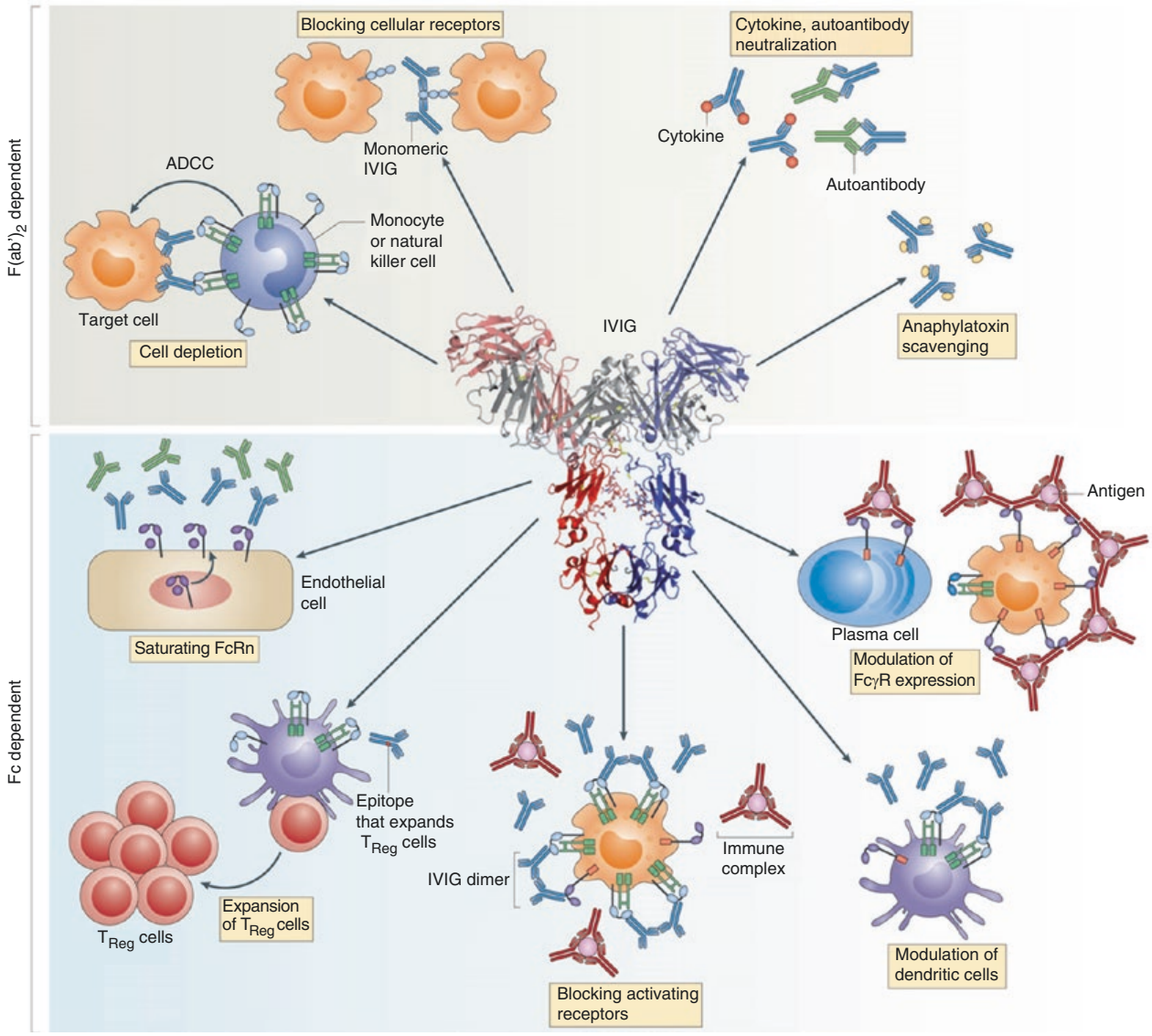

Fig. 6.2 Mechanism of Intravenous Immunoglobulin (IVIg) activity (Reused with permission from Schwab and Nimmerjahn [59])

graft loss [60]. In a study of sensitized LVAD recipients awaiting heart transplant [61], patients received monthly courses of either IVIg or plasmapheresis, in conjunction with cyclophosphamide. Prolongation in transplant waiting time was related to the presence of Class I antibodies. Infusion of IVIg (2 g/kg) caused a mean reduction of 33% in anti-HLA class I alloreactivity within 1 week. Waiting time to transplantation was significantly reduced by IVIg therapy and subsequently matched nonsensitized patients. Although plasmapheresis caused a similar reduction in antibodies, this effect was achieved after longer treatment. Plasmapheresis was associated with an unacceptably high frequency of infectious complications. In this study IVIg appeared to be more effective than plasmapheresis in reducing PRA with a superior safety profile.

Cyclophosphamide

Cyclophosphamide has been used to prevent B cell rebound. In one study [62], intravenous cyclophosphamide pulse therapy in conjunction with IVIg reduced waiting time and mortality in

sensitized patients to levels in non-sensitized patients. After transplant, cyclophosphamide prevented induction of IgG anti-HLA class II, prolonged the rejection-free interval, and reduced cumulative rejections to levels in non-sensitized patients. The risk of rejection was 3.7-fold higher in patients treated with mycophenolate mofetil than patients treated with cyclophosphamide. There were no differences in infectious or other significant complications. However, concerns for direct cardiac toxicity and other adverse effects have limited widespread use.

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20 expressed on pre-B and mature B lymphocytes and was developed for the treatment of lymphoma. CD20 has an important role in B cell maturation, regulating the early stages of cell cycle initiation and differentiation. Rituximab causes B cell depletion by complement dependent antibody dependent cytotoxicity and apoptosis. In sensitized patients awaiting renal transplantation, rituximab in conjunction with IVIg has been shown to significantly reduce PRA, shorten time to transplant and provide excellent 12 month graft and patient survival [63]. In heart transplantation [64], 21 patients treated with a combination of plasmapheresis, IVIg and rituximab had a mean reduction of PRA from 70.5 to 30.2%, resulting in a negative prospective donor specific crossmatch and successful heart transplantation. Compared with the control group (PRA <10%), the treated sensitized group had similar 5-year survival and freedom from cardiac allograft vasculopathy. In a prospective study, 14 sensitized pediatric patients awaiting heart transplant underwent desensitization with high dose IVIg and rituximab [65]. Eight patients had a significant decrease in cPRA, although six required multiple doses for a response. The total number of unacceptable antigens decreased for all eight responders leading to a median increase in the percentage of potential donors in the overall population from 10% pretreatment to 85% post-treatment.

Bortezomib

Although plasmapheresis, IVIg and rituximab variably reduce antibody burden, these modalities have no suppressive effect on the cell responsible for antibody production, the mature plasma cell. Bortezomib is a selective 26S proteosome inhibitor used in the treatment of multiple myeloma, a plasma cell neoplasm. In vitro, bortezomib demonstrated plasma cell apoptosis and blocked anti-HLA antibody production [66]. In contrast, IVIg, rituximab and anti-thymocyte globulin had no effect on suppressing antibody production by plasma cells. In one study, 34 highly sensitized patients awaiting living-related donor renal transplant underwent desensitization with a combination of plasmapheresis, bortezomib, rabbit-ATG, mycophenolate mofetil (MMF) and IVIg [67]. In total 29/34 patients responded within 1 month with a significant reduction in AHG-CDC and flow cytometry crossmatches. Side effects were noted in 38% of patients and were manageable. Two patients lost a graft at 1 year and acute rejections were noted in a quarter of the patients, which responded to steroids and rATG.

In heart transplantation, bortezomib in conjunction with plasmapheresis was studied in seven sensitized patients awaiting heart transplantation, who despite prior treatment with rituximab, IVIG and/or plasmapheresis continued to have high antibody levels and cPRA [68]. In this study, bortezomib appeared to be generally well tolerated, with treatable infection being the most common adverse effect. The protocol was effective at significantly reducing antibody concentrations. Mean cPRA was reduced from 62 to 35% following bortezomib with plasmapheresis ($p = 0.02$). 6/7 patients demonstrated significant decline in antibody levels. One patient remained refractory to desensitization therapy. Four patients successfully underwent cardiac transplantation without evidence of rejection or graft dysfunction. One patient developed early post-transplant graft dysfunction and died at 1 month from sepsis. All but one patient were listed Status 1A at the time of desensitization. In a subsequent follow-up of 22 patients [69], plasmapheresis and bortezomib was confirmed to be

effective at reducing HLA antibody burden in a majority of sensitized patients, including patients with high levels of antibodies as determined by 1:8 dilution LSA and C1q assay. Patients who received prior desensitization therapies with plasmapheresis, IVIg and rituximab appeared to have a greater response suggesting that combination therapies appear to be more effective. The majority of patients were able to undergo transplant with excellent 1 year survival and low treated rejection rates.

The primary route of synthesis of HLA class I molecules is dependent on peptide generation by the proteasome, whereas that of class II is not. Therefore, patients with Class I antibodies appear to have a greater response to desensitization compared to patients with Class II antibodies [70].

The combination of plasmapheresis with bortezomib may be more effective as removal of circulating antibody by plasmapheresis results in increased metabolic demands on B-cells, memory B-cells and plasma cells to produce more antibody. This metabolic stress enhances the sensitivity of plasma cells to proteasome inhibition. Plasmapheresis during bortezomib therapy also provides the additional benefit of removing preexisting circulating antibody. As this combination of treatment may be provided over a period as short as 2 weeks, it may be particularly useful for patients listed Status 1A for heart transplant.

Splenectomy

Splenectomy reduces plasma cells, precursor cells and impairs B-cell immune surveillance. It can be performed using minimally invasive techniques. It is however associated with a life-long risk of sepsis from encapsulated bacteria and its effect on the immune system is permanent. This significantly limits its use in highly sensitized patients already at increased infection risk due to other desensitization therapies.

Splenectomy has been shown to be effective in permitting ABO and HLA incompatible renal transplantation against a positive crossmatch when used in conjunction with plasmapheresis and immunoglobulin [71].

Eculizumab

Antibody-mediated injury predominantly relies on activation of complement. The complement system may be activated by three separate pathways which converge to C5 and the subsequent formation of the membrane attack complex (C5b-C9), which has proinflammatory and chemotactic properties and importantly promotes cell lysis. An approach preventing complement activation may therefore be effective in preventing AMR in sensitized patients after heart transplant. Eculizumab is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, and inhibits its cleavage to C5a and C5b, thus preventing the generation of the terminal membrane attack complex C5b-9. C5a is also a potent immunomodulator involved in chemotaxis, macrophage cytokine production and ischemia-reperfusion injury. One potential advantage of targeting the terminal components of the complement system is that the early components are preserved to remain active in immune defense. For example, C3b is an important opsonin against microbial infection. Eculizumab is approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

In renal transplantation, the incidence of biopsy-proven AMR in the first 3 months in 26 highly sensitized recipients treated with eculizumab was significantly reduced compared to a matched historical cohort (7.7% vs 41.2% ; $p = 0.0031$) [72]. A single-center pilot study of the use of eculizumab in highly sensitized patients after heart transplantation is currently enrolling patients (clinicaltrials.gov identifier NCT02013037). An interim analysis of the first ten patients enrolled was presented [73]. All patients were status 1A at transplant with a mean cPRA of 93.7%. All but one patient received prior desensitization therapies. Eight patients had DSA at transplant and the mean T- and B-cell flow crossmatches were strongly positive at 117 ± 145 and 220 ± 96 MCS. One-year actuarial survival was 90% with 100% freedom from ACR (ISHLT ≥2R), 77.8% freedom from AMR (AMR ≥2) with no patients having developed left ventricular dysfunction. Treatment appeared to be well tolerated with low rates of infection.

Monitoring of Sensitized Patients While Awaiting Transplantation

Antibodies may potentially rebound following completion of desensitization therapy and additional treatment may need to be considered. Further opportunities for sensitization may also present in patients receiving blood products, mechanical circulatory support or developing infection. Circulating antibodies therefore need to be periodically monitored while awaiting heart transplantation.

A consensus conference took place in 2008 [43] to assess the current status of sensitization in patients awaiting heart transplantation, the use and efficacy of desensitization therapies, and the outcome of desensitized patients after heart transplantation. A consensus statement for recommended interval for antibody screening and identification was published.

Conclusions

Heart transplant wait-lists continue to grow as demand for organs has vastly out-stripped a finite non-expanding donor pool. In this scenario, sensitized patients awaiting heart transplantation represent a particular challenge. Due to a limited donor supply, an increasing number of patients awaiting heart transplantation are on mechanical circulatory support and these patients are at particular risk for sensitization. Pre-transplant sensitization is associated with an increased waiting time to transplant, increased wait-list mortality and increased risk of rejection after transplant.

Solid phase immunoassays offer increased sensitivity and specificity for HLA antibody detection. These high-resolution tests allow patients to be listed for transplant by virtual cross match, thereby increasing the donor pool. However, unlike the CDC assay, these assays do not distinguish complement fixing from non-complement fixing antibody and antibody strength and serial dilution serve as surrogates for cytotoxicity. The C1q binding assay further distinguishes HLA antibodies that can bind the first component of complement and may further help expand the donor pool by identifying the most pathogenic antibodies.

Treatment options for sensitized patients remain an area of active investigation and focus on antibody removal (plasmapheresis and immunoadsorption), target B cells and immunomodulation (rituximab and IVIg), plasma cell depletion (bortezomib) and complement blockade (eculizumab). The most effective approach for reducing alloantibodies requires a combination of therapies.

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7 Donor Organ Preservation and Surgical Considerations in Heart Transplantation

Fardad Esmailian, Paul Perry, and Jon Kobashigawa

Clinical Pearls

- Currently, donor hearts are utilized from patients after brain death, which is diagnosed commonly by the Apnea Test.
- All potential donors are evaluated with standard laboratory values, toxicology screen, electrocardiogram, chest X-ray, and viral serologies (EBV, CMV). Donor hearts are examined with transthoracic echocardiogram and in older donors, coronary angiogram.
- Factors that may contraindicate donor acceptance include left ventricular hypertrophy (>1.4 cm), poor ventricular function, significant valvular abnormalities, insufficient sizing for recipient, older donor age, pre-existing coronary artery disease, active malignancy in the donor, and certain active infections.
- Optimal pre-operative donor heart management focuses on treating hypoxia, hypotension and hypertension and minimizing the neurohormonal adverse effects of brain death on the donor heart, including hypothalamic-pituitary axis derangement.
- Procurement offers an opportunity to directly examine the donor heart for dysfunction, ischemic damage, and trauma. The heart is then removed and placed in a hypothermic, cardioplegic solution.
- Ischemic time (in which the heart is not being perfused by circulation) should be minimized, as longer times (>6 h) are associated with poor post-transplant outcomes.
- The bicaval technique is the most common operative technique for heart transplant in the modern era, but the biatrial technique is useful where dissection of the vena cavae is hazardous.
- Transplant candidates with existing mechanical circulatory support devices or previous sternotomies usually have significant mediastinal adhesions; in these situations the operating team should be given sufficient time to prepare the recipient to minimize ischemic time.

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Introduction

Human heart transplantation represents one of the seminal accomplishments for the field of cardiac surgery. The first successful human heart implant was performed on December 3, 1967 by Dr. Christiaan Barnard in Cape Town, South Africa. Several weeks later, Dr. Norman E. Shumway of Stanford University performed the first adult heart transplant in the United States. Since the era of these early pioneers, nearly all elements of the procedure have undergone significant modification and refinement. In this chapter we review donor selection, organ procurement and preservation, and techniques for implantation.

Diagnosis of Donor Death and Preparation of Donors

Brain Death

In general, organ donors are diagnosed with brain death. When clinically suspected, there are multiple methods for establishing this diagnosis. The Apnea Test is the most widely used technique. It is performed by disconnecting a normothermic, hemodynamically stable, well oxygenated patient from mechanical ventilation and monitoring for spontaneous breathing. Absence of breathing with an absolute arterial carbon dioxide ($PaCO_2$) value >60 mmHg or an increase in $PaCO_2$ >20 mmHg from baseline at 10 min is considered positive. If the patient develops hypotension or hypoxia during the observation period the test is considered inconclusive [1]. The Apnea Test must be performed by an appropriately credentialed physician, typically a neurologist or intensivist, and the results clearly documented in the medical record. Brain death can also be diagnosed by demonstrating a lack of cerebral blood flow on imaging (e.g. computerized tomography angiogram, magnetic resonance angiogram, and nuclear medicine cerebral perfusion) [2]. Laws regarding explicit criteria for brain death diagnosis vary from state to state and these must be satisfied prior to proceeding with organ harvest.

Donor Identification and Referral

All healthcare providers who participate in end-of-life care delivery must be well informed on the importance of organ donation. Any patient with irreversible brain injury and preserved end-organ perfusion and function merits organ donation consideration. In such circumstances it is the responsibility of the managing providers to notify the regional organ procurement organization (OPO) for evaluation for organ donation. It is important that the OPO, rather than the patient's caregivers, be allowed to initiate discussion on organ donation with the patient's family in order to prevent any perception of conflict of interest.

Donor Evaluation and Consent

All potential donors are rigorously screened for clear contraindications to organ donation such as active cancer and prohibitive infectious disease. Standard laboratory values, EKG, and chest x-ray are obtained. Additional serum studies include Epstein-Barr virus, cytomegalovirus, and toxicity screen. All potential cardiac donors require an echocardiogram, with a transthoracic study usually being sufficient. Important echocardiographic parameters include preserved ventricular function, ventricular wall thickness less than 1.4 cm, and no evidence of significant valvular or functional abnormality. Coronary angiogram is obtained selectively and may be program dependent, but typical indications include older age (>40 years), strong risk-factors for coronary artery disease, and abnormalities on echocardiogram. Similarly, right heart catheterization may be obtained selectively. It is important to note that some studies, such as echocardiogram, may necessitate repeating if not initially favorable, as it is often possible for organ recovery to occur with continued resuscitation. Consent rules vary from state to state, but it is typically obtained via direct consent from the donor ante-mortem (e.g. Department of Motor Vehicle registry) or from next of kin.

Donor Procurement

Preoperative Management

Meticulous preoperative management of the donor is critical for successful organ recovery and post-implant function. The donor is managed by a qualified healthcare provider in an ICU setting. Typical monitoring adjuncts include arterial line for blood pressure, central venous catheter, continuous rhythm tracing, and Foley catheterization. Hypoxia, hypertension and hypotension must be countered to avoid end-organ injury. If hypotension cannot be avoided without the use of significant vasoactive drip support then the suitability of the heart for transplantation must be further assessed. Severe electrolyte derangements should be aggressively corrected to prevent dysrhythmias during or prior to organ harvest.

The onset of brain death may be associated with severe derangements in the hypothalamic-pituitary endocrine axis. For example, many potential donors will develop diabetes insipidus and require treatment with intravenous fluid and vasopressin infusion. Given these derangements, and in an effort to optimize organ availability and function, hormonal analogues are being increasingly utilized to supplement suspected autologous secretion deficits. Thyroxine infusion has been shown to decrease vasopressor requirement and improve hemodynamic stability in potential organ donors [3]. Other pharmacologic adjuncts, such as dobutamine and glucose-insulin-potassium solution have been employed in an effort to prevent myocardial dysfunction [4]. At this time, high-level evidence promoting the use of hormonal adjuncts in potential organ donors is lacking and further investigation is warranted [5].

Surgical Technique of Donor Heart Recovery

The donor is transported to the operating room from the Intensive Care Unit with a secure airway and continuous monitoring. They are positioned supine with tucked arms and a slight pad under the scapulae. Skin is cleansed with chlorhexadine or iodine and sterile draping is undertaken. A sternotomy is performed, taking care to avoid injury to the underlying heart and lungs. The pericardium is divided and retracted. The heart may then be assessed for donor suitability, with special attention given to the size of the organ, ventricular function, and evidence of gross abnormality such as trauma or coronary artery disease. Various surgical techniques for organ harvest exist, but key universal principles include (i) occluding or venting systemic and pulmonary venous return, (ii) ensuring excellent delivery of cardioplegia with rapid and effective arrest, and (iii) avoiding injury to any structure that is utilized in donor implant. It is also important to be conscientious of the needs of the other organs undergoing harvest, such as the length of the Inferior Vena Cava (IVC) for the liver and lengths of the atrial cuff and pulmonary arteries (PA) for lungs.

A typical operative sequence may proceed as follows: (i) encircle the ascending aorta with an umbilical tape; (ii) mobilize the cephalad segment of the superior vena cava (SVC) and place a snare around it superior to the azygos vein; (iii) ligate the azygos vein; (iv) administer heparin; (v) place an antegrade cardioplegia/pressure monitoring catheter in the ascending aorta and connect arterial pressure monitoring line; (vi) occlude SVC with tourniquet; (vii) rapidly incise left superior pulmonary vein or left atrial appendage (if the lungs are being procured); incise IVC just above diaphragm, cross-clamp aorta and begin antegrade cardioplegia with a goal aortic root pressure tracing of 60–80 mmHg (it is important to measure the aortic root pressure to ensure adequate delivery of the cardioplegia or preservation solution since finger palpation will not be accurate; one must be extremely cautious in accepting the organ if the preservation solution cannot be delivered with adequate aortic root pressure); (viii) place ice around heart and complete the cardioplegia infusion; (ix) divide IVC at junction with right atrium; (x) divide left and right pulmonary veins or left atrium if lungs are being procured; (xi) divide distal ascending aorta, (xii) divide pulmonary arteries, (xiii) divide SVC,

(xiv) inspect heart on back table for any abnormality (e.g. patent foramen ovale, valvular pathology), (xv) place heart in saline ice bath container and back in multiple layers of ice.

In cases of harvesting heart and lungs, care must be taken to avoid delivery of the pulmonary preservation solution into to the coronary circulation. This can be achieved by dividing the ascending aorta as soon as cardioplegia delivery is completed and ensuring a very large incision in the left atrial appendage and/or opening the interatrial groove to aspirate the return from the pulmonary veins.

Ischemic Times

It is the goal of all cardiac transplant centers to minimize ischemic time of donor organs, both 'cold' (during transport) and 'warm' (once in recipient operating room and out of ice). Upper limits for ischemic time may vary from center to center, but a typical goal is a total ischemic time of less than 6 h. When considering a potential organ, it is important to consider the age of the donor in conjunction with the anticipated ischemic time, as greater tolerance for prolonged ischemic times has been demonstrated with grafts from younger donors [6, 7].

Organ Preservation

Traditional Methods

The dominant goal in traditional organ preservation is to minimize the metabolic demand of the organ during the time period between initial arrest and reperfusion. This is accomplished by inducing rapid diastolic arrest (cardioplegia), ensuring that the heart chambers are empty (left atrial and caval venting or occlusion), and hypothermia (ice bath). Commonly utilized cardioplegia solutions include University of Wisconsin (UW), Histidine-Ketoglutarate-Tryptophan (HTK), Stanford, and St. Thomas. During the procurement procedure emphasis is placed on vigilant assessment of the organ during arrest and efficient excision and packaging of the organ for transport. From the time of diastolic arrest until initiation of the first anastomosis in the recipient operating room the organ is continuously submerged in hypothermic solution and surrounded by ice slush.

Organ Care System (OCS)

The Organ Care System (Transmedics, Andover, MA) represents a radically alternative strategy to organ preservation as compared to traditional methods. With this technique, the donor organ is maintained with continuous perfusion of oxygenated, nutrient-rich blood to the coronary arteries while maintaining pulsatility. The device is essentially a specialized, portable cardiopulmonary bypass module. After cardiac arrest and excision from the donor, the aorta and pulmonary artery are cannulated and connected to the device. The heart is then reanimated and receives a continuous infusion of maintenance solution, catecholamines, and oxygenated blood at a temperature of 34 °C. During the transport process the organ is carefully monitored for evidence of favorable metabolic balance and function. The organ is then cooled, re-arrested, separated from the device and implanted in the recipient.

The PROCEED-II trial was a prospective, open-label, multicenter, randomized, non-inferiority trial aiming to assess the clinical outcomes of the OCS compared with standard cold storage of human donor hearts. This study demonstrated short-term clinical outcomes of the OCS to be non-inferior to standard of care, with similar recipient survival at 30 days [8]. The recently initiated EXPAND Heart trial seeks to determine the utility of the OCS in organ preservation for extended cross-clamp time (>4 h) and 'high-risk' donor organs [9].

The Heart Transplant Operation

Standard (Biatrial) Orthotopic Cardiac Transplantation

Indications

The biatrial method represents the original operative technique for heart transplantation and was widely utilized in the 1980s. This operation has

largely been replaced by the bicaval method but it remains useful in certain surgical circumstances. A review of the UNOS database by Davies et al. revealed that the biatrial technique was associated with increased need for permanent pacemaker (OR 2.6, CI 2.2–3.1) and that the bicaval technique was associated with improved 30-day survival (OR 0.83, CI 0.75–0.93) [10]. The major advantage of the biatrial technique in the modern era is for circumstances in which dissecting out the SVC and IVC represent severe hazard, such as in redo operations with dense adhesions.

Technique

The recipient is brought to the operating room and appropriate monitoring lines are inserted including arterial line and central venous line. Once the donor heart is confirmed to be appropriate for harvest the implanting team can begin preparing for the implant operation. Sternal incision is made 60–90 min prior to the anticipated time of organ arrival, and preferably earlier in the setting of redo sternotomy. The ascending aorta is typically cannulated just proximal to the aortic arch, but the axillary or femoral arteries may prove useful in special circumstances such as a heavily calcified ascending aorta or a difficult reoperative mediastinum. The SVC and IVC are then cannulated somewhat distally to allow room for anastomoses. A left ventricular vent may be placed at the discretion of the implanting surgeon to avoid rewarming of the heart by the blood returning from the pulmonary veins from collateral flow during the implantation. Once the donor heart is confirmed to have arrived safely, cardiopulmonary bypass is initiated and the aorta is cross-clamped. The native heart is then excised, taking care to leave an appropriate cuff of tissue along the aorta, PA, right atrium and left atrium. Any defibrillator leads are excised as proximal as possible at this time without a forceful pull to avoid tearing of the SVC or innominate vein. The donor heart is inspected on the back-table and assessed for any potential valvular abnormalities, a patent foramen ovale requiring closure or structural injury requiring repair. Once the back-table preparation is complete, the organ is removed from the ice-bath and brought into the surgical field. The left atrial anastomosis is performed first. The donor right atrium is then opened from the right atrial appendage to the IVC, taking care not to injure the sinoatrial node. The donor SVC is oversewn. The donor right atrial cuff is anastomosed to the recipient right atrium, starting directly over the left atrial suture line and continuing circumferentially along the atrial free wall. Next, one half of the PA anastomosis is performed followed by the aortic anastomosis. Several minutes prior to release of the cross clamp, systemic glucocorticoids (e.g. solumedrol) are administered. The aortic cross-clamp is then removed with the aortic suture line partially open in addition to venting of the aortic root to prevent introduction of air into the coronary circulation. The aortic suture line is then tied down and the donor organ is now perfused. The remaining half of the PA anastomosis is completed. The patient is then weaned off cardiopulmonary bypass after initiation of the inotropic support and de-airing of the left ventricular apex via aspiration with a 22 gauge needle and a 10 cc syringe until no further air bubbles are seen by TEE. Protamine is administrated and decannulation is performed in the standard fashion. A partial left pericardectomy may be performed to decrease the chance of significant pericardial effusion in the postoperative period, especially in cases where there is a very large pericardial space in comparison to the size of the donor organ. The defibrillator generator and the remnant of the pacing leads, if present, are then removed with the chest still open. Chest tubes and pacing wires are placed. Hemostasis is optimized and the wound is closed. An illustrative comparison between biatrial and bicaval technique is demonstrated in Fig. 7.1.

Bicaval Technique

Operative Technique

Preparation of the recipient mediastinum is largely similar to the biatrial technique, with the major alteration being isolation of the SVC and IVC. The SVC is divided at the cavo-atrial junction, and the free wall of the right atrium is

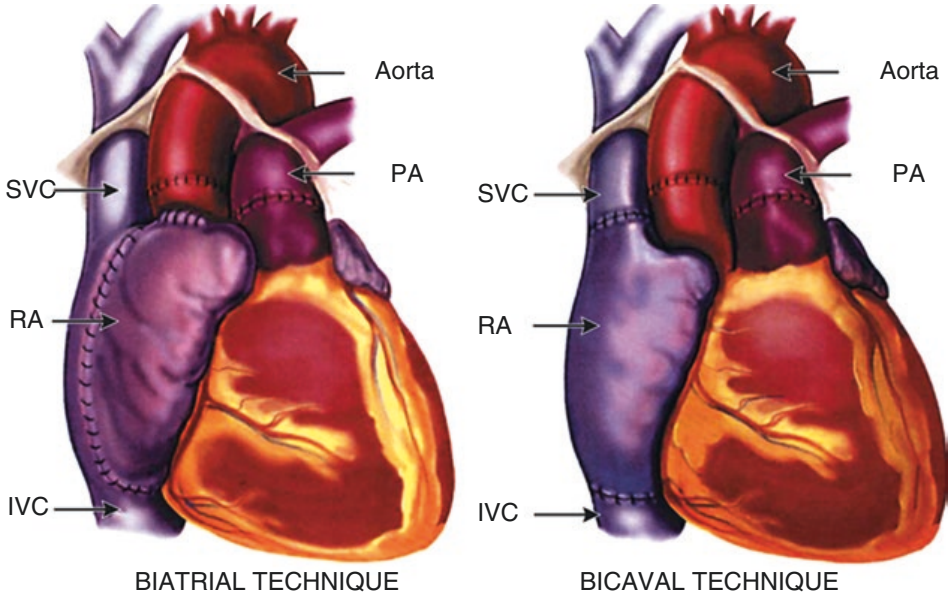

Fig. 7.1 Biatrial compared to bicaval technique for cardiac transplantation (Reused with permission from Chen et al. [15])

trimmed to allow for a sewing cuff just above the true IVC. The left atrial anastomosis is performed first, followed by only the posterior half of the IVC and PA anastomoses to reduce warm ischemic time. The aortic anastomosis is completed and the cross clamp is released as mentioned before. The remaining half of the PA anastomosis is completed. The donor SVC is then opened into the azygos vein to allow a large anastomosis and prevent postoperative stenosis. Care must be taken to keep the orientation of the SVC to avoid any kinking. The anterior anastomosis of the IVC is then completed. Weaning of the cardiopulmonary bypass is initiated and the operation is completed as discussed previously.

Heterotopic Heart Transplantation

Indications

Heterotopic heart transplantation is not widely utilized and is useful only for select circumstances. Accepted indications include [1] irreversible high pulmonary vascular resistance (PVR) in the recipient and [2] severe donor-recipient size mismatch. A potential third indication in the future may include xenotransplant bridging, as immuno-modulation advances may eventually make this a feasible option. As the donor graft serves to augment the native heart, it functions as a de facto bi-ventricular assist device. One advantage of the heterotopic technique is preservation of the native heart as a safety margin in case of graft dysfunction. Recognized complications include a high incidence of ventricular dysrhythmias, anatomic compression by the graft (e.g. right lung), and a high incidence of premature structural deterioration of the donor organ [11–13].

Operative Technique

Cardiopulmonary bypass is established and the right pleura is incised. An opening is made on the donor left atrium just below the interatrial groove, and this is anastomosed to a cuff of recipient right pulmonary vein. A longitudinal incision is then made on the recipient right atrium and extended to the SVC. The donor right atrium and SVC is similarly incised, and a running anastomosis is performed. The donor pulmonary artery and aorta are then anastomosed to their respective structures on the recipient in an end-to-side fashion; these connections often require prosthetic graft augmentation to provide adequate length [11]. An illustration of the technique is provided in Fig. 7.2.

Special Considerations

It is quite common for heart transplant recipients to require redo sternotomy, as many heart failure patients have undergone prior operations such as coronary artery bypass, valve replacement,

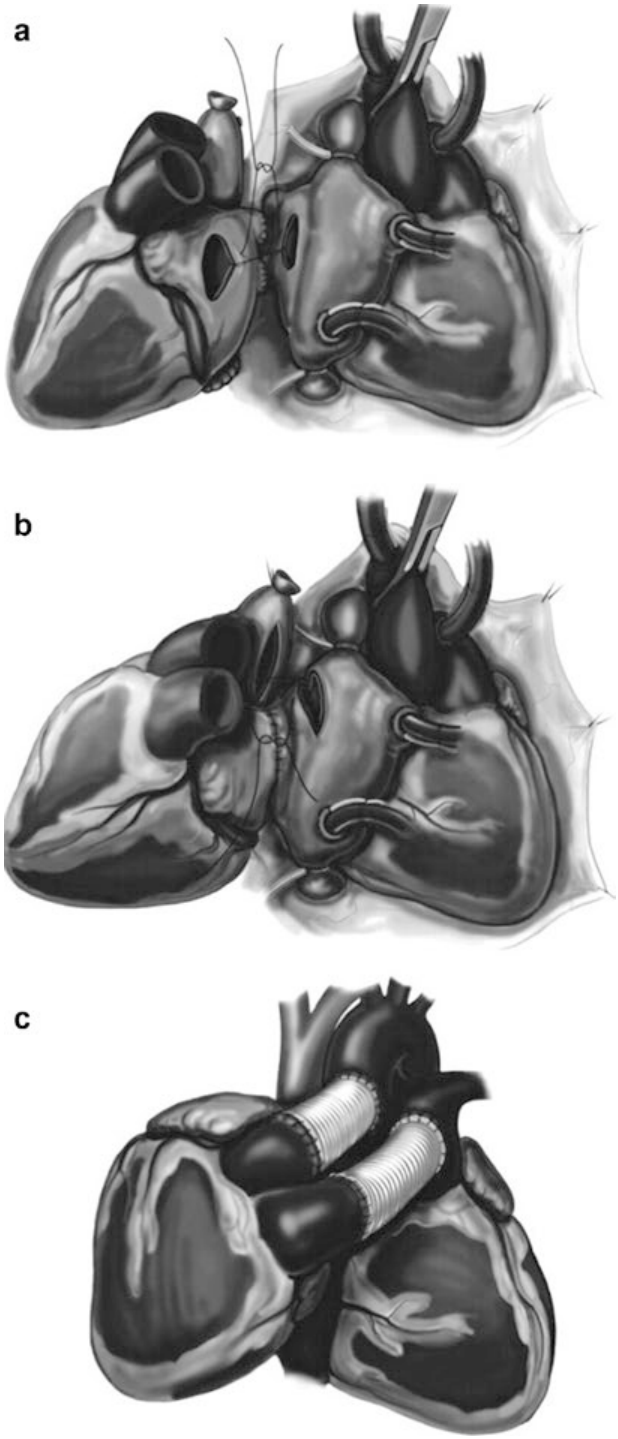

Fig. 7.2 Heterotopic heart transplantation (Reused with permission from Kadner et al. [11])

mechanical circulatory support device implantation, prior heart transplant, or correction of congenital abnormality. Previous thoracic operations can significantly elevate the complexity and hazard of the surgical dissection, and may result in increased use of blood products and operative time. Any patient being considered for heart transplantation via redo sternotomy should have a preoperative CT scan of the chest performed as part of the preoperative workup, in order to better evaluate the intrathoracic anatomy (e.g. course of the inominate vein and proximity of the right ventricle to the sternum). At the time of implant surgery, the operative team must have a clearly defined strategy that should include strong consideration of alternative cannulation options, such as femoral or axillary artery cannulation. The IVC may be cannulated percutaneously via the femoral vein using a guide wire and serial dilators. Utilizing peripheral vascular access can allow for initiation of cardiopulmonary bypass prior to sternotomy.

Durable mechanical circulatory support devices are increasingly utilized as a bridge to transplantation. Such devices are associated with a high degree of mediastinal adhesions and increased risk and difficulty at the time of redo sternotomy. In these instances, it is critical for the operating team to be given sufficient time to prepare the recipient for implant prior to arrival of the donor organ in order to minimize ischemic time injury. When prolonged donor organ ischemic time is encountered, the operative sequence may be altered by performing the aortic anastomosis immediately after the left atrial. This allows for early removal of the aortic cross clamp and organ perfusion. The remaining anastomoses may then be performed with the donor heart beating. When implanting durable mechanical circulatory support devices in potential transplant recipients, it is advisable to 'protect' the mediastinum with adhesion resistant prostheses (e.g. polytetrafluoroethylene membrane) to facilitate safe and efficient re-entry at the time of transplantation [14].

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Physiology of the Transplanted Heart

8

Jon Kobashigawa and Michael Olymbios

Clinical Pearls

- Surgical excision of the heart from the donor results in the immediate denervation of both the sympathetic and parasympathetic nervous fibers.
- The denervated heart is dependent on circulating catecholamines to respond to stress.
- The reliance on circulating catecholamines means that the denervated heart shows a much slower increase in heart rate and a lower peak heart rate in response to exercise.
- To compensate for chronotropic incompetence, the denervated heart must increase stroke volume to increase cardiac output, even during mild exercise.
- Heart transplant recipients have a much lower VO_2 max when compared with age-adjusted, non-transplant cardiac patients.
- Peripheral factors such as damage to the pulmonary capillary bed play significant roles in reducing the exercise tolerance of transplant patients.
- Exercise regimens help improve the exercise capacity of heart transplant recipients by improving peripheral factors and improving the chronotropic response.
- The loss of sensory fibers from the transplanted heart means that ischemia is often silent.
- Beta blockers dramatically decrease the exercise tolerance of heart transplant recipients and should be avoided where possible.
- Atropine and digoxin do not have any effect on the denervated heart and should not be used to treat arrhythmias in heart transplant patients.

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Introduction

The normal heart is innervated by sympathetic and parasympathetic fibers of the autonomic nervous system (ANS). The ANS exerts chronotropic and inotropic control over the heart and

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supplies visceral sensory fibers to the pericardium. Heart transplantation results in denervation of the donor heart by surgical dissection of postganglionic neurons. Within days, cardiac stores of norepinephrine become depleted and autonomic influence over the heart is lost.

The lack of parasympathetic tone means that heart transplant recipients have a higher average resting heart rate of 95 beats per minute (bpm) compared with 66 bpm for non-transplant cardiac patients [1]. Despite significant improvements in exercise tolerance compared with the end-stages of heart failure, patients still show a reduction in maximum achievable exertion when compared with normal individuals of the same age [2]. This is accounted for by the chronotropic incompetence of the denervated heart as well as peripheral factors that will be discussed later. The normal heart will show a rapid acceleration in HR in response to exercise that peaks during exercise and rapidly recovers. The transplanted heart shows a delayed chronotropic response to exercise due to a reliance on circulating catecholamines. Norepinephrine and epinephrine levels are either normal or elevated in the transplant recipient [3]. The lack of nervous supply and reliance on humoral mechanisms causes a shift from predominately type-1 to type-2 beta adrenergic receptors on cardiac myocytes [4].

The Autonomic Nervous System

Functional Anatomy

Cardiovascular regulation by the autonomic nervous system has its origins in the medulla oblongata. The medulla contains two regions, the cardioaccelerator and cardioinhibitor centers that regulate the heart rate (HR). The heart is able to contract independently of extrinsic innervation due to the specialized pacemaker cells found in the sinus node. Sympathetic innervation to the heart is from the cervical ganglia and T1-T4 of the thoracic ganglia of the sympathetic chain. Parasympathetic innervation comes from branches of the vagus nerve [5]. At the base of the heart, autonomic nerves form the cardiac plexus. This plexus contains the postganglionic sympathetic fibers and the preganglionic parasympathetic fibers. The cardiac plexus is found within the adventitia of the great vessels, the aortic arch, anterior to the right pulmonary artery and anterior to the bifurcation of the trachea.

Visceral sensory fibers arise from the phrenic and vagus nerves. The phrenic nerve innervates the fibrous pericardium and the parietal layer of the serous pericardium. The vagus nerve innervates the visceral layer of the serous pericardium.

Parasympathetic Fibers

The vagus nerve (cranial nerve X) contains both motor and sensory fibers. The preganglionic fibers of the parasympathetic nervous system supplying the heart are found within three nuclei (the nucleus ambiguus, the dorsal nucleus and the solitary nucleus). The right and left vagus nerves are contained within the carotid sheath, lateral to the carotid artery. The nerve travels through the lower brain stem and leaves the skull at its base. It follows the path of the carotid in the neck, penetrates the chest and supplies the heart and lungs. The vagus nerve then branches to supply the sinus node and the atrioventricular (AV) node as well as the atria and ventricles directly [5]. As with the majority of the parasympathetic nervous system, the presynaptic neurons synapse at ganglia within the target organ leaving short postsynaptic neurons to supply the organ itself.

Most parasympathetic innervation to the heart is directed at the sinus and AV nodes. Normally the right vagus supplies the sinus node and the left supplies the AV node. However, a normal anatomical variant exists where fibers from the right and left vagus cross over.

Sympathetic Fibers

The preganglionic sympathetic nervous supply to the heart arises in the lateral column of the spinal cord. The cervical ganglia and first four thoracic ganglia of the sympathetic chain supply the postganglionic fibers [5]. Sympathetic stimulation results in an increase in HR, contractility and faster conduction (positive dromotropy).

Cardiac Pacemaker

The cells of the sinus node have no resting membrane potential but instead have what is known as a pacemaker potential [6]. Other cells maintain a

resting potential as a result of potassium ions continuously flowing out of the cell through potassium channels. Pacemaker cells differ by having a membrane that decreases its permeability for potassium ions over time. Additionally, there is a slow influx of sodium ions through specialized channels forming what is known as the "funny" current [6]. These two currents cause the membrane potential to slowly increase until reaching a threshold potential of −40 mV when an action potential is initiated (see Fig. 8.1 for a comparison between the ordinary action potential and the pacemaker potential). Even without nervous stimulation, the sinus node will depolarize at a rate of 100 per minute.

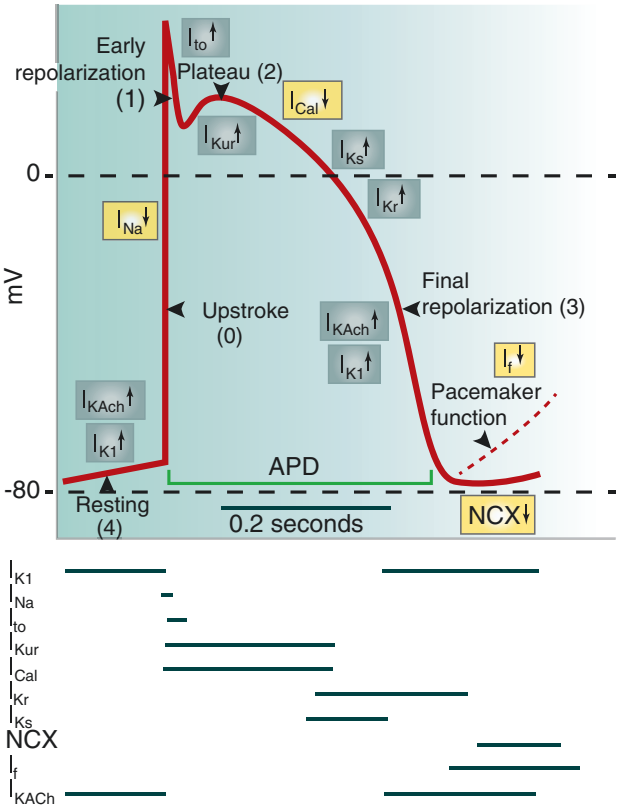

Fig. 8.1 Membrane currents that generate the normal action potential. Resting (4), upstroke (0), early repolarization (1), plateau (2), and final repolarization are the 5 phases of the action potential. A decline of potential at the end of phase 3 in pacemaker cells, such as the sinus node, is shown as a *broken line*. The inward currents, I_{Na}, I_{Ca}, and I_f, are shown in *yellow boxes*; the sodium-calcium exchanger (NCX) is also shown in *yellow*. It is electrogenic and may generate inward or outward current. I_{KAch}, I_{K1}, I_{to}, I_{Kur}, I_{Kr}, and I_{Ks} are shown in *gray boxes*. The action potential duration (APD) is approximately 200 ms (Reused with permission from Grant [84])

Autonomic Physiology

At rest the heart receives autonomic tone from both the sympathetic and parasympathetic nervous systems. However, vagal tone predominates to suppress the resting HR. The preganglionic neurons of both the sympathetic and parasympathetic nervous systems release acetylcholine that binds to nicotinic receptors on the cell bodies of the postganglionic neurons. Postganglionic sympathetic fibers synapsing at the heart release norepinephrine which binds to type-1 beta-adrenergic receptors. Postganglionic parasympathetic fibers of the vagus nerve release acetylcholine to stimulate type-2 muscarinic receptors (M_2) on the heart. Both receptors are G-protein coupled receptors. The type-1 beta receptor is a stimulatory G-protein linked receptor and the type-2 muscarinic receptor is inhibitory. G-protein dissociates upon ligand binding and either stimulates or inhibits adenylyl cyclase. This results in either increased or decreased cAMP production respectively. Increasing cAMP leads to an increase in HR and contractility and vice-versa [7]. Additionally, acetylcholine released from the parasympathetic fibers binds to ligand-gated potassium channels to decrease the rate of depolarization and slow the HR.

Both muscarinic and beta-adrenergic receptors are found on the sinus node, AV node and atria, however, only beta receptors are present on the ventricles. Thus the parasympathetic nervous system has no influence on ventricular contractility.

Homeostasis of the Cardiovascular System

Homeostasis of the cardiovascular system is controlled primarily by the baroreceptor and chemoreceptor pathways. Changes in arterial pressure, O_2 concentration and to a lesser extent CO_2 concentration are detected and result in appropriate autonomic responses to sustain the blood pressure in the short term [8].

Baroreceptor Reflex

A decrease in arterial pressure is detected by baroreceptors in the carotid sinus and aortic arch. They are stretch receptors that inhibit sympathetic stimulation to the heart. Signals are sent via afferent fibers of the vagus and glossopharyn-

geal nerves to the solitary nucleus in the medulla. When blood pressure falls, the baroreceptors detect a decrease in wall tension. The receptors in turn decrease their rate of firing that disinhibits the sympathetic nervous system resulting in an increase in total vascular resistance and HR and contractility [8].

Similar to the baroreceptor reflex is the atrial reflex (also known as the Bainbridge reflex) in which stretch receptors of the atria detect changes in venous return to the heart. An increase in venous return causes an increase in HR through the efferent limb of the reflex to the sinus node. The opposite is also true.

Chemoreceptor Reflex

Chemoreceptors located in the carotid and aortic bodies respond primarily to changes in the partial pressure of oxygen but also monitor the partial pressure of carbon dioxide and pH. Hypoxia, hypercapnia or acidosis will increase the firing rate of chemoreceptors and results in an increase in both the rate and depth of respiration. Sympathetic tone to the heart is then increased through both direct and indirect mechanisms [8]. Chemoreceptors have a direct effect on medullary vasomotor neurons supplying the heart. Indirectly, by increasing the depth of breathing, stretch receptors in the lung result in increased sympathetic stimulation to the heart [8].

Exercise and the Denervated Heart

Exercise tolerance post-transplantation is greatly improved compared with end-stage heart failure but peak oxygen uptake (VO_2 max) in recipients is reported at only 50–70% of age-adjusted expected values [2]. A lower VO_2 max correlates strongly with morbidity and mortality [9]. One of the goals in the long-term management of the HT patient, therefore, is to optimize exercise capacity. This lower observed exercise capacity is not only the result of the denervated heart but also due to peripheral factors. Examples include impairments to vasodilation and a decline in skeletal muscle function. These changes occur during heart failure pre-transplantation and are reversible through exercise although not entirely [10]. At levels of exercise below the maximum, appropriate cardiac outputs are observed in the HT recipient [9]. Ejection fraction and systolic function are normal during exercise. There is diastolic dysfunction that must be compensated for with higher filling pressures. Pulmonary artery wedge pressures of twice the resting value have been demonstrated during maximal exercise in HT patients [11].

Allograft Response to Exercise

Dynamic exercise requires an increase in cardiac output (CO) to meet the increased metabolic demands of skeletal muscle and maintain aerobic respiration. The two components of CO are heart rate and stroke volume (SV). The normal heart responds to exercise predominantly by increasing its HR in response to the neural and hormonal effects on the sinus and AV nodes. A decrease in vagal tone allows the HR to rise to the intrinsic rate of depolarization of the sinus node. A further increase in HR occurs due to sympathetic stimulation. This is augmented by circulating catecholamines. HR promptly drops after the cessation of exercise. During strenuous exercise, SV will also increase in the normal heart. Skeletal muscle vasodilation causes a decrease in peripheral vascular resistance, an increase in venous return and therefore an increase in SV.

In contrast, the denervated heart does increase its HR in response to exercise but more slowly and achieves a lower maximum HR. The increase in HR is in response to circulating catecholamines rather than from the effects of the autonomic nervous system [12]. HR is slower to normalize and actually peaks after exercise stops (Fig. 8.2). The transplanted heart is said to be “preload dependent” since stroke volume relies on venous return [13]. During mild exercise, left ventricular end-diastolic volume and pressure increase. This increase in venous return will further stretch the myocardial fibers leading to greater contractility (Frank-Starling’s mechanism). Over time the donor heart becomes increasingly sensitive to catecholamines [12].

In the normal individual isometric exercise causes muscles to produce metabolites such as lactate that stimulate the autonomic nervous sys-

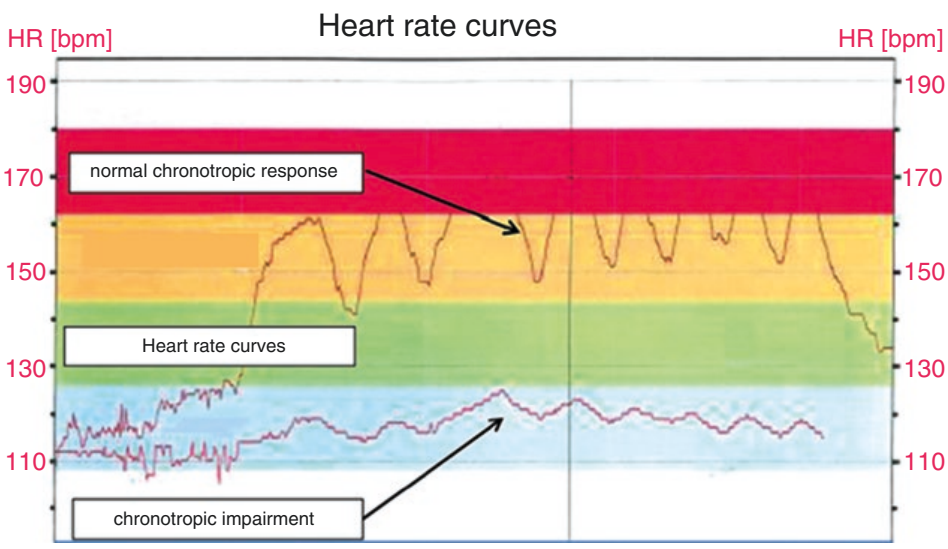

Fig. 8.2 A graphic of comparison between the chronotropic response of the innervated heart versus the denervated heart (Reused with permission from Dall et al. [32])

tem to increase the HR and constrict peripheral arterioles. The arterial blood pressure elevates and CO increases slightly [14]. The transplant patient shows a similar response to isometric exercise with a slight increase in CO and increases in systolic and diastolic arterial pressures [15]. Mechanisms controlling changes to peripheral vascular resistance remain intact. The significant difference is the lack of HR acceleration seen in normal individuals performing isometric exercise [16].

The transplanted heart is unable to reach the CO of the normal heart at rest and during exercise. Transplant patients cannot sustain exercise for as long as control individuals. Oxygen extraction is heightened, reflected in an increased arterio-venous (AV) oxygen gradient. Transplant recipients also undergo more anaerobic respiration when exercising as demonstrated by an increase in lactate concentration [17].

Peripheral Factors Affecting Exercise

Heart failure patients, especially those who ultimately undergo heart transplantation, spend prolonged periods of time in a state of deconditioning due to a decline in exercise capacity, decompensations, hospitalizations and being in a bed-ridden state. The peripheral skeletal muscles decrease in mass and on a microscopic level show fewer mitochondria and a shift towards a predominance of fast-twitch fibers, an increase in glycolytic enzymes and a decrease in oxidative enzymes and creatine kinase. As such, these muscles are preferentially glycolytic and produce more lactate [18]. Although the oxidative capacity of skeletal muscle normalizes after transplantation, the capillary beds do not regrow entirely. These persisting vascular abnormalities contribute to decreased exercise capacity post-transplantation [19].

Pulmonary function declines in severe heart failure. Although there is a marked improvement in pulmonary function tests after transplantation, the lung diffusion of carbon monoxide (DLCO) remains below the predicted value even when there is no underlying lung disease. This is because the pulmonary capillary wedge pressure is elevated in heart failure leading to the capillary endothelium becoming irreversibly damaged. In HT patients who have a DLCO of <50% of predicted, exercise results in respiratory acidosis and hypoxemia [20].

Exercise Protocols for the Heart Transplant Recipient

The chronotropic incompetence seen in HT patients improves after the first year post-transplantation with resting HR decreasing, maximum HR increasing and peak VO_2 increasing even without a prescribed regimen of exercise [21]. However, the benefits of exercise were demonstrated by Kobashigawa et al. in a randomized control trial [22] that has been affirmed by numerous studies since. Increases in VO_2 max after exercise regimens ranged from 13 to

28 mL/kg/min [23–29]. Patients who are motivated and follow a supervised training program show a 50% improvement in VO_2 max compared with recipients who remain sedentary [19].

Previously it was thought that the loss of chronotropy due to denervation meant that exercise regimens needed to be limited to moderate training protocols. It was also thought that central factors influenced exercise capacity more than others. Evidence now suggests that peripheral factors have a larger impact on the decreased exercise capacity post-transplantation [30]. It has also been demonstrated that chronotropy can normalize both early and late post-transplantation [31, 32].

High Intensity Interval Training

With an improved understanding of the physiology of the transplanted heart and the impact of peripheral factors on exercise tolerance in the heart transplant recipient, the effectiveness of high intensity interval training (HIIT) has been demonstrated [27–29, 32]. HIIT has long been a therapeutic tool in the long-term management of cardiovascular disease and heart failure. These patients have shown a marked improvement in exercise tolerance with an increase in VO_2 max of 46% and even a reversal of ventricular structural changes after 12 weeks [33].

HIIT requires the patient to engage in aerobic exercise until a VO_2 of 85–95% of max or a HR of 90–95% of predicted max is achieved (see Fig. 8.3 for a comparison between HIIT and continued moderate training). This is followed by a period of rest until HR falls to 60–70% of max. The cycle is then repeated four times [34]. The transplant patient must augment this regimen with both a cool-down and a warm-up period due to chronotropic incompetence and a reliance on circulating catecholamines to increase CO as discussed earlier. Compliance is an issue when prescribing exercise protocols to patients especially when psychological co-morbidities such as depression and anxiety exist.

HIIT improves VO_2 max and more so than moderate training programs. Some patients are able to attain a VO_2 max of 80–89% of predicted [29]. Systolic systemic blood pressure falls by an average of 3 mmHg. Resting HR decreases slightly with HIIT but no change is seen in patients on protocols of moderate exercise [32]. HR recovery time improves after both moderate exercise protocols and HIIT with HIIT proving slightly more beneficial. This is important because HR recovery time strongly correlates with mortality [35, 83]. Peripheral factors also show an improvement with skeletal muscle mass increasing and an increase in mitochondrial density [29]. Coronary allograft vasculopathy (CAV) remains a significant cause of mortality in HT patients. HIIT may reduce the progression of CAV, although the evidence is limited to animal models [36] and a single study in humans [37].

Improvements in VO_2 max are lost after 5 months of stopping exercise regimens. Patients also show more signs of depression and anxiety, highlighting the importance of continuing exercise on a life-long basis [35].

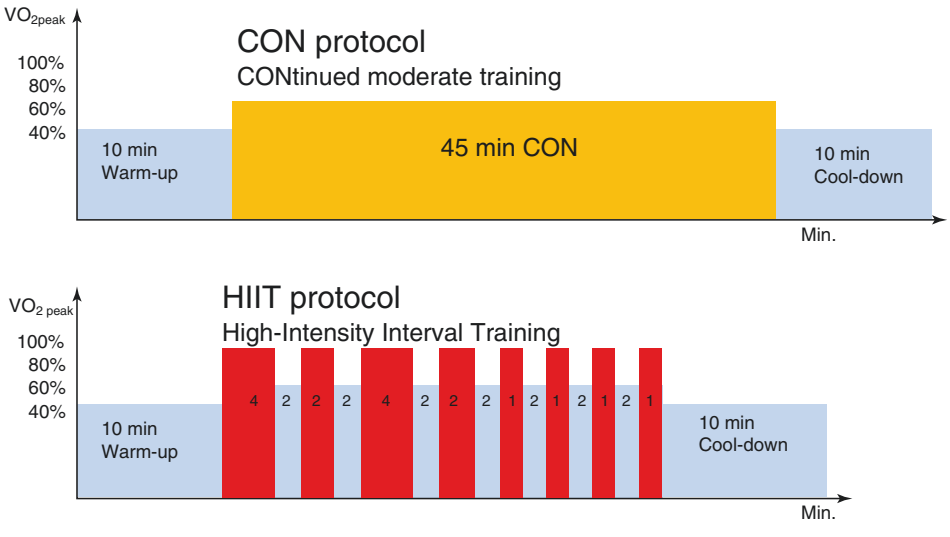

Fig. 8.3 The HIIT training protocol (10-min warm-up, 16 min of HIIT training [>80% of VO_2peak] + 14 min of recovery and 10-min cool-down) and the CON training protocol (10-min warm-up, 45 min of CON training [~60–70% of VO_2peak] and 10-min cool-down) (Reused with permission from Dall et al. [35])

Reinnervation

Reinnervation of the transplanted heart is a controversial topic but there is evidence that both sympathetic and parasympathetic reinnervation can occur, although it is highly variable between patients and even heterogeneous within the same patient [38]. Bengel et al. [39] in a longitudinal study, showed that complete reinnervation could take 15 years from the time of transplantation. It is uncertain whether exercise improves autonomic control or whether it occurs independently over time [24, 40]. Reinnervation is significant because resumption of chronotropic control is associated with better exercise capacity [41]. Reinnervation also allows for pain sensation such as angina [42] and improves regulation of blood flow to the myocardium [43].

Determinants of Reinnervation

The heterogeneous pattern of reinnervation [39] and regional differences in its prevalence [44] suggest that certain factors may influence whether or not reinnervation occurs. It is likely that donor age plays a role. This is possibly due to a reduction in neurotrophins. Neurotrophins are required for peripheral nerve growth and decline with age [45, 46]. Peripheral neuron axonal re-growth occurs along arteries [82]. Extensive scarring caused by increased cross-clamp times, and aortic complications negatively impact the reinnervation process. Pre-transplantation cardiac pathology is another factor. Patients who received a transplant for dilated cardiomyopathy were more likely to undergo reinnervation than those who had ischemic heart disease (IHD) [47]. This is possibly due to the sclerotic aorta seen in IHD being less amenable to nerve regrowth. Additionally, time spent on cardiopulmonary bypass correlates with the time taken for reinnervation to occur [40].

Quantifying Reinnervation

A physiological marker of autonomic innervation is heart rate variability. Due to simultaneous and varying degrees of input from the parasympathetic and sympathetic nervous systems, the HR subtly changes from contraction to contraction. Power spectrum analysis assesses heart rate variability and is non-invasive [48]. Another technique frequently employed is cardiac scintigraphy with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG). ^{123}I-MIBG is radioactive, behaves like norepinephrine and is taken up by myocardial sympathetic nerve fibers. Therefore, it is assumed that positive uptake is a sign of reinnervation [49]. Alternatively, cardiac norepinephrine release can be quantified directly in response to tyramine administration but this is an invasive method [50]. Immunohistochemical studies are also used to show histological evidence of new nerves extending through sutures lines [51] (see Fig. 8.4). Positron emission tomography (PET) is a powerful but expensive method for visualizing the norepinephrine analogue 11C-hydroxyephedrine which is taken up by cardiac neurons [39]. Again, it is assumed that uptake reflects reinnervation.

There is evidence that sympathetic reinnervation occurs in up to 40% of patients 1 year post-transplantation [4]. Denervation eliminates presynaptic sympathetic fibers and causes myocardial stores of norepinephrine to deplete [52, 53]. The reduced exercise capacity of the transplant recipient is a result of inotropic impairment as well as chronotropic incompetence.

Sympathetic reinnervation improves the chronotropic responsiveness of the heart and restores the ventricular inotropic response to exercise. The maximal HR increases and the VO_2 max also

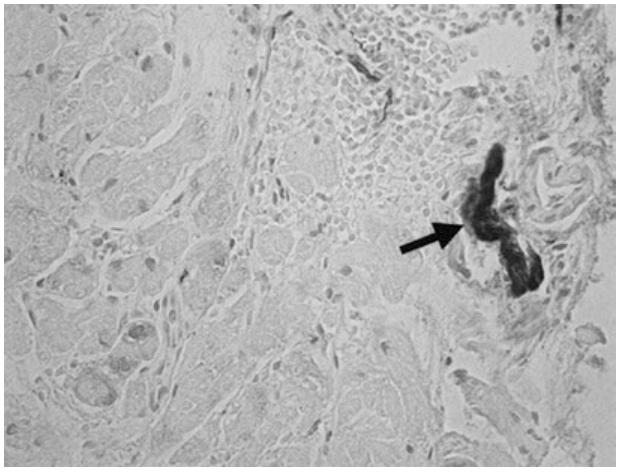

Fig. 8.4 Immunohistochemical study of an endomyocardial biopsy specimen using anti-S100 antibody (×400) shows clustered nerve fibers (*arrow*) (Reused with permission from Gallego-Page et al. [85])

rises. Patients with sympathetic reinnervation show an improved tolerance for exercise. In particular, patients with sinus node functional improvement show the greatest increase in exercise capacity. Attaining a maximal inotropic response requires local norepinephrine as well as catecholamines released by the adrenal medulla. Reinnervation results in the reappearance of presynaptic terminals and restoration of the myocardial norepinephrine stores [4]. Consequently, the inotropic response improves profoundly [54].

Chest pain from myocardial ischemia is transmitted through unmyelinated afferent fibers of the sympathetic nervous system. HT patients who undergo sympathetic reinnervation are able to experience during ischemic episodes. Those who remain denervated suffer silent ischemia [42].

Another role of the sympathetic nervous system is to regulate coronary blood flow. Even within the same patient there are prominent differences in myocardial blood flow depending on the extent of reinnervation. Areas with sympathetic reinnervation have increased blood flow [43].

Parasympathetic Reinnervation

The functional significance of parasympathetic reinnervation is unknown. The extent to which it occurs is contentious and not well defined due to difficulties in measuring parasympathetic activity in the heart. Early studies found that histological evidence of parasympathetic reinnervation only appeared 10 years after transplantation [55]. Physiological studies similarly only demonstrated parasympathetic tone after 8 years [56, 57]. These finding may be the result of surgical technique. The biatrial method was the standard until the mid-to-late 1990s until the bicaval method predominated. Parasympathetic reinnervation has been demonstrated in patients who underwent a bicaval anastomosis within a year of transplantation. This could be because the bicaval technique results in both the parasympathetic and sympathetic fibers of the recipient being dissected whereas the in the biatral technique approximately half of the sympathetic fibers are cut and the parasympathetic fibers of the recipient are left intact. Surgical dissection of nerves may stimulate axonal regrowth [58].

Heart transplant patients have markedly delayed HR recovery times. In healthy subjects HR recovery is associated with parasympathetic tone [59]. In addition to being lower than predicted, peak HR is achieved after the cessation of exercise, a feature unique to heart transplant patients. This is due to a lack of vagal innervation required to decelerate the HR and the time taken to metabolize circulating catecholamines [40]. Parasympathetic reinnervation might occur as early as 6 months post-transplantation [40] and may result in improved HR recovery times and a lower resting HR [29].

Electrophysiology of the Transplanted Heart

The transplanted heart invariably has a different electrophysiology from the normal heart. Surgical technique, denervation, ischemia, fibrosis, CAV and reinnervation all play a role in altering the conduction system, sometimes leading to clinically significant arrhythmias [60].

There is a wide range for the incidence of atrial arrhythmias post-transplantation in the literature. Atrial fibrillation (AF) is reported at 0.3–24% after HT [61–64]. Larger studies tend to report lower numbers [61, 62, 64]. Early AF is rarer after heart transplantation than after other forms of cardiac surgery such as coronary artery bypass grafting or valve replacement. This may be because the donor heart is usually healthier than the hearts of other cardiac patients.

Whether rejection causes AF or atrial flutter is equivocal. There may be an association between sustained AF or atrial flutter and episodes of rejection [61, 63–65]. Therefore, a finding of AF or atrial flutter should be investigated to exclude rejection [65]. Repeated episodes of rejection scar the atria which can lead to atrial flutter [61]. Atrial flutter is more common than AF in HT patients and usually occurs later after transplantation [63, 65]. Donor age and use of the biatrial method are risk factors [66]. Patients who develop atrial flutter are at increased risk of developing LV dysfunction and early death [61]. Once primary etiologies have been excluded, sustained atrial flutter can be treated with radiofrequency ablation.

Denervation and reinnervation impact the electrophysiology of the transplanted heart. As mentioned earlier, denervation results in a decrease in HR variability and an increase in resting HR. The corrected QT interval correlates with sympathetic reinnervation. Heterogeneous reinnervation increases the risk of ventricular arrhythmias [67].

After transplantation it is common for patients to become bradycardic as the result of sinus node ischemia [68]. A subset of these patients develops a form of sick sinus syndrome known as bradycardia-tachycardia syndrome [68]. Caution should be exercised in these patients if treating AF as some therapeutic agents can worsen bradycardia. Complete AV block manifests later on after transplantation and is probably due to progressive ischemic injury to the conduction system from CAV [69]. Approximately 10% of HT patients with bradycardia will need a permanent pacemaker [70]. This number may decline in the future because biatrial anastomosis is a major risk factor for needing a permanent pacemaker. Interestingly, needing a permanent pacemaker does not impact survival [71].

Ventricular arrhythmias are relatively common immediately following transplantation. Later on, ventricular tachycardia (VT) could be the result of CAV and should be followed up with coronary angiography and an endomyocardial biopsy [72]. The placement of an ICD may be required [73].

Improvements in the survival of HT recipients mean that the electrophysiology of the transplanted heart and resultant arrhythmias are important causes of morbidity and mortality.

Pharmacology of the Transplanted Heart

The donor heart is distinct from the normal heart in its response to certain drugs. As discussed earlier, denervation means that normal autonomic regulation during exertion can be diminished or absent. This creates a dependence on circulating catecholamines to increase CO even with minimal stress. Cardiac myocytes shift from a predominance of type-1 to type-2 beta-adrenergic receptors. The most profound differences in the pharmacokinetics of the transplanted heart are unsurprisingly found with beta blockers and drugs targeting the autonomic nervous system.

Beta Blockers

Beta blockers are sometimes used post-transplantation to treat hypertension that is refractory to other agents [74]. The innervated heart can respond to mild and moderate exertion with little or no increase in SV. The denervated heart, however, increases CO principally via the Frank-Starling mechanism, increasing SV as a result of increased venous return, even with mild exercise. Beta blockade in HT patients has the unsurprising effect of reducing exercise capacity by 34% [75]. When compared with a control group, ejection fraction and cardiac index were significantly lower in HT patients, highlighting the detrimental impact of beta-blockers on ventricular function [76]. However, the use of beta blockers later after transplantation (more than 6 months) appears to be tolerated. In addition, using beta blockers for atrial arrhythmias is acceptable. The reduction in CO is not too profound in most patients.

Beta Adrenergic Receptor Agonists

Beta receptor agonists are positive inotropes used to treat ventricular dysfunction. They have a positive chronotropic effect by directly stimulating type-1 beta receptors on the heart and indirectly by inducing a reflex tachycardia in response to vasodilation from type-2 beta receptor stimulation [77]. The donor heart shows an increased sensitivity to beta agonists with HR increasing more than those of controls [78]. Despite this increase in responsiveness there is no upregulation or increased sensitivity of beta receptors on the donor heart [79]. The supersensitivity is because of presynaptic nerve terminals at the sinus node not clearing beta agonists [80].

Atropine

Atropine is an anticholinergic drug normally used to treat bradyarrhythmias. The mechanism of action is via the parasympathetic nervous system,

specifically by inhibition of the vagus nerve. As such, even though bradycardia and heart block are common in the immediate postoperative period, atropine is not effective on the denervated heart and should not be used in heart transplant patients.

Adenosine

Adenosine is a purine nucleoside that binds to type-1 adenosine (A_1) receptors found on the sinus and AV nodes. Receptor binding inhibits the "funny" current, slowing the rate of depolarization of pacemaker cells thereby slowing the HR. Adenosine is used in the treatment of supraventricular tachycardia. As with beta-receptor agonists, there is increased sensitivity of the donor heart to adenosine. Both sinus and AV nodes have a three-fold increase in duration of action compared with normal hearts [81]. Therefore, the dose must be significantly reduced when administering adenosine to HT recipients.

Digoxin

Digoxin is a second-line agent for the treatment of atrial fibrillation and atrial flutter. The chronotropic effects of digoxin are mediated through the parasympathetic nervous system: vagal activity is increased, thereby increasing the duration of the action potential of pacemaker cells in the AV node. This in turn decreases the heart rate. The direct effect of digoxin on the heart is only inotropic, rendering the drug ineffective for treating atrial fibrillation or atrial flutter in the denervated heart.

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9 Immediate Post-operative Management After Heart Transplantation

Jon Kobashigawa and Minh Luu

Clinical Pearls

- Intraoperative transesophageal echocardiography to assess systolic function is recommended; invasive monitoring of arterial pressure, central venous pressure, pulmonary artery pressure, wedge pressure, cardiac output and oxygen saturation should also be performed immediately following transplantation.
- Continuous inotropic infusions of isoproterenol, dobutamine, dopamine and/or milrinone are warranted for early ventricular dysfunction. Alpha-adrenergic agonists (norepinephrine, epinephrine) may also be used to treat persistent systemic hypotension.
- Mechanical circulatory support including intra-aortic balloon pump or temporary assist device should be considered if there is failure to wean from cardiopulmonary bypass or if there is persistent hemodynamic instability despite multiple high-dose inotrope administration.
- Extra-corporal membrane oxygenation (ECMO) is an option in severe graft dysfunction with cardiogenic shock unresponsive to pharmacologic treatment.
- Causes of early hemodynamic instability include hyperacute rejection, cardiac tamponade, primary graft dysfunction, and elevated pulmonary vascular resistance (causing right ventricular dysfunction).
- Right ventricular dysfunction may be additionally treated with pulmonary vasodilators such as inhaled nitric oxide, sildenafil, and prostacyclin analogues to lower pulmonary vascular resistance.
- Sinus node dysfunction is common post-transplant, resulting in post-transplantation bradycardia that may be treated with chronotropic agents or temporary pacing; rarely, permanent pacing may be required.
- Tachyarrhythmias should prompt investigation for rejection and may be treated with rate controlling agents such as diltiazem or amiodarone; digoxin is not effective for rate control of atrial fibrillation in the denervated heart as requires an intact vagus nerve to lower heart rate.

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- Renal dysfunction is common in the 24–48 h post-transplant; therefore continuous assessment of urine output in the early post-operative period is crucial.
- Immunosuppression and anti-microbial prophylaxis should be initiated peri-
- operatively.
- Early ambulation and physical therapy is important, with subsequent cardiac rehabilitation demonstrated to be beneficial.
- Prior to discharge patients should be educated regarding their immunosuppression regimen and the symptoms and signs of potential rejection episodes.

Introduction

Ultimately, the purpose of cardiac transplantation is to provide a means to high quality long-term survival in patients with end-stage heart disease. The immediate post-operative period is crucial in determining the probability of this outcome. Heart transplant clinicians should be familiar with and be comfortable treating multiple simultaneous medical and transplant-specific issues in patients that have often been critically ill prior to transplant. This chapter aims to provide an overview of the post-transplant hospitalization period, including perioperative management strategies, frequently encountered early morbidities, and short-term outcomes. Although induction and immunosuppression agents are discussed in depth in Chap. 9, their initiation, which is crucial in the perioperative period to prevent graft rejection, will also be covered briefly.

Hemodynamics

Most important in determining post-transplant survival is the ability of the newly transplanted heart to generate sufficient cardiac output in the early hours and days following transplantation. As initial donor heart dysfunction is relatively common, with reports of occurrence in up to 50% of patients [1], adequate hemodynamic monitoring of the post-transplant patient is crucial. The latest ISHLT guidelines for post-heart transplant monitoring are listed in Table 9.1. Assessment and management of cardiac function starts in the operating room during the final phases of surgery and the discontinuation of cardiopulmonary bypass, prior to transfer to the intensive care unit (ICU).

Table 9.1 ISHLT guidelines for monitoring post-heart transplant

Post-operative 12-lead ECG	Invasive arterial pressure monitoring
Right atrial or central venous pressure monitoring	Left atrial or pulmonary artery wedge pressure monitoring
Intermittent measures of cardiac output	Arterial oxygen saturation monitoring
Intra-operative transesophageal echocardiogram	Continuous assessment of urinary output

Monitoring

Systolic function should be directly assessed intra-operatively with trans-esophageal echocardiography, while invasive arterial pressure monitoring should subsequently be established [2]. Right atrial or central venous pressure should be monitored, as well as measurement of left atrial or pulmonary artery wedge pressures. In particular, one should pay attention to the relationship between right and left atrial pressures, in case of isolated right or left ventricular dysfunction. In recipients with a prior history of pulmonary hypertension, particular attention should also be given to pulmonary artery pressure as high pulmonary artery pressures may lead to right ventricular failure. Intermittent measurement of cardiac output is considered prudent, along with continuous measurement of arterial oxygen saturation [2].

Inotropic and Vasoactive Support for Ventricular Dysfunction

Hemodynamic instability early post-transplant is relatively common and may be secondary to graft reperfusion injury, post-bypass inflammation,

hyperacute rejection, cardiac tamponade, primary graft dysfunction, elevated pulmonary vascular resistance or labile fluid status. As such, inotropic and vasoactive pharmacologic support is routinely necessary to augment the marginal cardiac output mediated by ventricular dysfunction and associated systemic hypotension. Furthermore, the catecholamine stores of the newly transplanted heart are often depleted, requiring exogenous supplementation [3]. An ISHLT-recommended list of acceptable pharmacologic supportive agents with appropriate dosing recommendations is displayed in Table 9.2; their properties are displayed in Table 9.3.

Continuous infusions of isoproterenol, dobutamine, dopamine and/or milrinone all increase left ventricular contractility as well as right ventricular function if applicable, without the negative

Table 9.2 Recommended dosing for pharmacologic agents used for inotropic/vasoactive support post-transplant

Drug	Indication	Suggested dosage
Dopamine	Ventricular dysfunction	IV 1–10 μg/kg/min
Dobutamine	Ventricular dysfunction	IV 1–10 μg/kg/min
Milrinone	Ventricular dysfunction	IV 0.25–0.75 μg/kg/min
Isoproterenol	Ventricular dysfunction/post-transplant bradycardia	IV 1–10 μg/kg/min
Epinephrine	Low mean arterial pressure	IV 0.01–0.1 μg/kg/min
Norepinephrine	Low mean arterial pressure	IV 0.01–0.1 μg/kg/min
Phenylephrine	Low mean arterial pressure	0.1–1 μg/kg/min
Vasopressin	Vasodilatory shock/low mean arterial pressure	IV 0.03–0.1 U/min
Methylene blue	Vasodilatory shock/low mean arterial pressure	IV 1.5–2 mg/kg over 15–20 min, then continuous infusion of 0.25–2 mg/kg/h
Enoximone	Right ventricular dysfunction	Loading dose of 0.5–1 mg/kg over 30 min, then continuous infusion of 5–20 μg/kg/min
Nitroglycerin	Pulmonary vascular hypertension	0.5–2 μg/kg/min
Sodium nitroprusside	Pulmonary vascular hypertension	0.3–10 μg/kg/min
Alprostadil	Pulmonary vascular hypertension	0.01–0.1 μg/kg/min
Epoprostenol	Pulmonary vascular hypertension	2–8 ng/kg/min
Inhaled Iloprost	Pulmonary vascular hypertension	2.5 μg initially, increasing to 5 μg as needed, 6–9 times/day
Inhaled Nitric Oxide	Pulmonary vascular hypertension	20–60 parts per million, monitor methemoglobin levels and adjust dose if levels exceed 4 mg/dL
Sildenafil	Pulmonary vascular hypertension	2.5–10 mg, IV bolus three times a day.

Abbreviations: *IV* intravenous, *min* minute, *μg* micrograms, *ng* nanograms, *kg* kilograms, *mg* milligrams, *dL* deciliters

Table 9.3 Properties of intravenous vasoactive drugs used after heart transplantation

	Peripheral vasoconstriction	Cardiac contractility	Peripheral vasodilation	Chronotropic effect	Arrhythmia risk
Isoproterenol	0	++++	+++	++++	++++
Dobutamine	0	+++	++	+	+
Dopamine	++	+++	+	+	+
Epinephrine	+++	++++	+	++	+++
Milrinone/enoximone	0	+++	+	++	++
Norepinephrine	++++	+++	0	+	+
Phenylephrine	++++	0	0	0	0
Vasopressin	++++	0	0	0	0

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vasoconstrictive effects of alpha-adrenergic agonists such as norepinephrine and epinephrine. The ISHLT recommends regimens including isoproterenol, dobutamine with dopamine, isoproterenol with dopamine, or milrinone alone, but this varies by center [2].

However, occasionally there may be incidences of low systemic vascular resistance where mean arterial pressures remain low following cardiopulmonary bypass. In this situation, continuous infusion of alpha-adrenergic agonists including phenylephrine, norepinephrine and/or epinephrine may be used to maintain adequate mean arterial pressure. Low dose vasopressin or methylene blue may also be used to treat cases of vasodilatory shock, where alpha-agonists have been ineffective in countering low systemic vascular resistance [2].

In cases where hemodynamic instability is profound, with persistently poor ventricular function and low systemic vascular resistance despite maximal inotrope/vasoactive agent use, underlying causes such as cardiac tamponade or hyperacute rejection should be considered. Direct surgical exploration should be used to check for tamponade, while hyperacute rejection should be treated aggressively (see below). Nevertheless, if pharmacologic treatment alone is insufficient to support graft function, mechanical circulatory support (MCS) is required [2].

Mechanical Circulatory Support for Ventricular Dysfunction

According to the ISHLT guidelines [2], MCS should be considered as early as during the operation, prior to bypass; if there is failure to wean from cardiopulmonary bypass (CPB) or there is other evidence of heart allograft failure such as the requirement for multiple high-dose inotropic agents to allow separation from CPB, then MCS should be initiated. Subsequently, MCS should continue to be considered if there is persistent hemodynamic instability with decreased cardiac index and falling myocardial oxygen consumption that is resistant to resuscitation.

There are a variety of MCS devices that may be used in such a situation: the ISHLT recommends that an intra-aortic balloon pump (IABP, covered in detail in Chap. 2) is attempted first in cases of LV failure prior to other forms of MCS being attempted. The IABP is often effective in establishing sufficient pulsatility to improve coronary perfusion and cardiac performance prior to discontinuation of bypass. However, small temporary ventricular assist devices such as the Levitronix Centrimag may also provide adequate support for RV, LV or biventricular failure, and are easily implanted and explanted [2].

Extra-corporeal membrane oxygenation (ECMO, covered in detail in Chap. 2) is an option for patients suffering from severe graft dysfunction and/or cardiogenic shock unresponsive to pharmacologic agents and IABP, and where there may not be time to implant a temporary VAD. For pediatric patients, it is recommended by the ISHLT as the first-line treatment for primary graft dysfunction [2]. For adults, the threshold of graft dysfunction for ECMO initiation post-transplant varies by center. Factors such as risk of infection, immobility and the need for anti-coagulation should be considered [2].There is increasing evidence that ECMO can be used successfully as salvage therapy post-transplant with acceptable survival [4].

Treating Specific Causes or Features of Early Hemodynamic Instability

Hyperacute Rejection

Hyperacute rejection, though now rare, is mediated by preformed antibodies to the allograft in the recipient. It typically presents following surgical engraftment and restoration of native circulation as an almost immediate, aggressive and potentially lethal immune attack on the organ mediated by preformed antibodies to predominantly HLA antigens. This phenomenon is covered in more detail in Chap. 12. The development of the modern prospective cytotoxic crossmatch, and subsequently the virtual cross-match (mentioned in Chap. 6) has greatly reduced the occurrence of this feared complication.

Treatment for hyperacute rejection should be initiated as soon as diagnosis is made, preferably when the recipient is still in the operating room [2]. In addition to aggressive inotropic and mechanical support for the ailing graft if necessary, aggressive treatment consisting of high dose intravenous corticosteroids, plasmapheresis, intravenous immunoglobulin, anti-thymocytye globulin as well as immediate initiation of immunosuppression maintenance therapy (calcineurin inhibitor, anti-proliferative) should also be administered. The role of complement blockade in hyperacute rejection has not yet been established.

Cardiac Tamponade

The sudden appearance of right or left ventricular dysfunction during the first few days post-transplant may indicate the accumulation of blood or other fluid in the mediastinum. Cardiac tamponade should be excluded as a possible cause by direct surgical exploration in the event of persistent hemodynamic instability, and if present, evacuated appropriately.

Primary Graft Dysfunction

Primary Graft Dysfunction is defined as left, right or biventricular dysfunction developed within 24 h after completion of cardiac surgery with no identifiable etiology. It is the most frequent cause of death in the first 30 days after transplant, occurring on average in 7% of patients [1]. The cause is thought to be multifactorial, and has been speculated to include trauma from brain death in the donor, insufficient preservation, hypothermic ischemia during transport, reperfusion injury and adverse systemic factors in the recipient such as persistent hypotension [1]. Until recently, there was no official definition for this phenomenon; however, a consensus conference in 2014 led to universal parameters for PGD with official classifications of mild, moderate and severe left ventricular PGD, as well as right ventricular PGD (see Table 9.4.). Classification is determined by the level of pharmacologic or mechanical support required in the patient. The severe category requires the presence of circulatory support such as ECMO or other mechanical assist devices. Recent data demonstrate 80% survival at 30 days among patients requiring ECMO, compared to previous rates of 50% [1]. It is hoped that a universal definition will enable more consistent recognition of this phenomenon and that treatment modalities for PGD will be more comparable. In turn, this should lead to better understanding of PGD and prevention/minimization of its adverse outcomes.

Table 9.4 Classification of primary graft dysfunction

PGD-Left ventricle (PGD-LV):
(a) Mild PGD – Left ventricle (Mild PGD-LV): One of the following criteria must be met:
(i) LVEF≤40% by echocardiography
or
(ii) Hemodynamics with RA >15, PCW >20, CI <2.0 (lasting more than 1 h) requiring low dose inotropes
(b) Moderate PGD – Left ventricle (Moderate PGD-LV): Must meet one criterion from Section I AND another criterion from Section II below:
I. One criterion from the following:
(i) LVEF ≤40%
or
(ii) Hemodynamic compromise with RA >15, PCW >20, CI <2.0 , hypotension with MAP < 70 mmHg (lasting more than 1 h)
II. One criterion from the following:
(i) High dose inotropes—Inotrope score ≥10*
*Inotrope score: dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) [66]
Each drug dosed in mcg/kg/min
or
(ii) Newly placed IABP (regardless of inotropes)
(c) Severe PGD – Left ventricle (Severe PGD-LV)
(i) Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD or percutaneous LVAD. Excludes requirement for IABP.
PGD- Right ventricle (PGD-RV)
Diagnosis requires both (i and ii) of the following criteria to be met:
(i) Hemodynamics with RA >15, PCWP <15, CI <2
(ii) Transpulmonary gradient (TPG) ≤15 and/or pulmonary artery systolic pressure (PAS) <50 mmHg
or
(iii) Need for RVAD

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Pulmonary Vascular Resistance and Associated Right Ventricular Dysfunction

Elevated recipient pre-transplant pulmonary vascular resistance (PVR) is known to be a significant risk factor for early post-transplant right ventricular dysfunction and subsequent mortality [2, 5, 6]. Relevant literature demonstrates an RV failure risk up to 75% with a 15% mortality risk among patients with pre-transplant PVRi (indexed to body surface area) >6 Wood units × m^2. In contrast, patients without increased pre-transplant PVR only demonstrate a 20% risk of RV failure [7, 8].

The mechanism of RV failure in the immediate post-transplant period is thought to be multifactorial. The donor right ventricle is particularly vulnerable to periprocedural myocardial strain, ischemia, cardioplegia, and surgical trauma. When exposed to elevated recipient PVR, factoring in complications from transitional pulmonary vascular hyper-reactivity resulting from cardiopulmonary bypass [9], the sudden and dramatic increase in PVR can cause rapid and potentially irreversible RV failure. Such a situation might also be further exacerbated by a donor heart that is too small for a larger recipient.

Thus, in all patients, particular attention should be given to continuous monitoring of the post-operative PA pressures. An invasive pulmonary arterial line, as per ISHLT recommendations [2], permits continuous post-operative pulmonary arterial pressure monitoring and facilitates treatment when elevated to prevent subsequent RV myocardial strain-related failure. The consensus criteria for the diagnosis of right ventricular primary graft dysfunction (RV-PGD) are specified in Table 9.4. [1].

The ISHLT algorithm for treatment of acute right ventricular dysfunction post-transplant is summarized in Fig. 9.1 [2]. Broadly speaking,

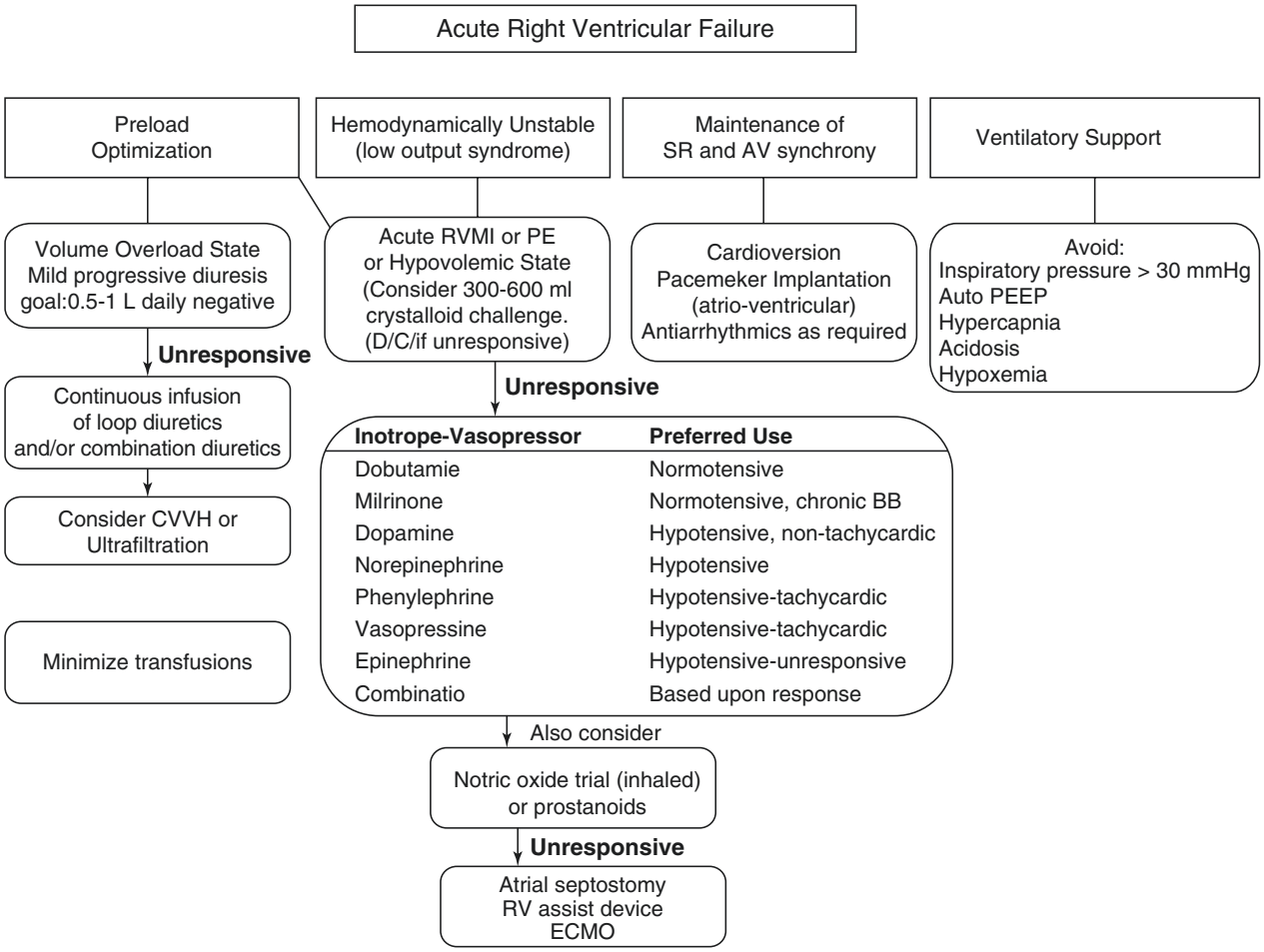

Fig. 9.1 ISHLT algorithm for management of acute right ventricular dysfunction post-transplant. *Abbreviations*: *AV* atrioventricular, *CVVH* continuous venovenous hemofiltration, *MI* myocardial infarction, *PE* pulmonary embolism, *PEEP* positive end-expiratory pressure, *SR* sinus rhythm (Reused with permission from: Constanzo et al. [2])

management can be approached on four fronts: preload optimization with CVP maintained at 5–12 mmHg (diuresis as appropriate to address volume overload, with continuous venous hemofiltration or ultrafiltration if necessary), maintenance of sinus rhythm and atrio-ventricular synchrony (using cardioversion if necessary), ventilatory support (to avoid hypercapnia and hypoxia, targeting 25–35 mm Hg PCO_2 and 95% O_2 saturation), and appropriate pharmacologic and/or mechanical support to stabilize hemodynamic function. After stabilization of graft function, the aim is then to wean the patient from ventilatory and pharmacologic therapy as soon as possible.

The basis of pharmacologic support for right ventricular dysfunction is exactly the same as that for general (LV and/or RV) dysfunction; inotropic agents such as isoproterenol, milrinone, enoximone, dobutamine and epinephrine [2]. However, to specifically target pulmonary vascular hypertension, systemic vasodilators with pulmonary vasodilating properties have also been demonstrated to be useful in this setting; such agents include nitroglycerine and sodium nitroprusside, which may be used in the absence of systemic hypotension (see Table 9.2 for dosing recommendations). In recent years, the use of selective pulmonary vasodilators to reduce PVR and hence treat perioperative RV dysfunction has become more popular. At some institutions, they are used as a first-line treatment and may be administered perioperatively. Examples of selective vasodilators include prostaglandin E1 analog alprostadil, the prostaglandin I2 derivatives epoprostenol or iloprost, inhaled nitric oxide, and sildenafil (see Table 9.2). All of the aforementioned agents have proven effective at decreasing PVR and improving pulmonary artery pressures in small series of adult post-transplant recipients [10–14]. While nitric oxide exerts perhaps the most specific and pronounced effect on PVR, it should be used with caution due to its potential toxicities (methemoglobinemia), requirement for continuous delivery, and excessive cost.

Generally, milder cases of right ventricular dysfunction will respond favorably to a vasodilating agent with concomitant inotropic support. In the event that vasodilatory therapy results in systemic arterial hypotension, alpha-adrenergic agents such as phenylephrine or epinephrine may be infused through a separate left atrial catheter to maintain systemic perfusion pressure; if these are ineffective, an IABP may be deployed to maintain systemic perfusion pressure while simultaneously allowing vasodilatory treatment of pulmonary hypertension. For more severe forms of right ventricular dysfunction resistant to pharmacologic treatment, a right ventricular assist device (RVAD) or ECMO may be necessitated [2].

Post-transplant Rate and Rhythm

While the majority of transplanted hearts exhibit normal sinus rhythm in the operating room shortly after reperfusion and clinically important arrhythmias are rare in the proceeding weeks, sinus node dysfunction post-transplant is very common with prevalence as high as 50% [15]. The parameters affected may include prolonged sinus node recovery time, prolonged corrected sinus node recovery time, and abnormal sino-atrial conduction time. While the etiology is unclear, sinus node dysfunction is believed to be multifactorial in origin, including surgical trauma, cardiac denervation, myocardial ischemia and preservation injury [16]. Sinus node dysfunction is seen more commonly with the biatrial cuff surgical technique due to manipulation of the sinus node of the donor heart during implantation. Sinus bradycardia is also common for patients on preoperative amiodarone as this medication has a 30-day half-life and can temporarily slow the sinus node of the donor heart early after transplant.

Monitoring

The post-operative 12-lead electrocardiogram (ECG) is considered a cornerstone of the ISHLT guidelines for post-transplant monitoring [2]. Furthermore, it is recommended that both atrial and ventricular temporary epicardial

pacing wires should be placed at the time of heart transplantation, even if the initial rhythm is sinus.

Management

Post-transplantation bradycardia resulting from sinus node dysfunction is perhaps the most common rate disorder after transplantation. In order to maintain sufficient heart rate and atrioventricular synchrony, and thus cardiac output early post-transplant, the ISHLT guidelines recommend pharmacologic treatment or temporary pacing to maintain a minimum heart rate of at least 90 bpm [2]. Such pharmacologic chronotropic agents may include isoproterenol, terbutaline or theophylline, an adenosine receptor antagonist, while awaiting return of normal sinus node function.

Asymptomatic transient arrhythmias, both atrial and ventricular, are common post-transplantation. Persistent post-operative tachyarrhythmias, regardless of being atrial or ventricular, should prompt investigation for possible rejection, and if rejection is absent, electrophysiology and coronary angiography evaluation.

Atrial arrhythmias after heart transplant include atrial fibrillation (AF) and atrial flutter, of which AF is the most common. Many factors predispose to AF in the immediate post-operative period, and high incidence is reported [17]; while AF within 2 weeks of surgery can be associated with rejection [18, 19], there is no clear correlation between AF incidence and rejection. In contrast, atrial flutter tends to occur beyond the first 3 weeks post-transplant, and has been associated with incidence of LV dysfunction and earlier mortality [19, 20]. Nonsustained ventricular tachycardia (VT) can also be relatively common in the early post-operative period, with unclear association with rejection and PGD [17]. Ventricular arrhythmias may result from ischemia-reperfusion injury and metabolite disturbances, but are rarely malignant except when seen in the presence of hyperacute rejection.

Treatment of post-operative tachyarrhythmias should be aimed at rate control to around 90–100 bpm [2]. Class III anti-arrhythmics such as sotalol and amiodarone may be administered briefly for rate control; non-dihydropyridine calcium channel blockers such as diltiazem and beta blockers (assuming stable blood pressure) may also be safely used. It is important to note that prolonged anti-arrhythmic therapy (>3 months) is generally not indicated, as most arrhythmias post-transplant are transient. Furthermore, amiodarone is associated with significant drug interaction with calcineurin inhibitors, requiring close monitoring of drug levels; beta blockers and calcium channel blockers should also be used cautiously, due to the risk of bradycardia and interactions with immunosuppressants.

Although sinus node dysfunction is typically transient [21], some patients display permanent sinus node dysfunction and require permanent pacing. Pacemaker implantation is usually delayed until the third week post-transplantations. A 2–10% prevalence of pacemaker placement during the transplant hospitalization has been reported, although the data are somewhat outdated and in practice the rate is likely far lower; sick sinus syndrome and complete heart block are the most common indications [22, 23].

Renal Function and Fluid Balance

Renal Function

Renal reserves are often impaired prior to transplantation simply due to the prolonged low cardiac output and chronic administration of diuretics that occurs in end-stage heart failure. Given this scenario, the kidneys are vulnerable given the combination of underperfusion induced by cardiopulmonary bypass, potential for post-transplant underperfusion due to graft dysfunction, as well as the nephrotoxic effects of calcineurin inhibitors (CNIs), a mainstay of post-transplant immunosuppression. Hence, appropriate management in order to maintain sufficient cardiac performance (as detailed

above) is particularly important in minimizing negative renal outcomes.

As defined by ISHLT guidelines, continuous assessment of urinary output is essential in the immediate period post-transplant. Due to the factors mentioned above, oliguria (<50 ml/h) and an increase in serum creatinine (>1.7 mg/dL) in the first 24–48 h post-transplant are common, occurring in 3–10% of transplant recipients [24]. This may occur particularly in patients who were on high-dose diuretics prior to transplantation due to end-stage heart failure. In these oliguric patients, aggressive diuretic therapy targeting urine output of >50 ml/h may be required. However, special care is also required to maintain intravascular volume during administration of diuretics; in cases of brisk diuresis, hourly urine output should be matched to a corresponding colloid infusion in order to maintain appropriate preload (5–12 mmHg as per ISHLT guidelines). Patients with pre-existing renal insufficiency (serum creatinine >2 mg/dl) may receive a course of antithymocyte globulin, a polyclonal immunosuppression agent (see Chap. 10 for details), in order to delay initiation of CNIs, and thus reduce the chance of further renal insult.

Should renal dysfunction remain severe and refractory to pharmacologic treatment despite adequate cardiac output, temporary hemodialysis is an option until renal function improves. This option should be considered in anuric or oliguric patients who display a sharp increase in serum creatinine within 2–4 h after heart transplantation that is not adequately correctable by diuresis. In such cases, it is advisable to consult nephrology as soon as possible.

Fluid Management

Extravascular fluid tends to accumulate during surgery given the situations of cardiopulmonary bypass and volume resuscitation as response to intraoperative hypotension. Consequently, maintenance intravenous fluid administration is considered unnecessary in the first 24–48 h, especially given that fluid is already administered through intravenous medications and as part of the requirement for invasive monitoring. As a result, volume overload is relatively common post-transplant, and intravenous loop diuretics such as furosemide should be given to decrease this, with adjunct thiazide diuretics and aldosterone antagonists such as spironolactone if necessary; these diuretics also help to maintain urine output in otherwise oliguric patients. However, as mentioned above, in cases of brisk diuresis to maintain urine output, slow intravenous colloid replacement of this urine output may be warranted to maintain sufficient preload.

Bleeding and Transfusions

Serious post-operative bleeding, although uncommon, has the potential to create significant hemodynamic instability. Caused by clotting abnormalities, bleeding is thought to be multifactorial in etiology, including previous congenital cardiac surgery necessitating extensive dissection, cardiopulmonary bypass, multiple suture lines, pre-transplant heparinization for VAD or ECMO support.

Compatible blood products may be safely administered where necessary post-heart transplant without increasing the risk for rejection; hemorrhage can be addressed by administration of platelets and fresh frozen plasma infusions as necessary [2]. Volume resuscitation including packed (ideally leukocyte reduced/filtered and CMV negative) red blood cells may also be necessary. Patients with refractory hemorrhage or those demonstrating clinical evidence of cardiac tamponade (i.e. persistent graft dysfunction) should be surgically investigated [2].

Other Important Medical Issues

Nutrition

Post-transplant patients are usually initiated on low-calorie enteral nutrition while in the ICU. Feeding is administered via nasogastric tubes, along with metoclopramide to counter post-operative gastroparesis. Following bowel movements,

nutrition is gradually increased. Parenteral nutrition generally consists of an adequate supply of electrolytes, albumin and vitamins. Given the recent surgery, steroid administration and cardiopulmonary bypass, electrolyte abnormalities (potassium, magnesium, phosphate) are common with refeeding and should be monitored and corrected accordingly. Once the patient is tolerating parenteral nutrition adequately and graft function is stable, oral nutrition starting with liquid food may be initiated and gradually stepped up to solid foods.

Hyperglycemia

Many transplant recipients have diabetes mellitus as a comorbidity. Because oral hypoglycemic agents are routinely discontinued pre-operatively [2], and due to the stressors involved in major surgery, hyperglycemia often occurs in patients post-operatively. This should be managed aggressively. A continuous insulin infusion regimen should be used to maintain blood glucose below 200 mg/dL [2] during ICU, with transition to an oral or subcutaneous regimen (if applicable) closer to the time of discharge.

Neurological Dysfunction

Neurological dysfunction in the early post-transplant period may arise from a number of mechanisms, including hypotension associated with low cardiac output, cerebral embolus from a left ventricular thrombus, and medication side-effects. An encephalopathy that develops within the first 48 h post-transplantation is most often caused by an operative hypoxic-ischemic insult or metabolic abnormalities, but may also be caused by the side effects of calcineurin inhibitors. Tacrolimus in the presence of low lipid levels has been associated with altered mental status as more free tacrolimus can more easily cross the blood brain barrier. Furthermore, encephalopathy may vary, from mild confusion, to severe obtundation and coma. Focal cerebral abnormalities are typically caused by embolic events, while seizures are normally a result of calcineurin inhibitor- toxicity. Furthermore, anticonvulsants should be chosen carefully, as they may affect the levels of calcineurin inhibition (cytochrome p-450 metabolism). Seizures should be investigated with a prompt MRI and EEG, in order to confirm diagnosis and guide therapy.

Gastrointestinal Dysfunction

In nutritionally compromised patients with advanced heart failure who undergo transplant, with its accompanying stressors and high dose immunosuppression, intra-abdominal complications are a potential risk. Acute cholecystitis is the most common biliary complication after cardiac transplant, presenting with right upper quadrant tenderness; ultrasound should be performed to confirm, and surgical intervention may be required if there is no response to conservative therapy. Pancreatitis, which presents with epigastric pain, may also occur, though it is more common later after transplant; if suspected, amylase and lipase levels should be obtained and CT scan performed to assess for pancreatic inflammation. Persistent epigastric tenderness may also be caused by gastric or duodenal ulcers, which are exacerbated by corticosteroid administration. As a result, antacids are often given early post-operatively to reduce this risk.

Facilitating Graft Acceptance

Allograft rejection is one of the most common causes of death in the first year after transplantation and has historically been the barrier to long-term survival. Rejection episodes and their surveillance and management will be covered in Chap. 12. Nevertheless, comprehensive immunosuppression is required. While immunosuppression will be covered in more detail in Chap. 10, a brief overview as relevant to the initial post-transplant period will be given here.

A variety of protocols for immunosuppression exist, with no accepted gold standard, but the most common is a triple therapy protocol that is initiated soon after transplantation [2]. The protocol consists of a calcineurin inhibitor (cyclosporine or

tacrolimus), an antiproliferative agent (mycophenolate mofetil, azathioprine or everolimus/sirolimus), and corticosteroids. These agents target different aspects of the T-cell activation pathway in order to prevent rejection. Methylprednisolone is typically administered intravenously at the end of cardiopulmonary bypass, with subsequent doses at 8 h intervals; oral prednisone is then initiated on the first post-operative day. Mycophenolate (or rarely, azathioprine) is also initiated immediately post-transplant, whereas calcineurin inhibitors are typically withheld for the first 12 h post-transplant. For full dosing details, see Chap. 10.

Furthermore, some centers use adjuvant induction therapy; induction therapy refers to the administration of a special group of immunosuppressant agents in the peri-operative period (first dose intra-operatively) to rapidly disable the normal host response toward the transplanted graft [2]. Although there has been a recent trend toward increased usage, induction therapy is not considered a universal standard of care and only 50% of centers currently report its use [25]. Examples of the two most popular induction therapy agents include anti-thymocyte globulin, a polyclonal antibody against human T-cells, and basiliximab, an IL-2 receptor antagonist. Dosages are detailed in Chap. 10. While it is controversial as to whether induction therapy prolongs survival post-transplant, it has been associated with increased risk of infection [26].

Induction therapy is frequently used in patients with preformed anti-HLA antibodies and donor-specific antibodies; it is also used in patients with known pre-existing renal insufficiency who are at risk to develop renal failure soon after transplantation. This induction therapy enables delayed initiation of CNIs to minimize the CNI nephrotoxic effects. Typically, CNIs are delayed for 3–5 days while the induction agent is administered, allowing time for the kidneys to recover.

Minimizing Infection

Infection is a major cause of morbidity and mortality early after cardiac transplantation; approximately 25% of patients are affected within the first 2 months post-transplant [25]. Patients are susceptible due to the powerful immunosuppressive medications administered, allowing opportunistic infections to attack. While the most common infectious micro-organisms and antimicrobial agents in heart transplantation will be covered in depth in Chap. 11, a brief overview as relevant to the initial post-transplant period will be provided here.

Antimicrobial Therapy

In the first month post-transplant, infections are most commonly bacterial and typically related to indwelling catheters and wound infections. Examples of nosocomial pathogens involved include *Legionella, Staphylococcus, Pseudomonas, Proteus, Klebsiella,* and *Escherichia coli.* They may present in the form of pneumonias, urinary tract infections, sternal wound infections and mediastinitis, or bacteremia. Thus, ISHLT guidelines recommend preoperative antibiotic prophylaxis [2], with individual circumstances to be considered, for example, if the donor had an ongoing bacterial infection, or if a chronically infected device such as a VAD or pacemaker is present, antibiotics should be selected based on appropriate microbiologic sensitivities. For prophylactic purposes, broad spectrum antibiotics such as vancomycin and ceftazidime are often employed against bacterial infections (see Chap. 11 for recommended dosing); trimethoprim sulfamethoxazole for pneumocystis prophylaxis; acyclovir (if low risk for CMV infection) or valganciclovir (if higher risk) for viral prophylaxis; and nystatin or clotrimazole for anti-fungal prophylaxis against mucocutaneous candidiasis. In the presence of systemic features of infection post-transplant, blood cultures should be taken and antibiotic regimen adjusted to the organisms found. More details on organisms, further antibiotic agents and antibiotic dosing can be found in Chap. 11.

Wound Management

Strict adherence to the surgical principles of asepsis, hemostasis and secure would closure during the closure of the sternum is of obvious

Table 9.5 Suggested routine medical investigations in the post-operative period

Blood count	Coagulation	Chemistry	Infection screens	Drug levels	Serology	Imaging
Hemoglobin, hematocrit, leucocytes, platelets, arterial blood gas analysis	PTT, INR	Troponin I, CK, CK-MB, γGT, albumin, creatinine, urea, glucose, bilirubin, ALT, AST, lactate, sodium, calcium, chloride, potassium, phosphate, lipase TSH, T3, T4	Urine (indwelling catheter), tracheal secretions	CNI levels, antibiotic levels, anti-arrhythmic levels	Hepatitis A, B, C	Chest X-ray

Abbreviations: *PTT* Partial Thromboplastin Time, *INR* International Normalized Ratio, *CK* Creatine Kinase, *CK-MB* Creatine Kinase-MB, *γGT* Gamma- GlutamylTranspeptidase, *ALT* Alanine Transaminase, *AST* Aspartate Transaminase, *TSH* Thyroid-Stimulating Hormone, *CNI* Calcineurin Inhibitor

importance. At some centers, the mediastinum and surgical wounds are irrigated with dilute broad spectrum antibiotics to reduce growth of skin gram-positive flora, although this is controversial. The surgical dressing is typically left in place for 48–72 h to allow sealing of the skin edges; for further asepsis, the wound is treated with an iodine solution such as Betadine twice daily for several days until successful sealing of the wound. Any evidence of bleeding, however, requires the wound to be examined immediately.

The Patient's Perspective

The clinical course of a patient short-term post-heart transplant depends on a host of donor, recipient and periprocedural factors. Donor factors include relative sizing, age and ventricular function, while recipient factors include patient health status prior to transplant and pre-existing co-morbidities, as well as infection status. Periprocedural factors include complexity of the operation, whether or not there was bleeding, and prolonged ischemic time. While the length of hospitalization post-heart transplant varies depends by situation, it is typical for patients to be hospitalized for up to 2 weeks or more, although some patients can recover sufficiently to be discharged within 10 days. In addition to being monitored from a cardiac standpoint (hemodynamics, rate, etc.) patients must also be medically monitored for the complications mentioned in this chapter. A summary of suggested routine investigations is listed in Table 9.5.

Assuming an uncomplicated course, patients typically remain in the ICU for 2–3 days post-operatively for the purposes of hemodynamic monitoring and support (with ventilation if needed) until they are fully weaned off inotropic support. Following extubation, early ambulation and physical therapy is crucial; a program of progressive ambulation and physical therapy is employed. For those patients who are severely physically deconditioned due to severe heart failure prior to transplant, intensive physical programs are necessary. A patient is considered clinically dischargeable if the sternal wound is healed appropriately, the patient is free from any acute medical issues, is clinically stable (vital signs normal), is relatively pain-free, able to self-ambulate, and has undergone appropriate counseling. After 6 weeks, if appropriate, cardiac rehabilitation is recommended to improve physical conditioning and exercise capacity [27].

Most major heart transplant programs have organized protocols for education of transplant patients and their families by coordinators, physicians and pharmacists. It is vitally important the patients are knowledgeable regarding their immunosuppression regimen prior to discharge, in order to assure compliance. Typically,

instruction will consist of timing of medications, dosage and potential side effects, being aware of potential signs and symptoms of rejection and infection so that they can be treated as soon as possible. These factors are crucial in long-term outcome and rehabilitative potential [28].

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Immunosuppression Strategies in Heart Transplantation

10

Jon Kobashigawa and Minh Luu

Clinical Pearls

- Developments in immunosuppression in the last 30 years have made heart transplantation a definitive option for end-stage heart failure, with 1-year survival of 90%.
- While there is no accepted universal protocol for immunosuppression, common standard practice consists of "triple" therapy consisting of a calcineurin inhibitor, an anti-proliferative agent, and corticosteroids.
- Corticosteroid wean-to-off protocols are successful in a majority of patients at low risk for rejection with best results occurring when initiated within the first year post-transplant.
- Tacrolimus is generally preferred to cyclosporine due to reduced rejection and a more tolerable adverse-effect profile.
- Known side-effects of calcineurin inhibitors include hypertension, nephrotoxicity, hyperglycemia, hyperlipidemia, and neurotoxicity.
- Calcineurin inhibitors are metabolized by the cytochrome P-450 liver enzyme pathway and thus are susceptible to interactions, most notably with cytochrome P-450 inhibitors such as the –azole antifungals and grapefruit juice.
- Within the antiproliferatives, mycophenolate mofetil (MMF) is superior to azathioprine with improved survival, decreased incidence of rejection and a reduced adverse effect profile.
- Known side effects of the antiproliferatives include myelosuppression, fluid retention and nausea/vomiting.
- The proliferation signal inhibitors everolimus/sirolimus are superior to MMF in retarding cardiac allograft vasculopathy and may also enable early avoidance of calcineurin inhibitors; however they have also been associated with impaired wound healing and renal insufficiency as they potentiate calcineurin inhibitor nephrotoxicity.
- Immunosuppression regimens should be individualized to each patient's risk profile and medical history.

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- In patients with pre-existing renal dysfunction or circulating anti-HLA antibodies, peri-operative induction therapy with anti-thymocyte globulin or basiliximab may be warranted.
- Because of the long-term adverse effects including malignancy, a general aim in stable patients is to minimize immunosuppression while still maintaining protection against rejection.

Introduction to Transplant Immunosuppression

Initial immunosuppressive efforts in human cardiac transplantation were hindered by poor outcomes that resulted from suboptimal regimens, with the result frequently being overwhelming infection or allograft rejection. Initially, at the advent of modern cardiac transplantation, 1-year survival in the 1970s hovered around 50% [1]. At this stage, the only viable immunosuppressive techniques were the use of azathioprine, a purine analogue, and total body irradiation, both with many adverse effects.

In the subsequent 30 years, improved donor heart management, refinement of donor and recipient selection methods, and the introduction of the calcineurin-inhibiting agent cyclosporine, followed by even more successful immunosuppressive agents and regimens, has improved survival considerably. With 1-year survival at 90%, a 5-year survival rate of approximately 70%, and a median survival in excess of 11 years, developments in immunosuppression have enabled heart transplantation to become a definitive option for selected patients with end-stage heart failure [2].

There are three possible outcomes in the use of immunosuppressive drugs, some or all of which may overlap: the desired immunosuppressive effects; adverse effects of immunodeficiency such as infection and malignancy; and non-immune toxicities such as diabetes, hypertension, and renal insufficiency. In particular, malignancy is one of the most common causes of death post-cardiac transplant, accounting for 24% of deaths after 5 years [2]. The impaired immunoregulation that results from immunosuppression is synergistic with carcinogens such as nicotine or ultraviolet light exposure, and oncogenic viruses such as the Epstein–Barr virus (EBV) and the human papilloma virus (HPV) [3]. Lymphoproliferative diseases, skin cancers, and Kaposi sarcoma have a particularly high incidence relative to the general population.

In this field, it has always been crucial to maintain a delicate balance between the risk of rejection and the risk of immunosuppression-related adverse effects. Minimizing immunosuppression and immunosuppression-associated complications without sacrificing efficacy are the goals of post-transplantation management. Modern immunosuppression strategy hinges on the deployment of a combination of immunosuppressive agents, with each affecting a different pathway of T-cell activation (Fig. 10.1).

This chapter will cover the different categories of induction and maintenance immunosuppressive agents used in transplantation, their clinical utility, and strategies involving different combinations of these agents. Non-infectious adverse effects of immunosuppression and monitoring strategies will also be covered. While infection remains the most major adverse effect of over-immunosuppression, this topic will be addressed in Chap. 11.

Immunosuppressive agents commonly used in heart transplant patients and their mechanisms of action and common side effects are listed in Table 10.1 which gives trade names, pharmacology, necessary adjustments for renal or hepatic dysfunction, and dosing and general monitoring guidelines for each of the drugs. Table 10.2 lists the major adverse effects of immunosuppressive drugs.

Immunosuppressive Agents for Maintenance Regimens

Immunosuppression regimens can be generally defined as induction, maintenance, or rejection regimens. Whereas "rejection" regimens refer to agents specifically used to treat rejection episodes (covered in Chap. 12) and "induction" refers to a brief period of intense perioperative immunosuppression, and will be covered later in this chapter, maintenance therapy refers to the

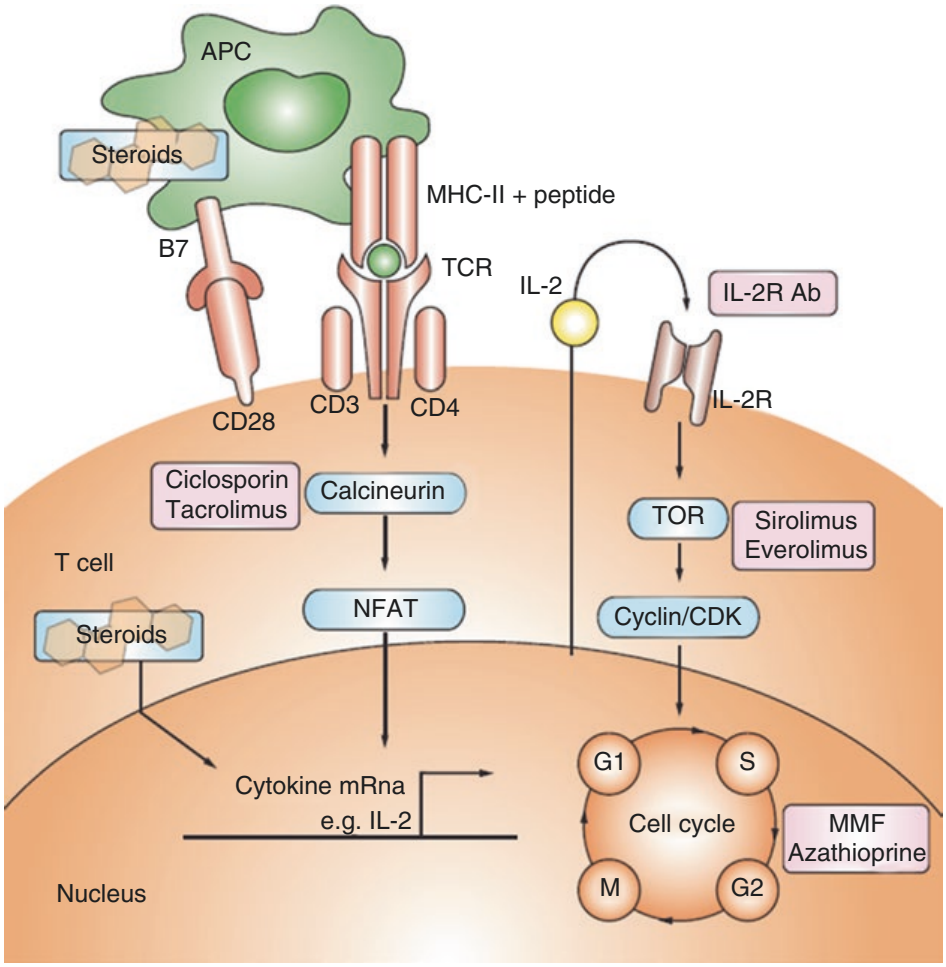

Fig. 10.1 Diagram of mechanisms of action of common immunosuppressants in heart transplant. Through various pathways, the drugs inhibit T-cell proliferation. Abbreviations: *G1* (first growth phase), *S* (synthesis of DNA), *G2* (second growth phase), and *M* (cell division) represent the phases of the cell cycle. *APC* antigen-presenting cell, *CDK* cyclin-dependent kinase, *IL-2* interleukin-2, *IL-2R* interleukin-2 receptor, *IL-2R Ab* interleukin-2-receptor antibody, *MHC* major histocompatibility complex, *MMF* mycophenolate mofetil, *mRNA* messenger RNA, *NF-AT* nuclear factor of activated T cells, *TCR* T-cell receptor, *TOR* target of rapamycin protein (Reproduced with permission from Lindenfeld et al. [106])

ongoing immunosuppressive regimen that a cardiac transplant patient must undergo for the rest of their lives, to prevent rejection.

Remarkably, there remains no accepted uniform protocol for maintenance immunosuppression in cardiac transplant patients. The most common long-term regimen consists of a triple therapy regimen, consisting of a corticosteroid, calcineurin inhibitor, and antiproliferative. However, there remains controversy over which specific agents and combinations of agents are most effective. This section will cover the most commonly used immunosuppressive agents in maintenance regimens.

Corticosteroids

Corticosteroids, or simply steroids, are among the first immunosuppressive agents ever used in clinical transplantation, and to this day remain a cornerstone of post-transplant management. They exert potent immunosuppressive and anti-inflammatory effects. Uniquely, they play a major role in the induction phase immediately post-transplant, during maintenance and as part of anti-rejection regimens. While highly effective for the prevention and treatment of acute rejection, their long-term use is associated with a number of adverse effects.

Table 10.1 Overview of commonly used immunosuppressive drugs in cardiac transplantation, including both maintenance and induction agents

Drug	Trade name(s)	Pharmacology	Adjustment for renal/hepatic dysfunction	Dosing			Monitoring
				Oral	Intravenous	Comments	
Prednisone	Deltasone Generic	Processed in the liver and metabolites excreted in the urine	Consider prednisolone if hepatic dysfunction	×		Intra and post: Solumedrol 5–10 mg/kg pre- or intraoperatively and 5–7 mg/kg in 3 divided doses over next 24 h; then rapidly tapered from 1 to 0.3 mg/kg/day at 3–6 months to 0.1 mg/kg/day at 6 months For rejection: prednisone 1–3 mg/kg/day PO for 3–7 day or solumedrol 3–10 mg/ kg/day IV; Lower doses have been used successfully	No currently available monitoring tool except clinical response
Prednisolone	Generic	Prednisone is converted to Prednisolone in liver	No	×			
Methylprednisolone	Medrol	Prednisone and Prednisolone have 4–5 times potency of hydrocortisone	No	×			
	Solumedrol			×			
Azathioprine	Imuran	Converted in liver to 6-mercaptopurine, which is inactivated by xanthine oxidase or TMPT predominantly in the liver	Decrease doses for renal dysfunction and lower dose range for hepatic dysfunction	×	×	1–2 mg/kg per day PO or IV Rarely used >3 mg/kg IV and oral the same dose	Monitoring of levels not clinically available Dose is decreased if white blood cells <3000–4000 Major drug interaction with allopurinol Polymorphisms in *TMPT* may increase effect
MMF	Cellcept Generic	Rapidly hydrolyzed to mycophenolic acid (MPA) and MPA to its gluronide, which is excreted in urine and bile	≤1000 mg BID	×	×	500–1500 mg BID Higher doses have been used when monitoring trough MPA levels IV and oral the same dose	Monitoring of MPA levels is controversial, but trough levels of 2.5–5.0 μg/mL have been suggested CSA inhibits enterohepatic circulation of MPA, decreasing exposure and levels

Drug	Trade name(s)	Pharmacology	Adjustment for renal/hepatic dysfunction	Dosing			Monitoring
				Oral	Intravenous	Comments	
Calcineurin inhibitors							
Cyclosporine							
Oil-based	Sandimmune Generic	Oil-based formulation has unpredictable absorption secondary to need for emulsification by bile salts	Hepatic dysfunction: Decrease dose by half and follow levers	4–8 mg/kg per day in 2 divided doses	1–2 mg/kg per day in 2 divided doses or as continuous infusion	Dosing is high early after transplantation and gradually decreases over time Drugs that inhibit CYP-3A4 and p-GP may result in significantly higher levels IV dose is 1/3–1/4 of oral dose IV may be best administered in 2–6 h infusions	Abbott TDX assay most commonly used CSA trough levels have been routinely used with levels of 300–350 ng/ml early postoperatively decreasing to 100–200 by 1 year Levels at 2 h postdose appear to more accurately estimate area under the curve and may result in lower doses
Modified (oil-based formulation is not bioequivalent to modified preparation)	Neoral Gengraf Other generics	Modified for more predictable absorption Both forms extensively metabolized by CYP-3A4 and are substrates and inhibitors of p-GP					
Tacrolimus	Prograf Generic	Metabolized by CYP-3A4 and are substrates and inhibitors of p-GP	Follow levels for hepatic dysfunction	0.05–0.1 mg/kg per day in 2 divided doses	0.01–0.02 mg/kg per day in 2 divided doses or as continuous infusion	Doses are high early after transplantation and decrease over time Drugs that inhibit CYP3A4 or p-GP may result in higher levels	Whole-blood levels of 10–15 ng/ml early after transplantation and 5–10 ng/ml by 1 year are targets
mTOR inhibitors							
Sirolimus	Rapamune	CYP-3A4 and p-GP substrate	≤33% ↓ if hepatic dysfunction	×		2 mg/day in 1 dose (may be preceded by a single 6-mg loading dose)	Whole-blood trough levels of 4–15 ng/ml Coadministration with CSA may increase CSA levels as much as 100% Dose 4 h apart with CSA or tacrolimus

(continued)

Table 10.1 (continued)

Drug	Trade name(s)	Pharmacology	Adjustment for renal/hepatic dysfunction	Dosing			Monitoring
				Oral	Intravenous	Comments	
Everolimus	Zotress (US) Certican (EU)	CYP-3A4 and p-GP substrate	≤33% ↓ if hepatic dysfunction	×		0.75 mg BID	Therapeutic drug monitor is 3–8 ng/ml Early renal insufficiency seen when used with sd-CSA. rd-CSA recommended
Induction agents							
Polyclonal anti-lymphocyte preparations		Elimination by proteindegradation and antibody formation to equine (ATGAM) or rabbit(Thymoglobulin) protein	No				ATGAM requires skin test before first dose. Premedication to prevent cytokine release syndromeis required: antipyretics, IV steroids, antihistamines, H2 blockers. Monitoring is done by following CD3 counts. Various targets include CD3 at 5–10% baseline, <50 CD3+ cells/ml, 50–100 CD3+ cells/ml Repeating daily dose when CD3+ cells increase may decrease number of daily doses, especially with Thymoglobulin
Anti-Thymocyte Globulin	ATGAM					10–15 mg/kg/day IV over 6–8 h for 5–14 days	
	Thymoglobulin					1.5 mg/kg/day IV over 6–8 h for 3–7 days	

Drug	Trade name(s)	Pharmacology	Adjustment for renal/hepatic dysfunction	Dosing			Monitoring
				Oral	Intravenous	Comments	
Monoclonal preparations							
Alemtuzumab	Campath	CD52 antibody, depleting T cells as well as B cells and other lymphoid subsets	No			30 mg IV over 2 h once intraoperatively	Premedication is required. Monitoring total lymphocyte counts should also be performed
Basiliximab	Simulect	Elimination via protein degradation similar to IgG	No			20 mg IV within 2 h of surgery and 4 day course postoperatively	CD3 counts do not change. IL-2R+ lymphocytes may be measured but are generally followed clinically. Hypersensitivity may occur rarely

Adapted with permission from Lindenfeld et al. [106]

CNI calcineurin inhibitor, *CSA* cyclosporine, *CYP* cytochrome P450, *MMF* mycophenolate mofetil, *p-GP* p-glycoprotein, *rd-CSA* reduced-dose cyclosporine, *sd-CSA* standardized-dose cyclosporine, *TOR* target of rapamycin, *TMPT* thiopurine methyltransferase

Table 10.2 Overview of major adverse effects of immunosuppressive drugs used in cardiac transplantation- listed by frequency scoring

	Steroid	AZA	MMF	CSA	TAC	SIR	EVR	OKT3	Atgam	Thymo
Potential for drug–drug interactions	1	1	1	4	4	4	4			
Hypertension	2			4	3	2		3	3	3
Diabetes	3			1–2	2–3					
Obesity	2									
Hyperlipidemia[a]	2			3	3	3–4	3–4			
Renal insufficiency				3	3		4[b]			
Osteoporosis	3			1–2	1–2		1–2			
Avascular necrosis	1									
Poor wound healing	2					2[c]	1–2			
Neurological minor tremors, paresthesias				3	3					
Neurological major seizures, cerebritis				1	1			1	1	1
Hirsutism	2			3						
Alopecia		1			2					
Gingival hyperplasia				3						
GI[d]		2	3	2	3	3	3	3	2	3
Hepatic toxicity		2		1	2	1	1		1	
Hypomagnesmia				3	3					
Hyperkalemia				2	2	2				
Hyperuricemia				3	3	3				
Anemia		2	3			3	3			
Thrombocytopenia		1	2		3	3	3		3	3
Neutropenia		3	3			3	3	1	1	1
Cushingoid features	3									
Cytokine release syndrome—mild								4	3–4	3–4
Cytokine release syndrome—severe								1–2	0–1	0–1
Serum sickness									1	0–1

Reproduced with permission from: Lindenfeld et al. [106]

AZA azithoprine, *BAS* basiliximab, *CSA* cyclosporine, *EVR* everolimus, *GI* gastrointestinal, *MMF* mycophenolate mofetil, *OKT3* muromonab-CD3, *SIR* sirolimus, *TAC* tacrolimus, *Thymo* thymoglobulin

1 rare (<5%), *2* common (5–15%), *3* very common, *4* most patients

[a]Hyperlipidemia defined as: (↑ total cholesterol, ↑↑LDL cholesterol, ↑ triglycerides) (16–50%)

[b]When used concomitantly with cyclosporine

[c]Wound healing (especially early after operation), >50%

[d]GI problems: diarrhea, nausea, vomiting

Mechanism of Action

Corticosteroids act by altering transcriptional regulation of multiple genes that affect leukocytes (T and B lymphocytes, granulocytes, macrophages, and monocytes) as well as endothelial cell function [4]. The major effect on lymphocytes is mediated by inhibition of the transcription factor activator protein 1 and nuclear factor kappa B (NF-kB), which negatively affect expression of several genes, including those controlling cytokine production, growth factors and adhesion molecules. Furthermore, steroids cause a decrease in the production of vasoactive/chemoattractant factors and lipolytic/proteolytic enzymes in non-lymphoid cells. Downstream, this results in inhibition of neutrophil adhesion to endothelial cells, prevention of macrophage differentiation, and down-regulation of endothelial function.

Glucocorticoids also exert their anti-inflammatory effects through inducing the release

of lipocortin, which acts by inhibiting phospholipase A2, in turn suppressing the production of prostaglandins and leukotrienes [5, 6].

Adverse Effects

While effective at preventing rejection, steroids are associated with a significant number of long-term adverse effects. Hypertension, poor wound healing, gastric ulcers, emotional lability, cataracts, and proximal myopathy are all associated with corticosteroid therapy. Furthermore, cosmetic side-effects such as hirsutism, acne, moon facies, easy bruising, skin fragility, "buffalo hump", and truncal obesity may also occur. From a metabolic point of view, hyperlipidemia, salt and water retention, diabetes mellitus, osteopenia, and growth retardation in children may result [6, 7]. If high-dose steroids are administered long-term, chronic adrenal suppression may result (via negative feedback mechanisms). Adrenal insufficiency may also follow a steroid taper or physiologic "stress" (illness, surgical procedures, infections).

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

The calcineurin inhibitors (CNIs), which include cyclosporine and tacrolimus, have become cornerstones of maintenance immunsuppressive therapy for transplant patients. Cyclosporine is a lipophilic undecapeptide which was initially isolated from the fungus *Tolypocladium inflatum*. The discovery of cyclosporine and subsequent use in heart transplants in the late 1970s enabled survival rates to drastically improve. Tacrolimus, in contrast, was more recently discovered in 1987 and only since the late 2000s has it become widely used in heart transplant patients. Tacrolimus is a macrolide and is produced by the fungus *Streptomyces usukubaensis*; it has a very similar mode of action to cyclosporine and is frequently used as an alternative to it.

Mechanism of Action

Cyclosporine and tacrolimus both function by blocking calcium-activated calcineurin (see Fig. 10.1) [8, 9]. The agents are able to enter cells through diffusion and bind to different immunophilins: cyclosporine binds to cyclophilin and tacrolimus to FK binding protein-12 (FKBP-12). This drug-immunophilin complex proceeds to bind to calcineurin, a phosphatase that dephosphorylates multiple molecules, including nuclear factor of activated T cells (NF-AT). In turn, dephosphorylated NF-AT translocates to the nucleus, where it binds to specific DNA sites in the promoter regions of several cytokine genes, including interleukin (IL)-2. Through this series of actions, cyclosporine and tacrolimus inhibit transcription of IL-2 and other cytokines, tumor necrosis factor alpha (TNF-a), granulocyte-macrophage colony-stimulating factor, and interferon-gamma [10]. In a mechanism specific to cyclosporine, transforming growth factor-ß (TGFß) production is also stimulated, augmenting its immunosuppressive activity [11]. Furthermore, cyclosporine has been found to suppress delayed-type hypersensitivity skin reactions to tuberculin in guinea-pigs but appeared have no effects on antibody synthesis, suggesting a mechanism of immunosuppression specific to T cells.

Notes

Cyclosporine is available as oil-based or microemulsion formulations, as well as intravenous solution (for post-operative administration). Due to an improved pharmacokinetic profile and clinical data, microemulsion preparations are generally preferred over the older oil-based formulations [12]. Indeed, randomized studies comparing the two demonstrated similar survival at 2 years, but lower rates of treated rejection in the microemulsion group [13–15]. Furthermore, the microemulsion formulation exhibited better tolerance and fewer discontinuations, and allowed lower average doses of corticosteroids compared to the oil-based formulation.

Tacrolimus has become the most widely used CNI in recent years, preferred over cyclosporine. There is evidence from uncontrolled studies that tacrolimus results in lower rates of rejection and fewer adverse effects as compared to cyclosporine [16–18]. While there is no demonstrated difference in post-transplant survival between tacrolimus and oil-based cyclosporine [19, 20], randomized controlled trials show patients on tacrolimus display lower moderate-severe cellular rejection rates at 6 months compared to those on microemulsion cyclosporine [21]. Despite this, tacrolimus patients have been noted to display a higher incidence of de novo diabetes mellitus compared to microemulsion ciclosplorin.

Adverse Effects

While not an adverse effect per se, cyclosporine treatment has been previously noted to mask the clinical signs and symptoms of acute allograft rejection, making endomyocardial biopsy essential for rejection surveillance (Chap. 12).

Cyclosporine is also noted to cause acute or chronic dose-related nephrotoxicity, with the possible sequelae of arteriolar sclerosis and tubulointerstitial fibrosis (see Table 10.2). In most patients, hypertension and hyperlipidemia tend to occur [22] and the development of de novo diabetes mellitus is fairly common. Electrolyte abnormalities are common, especially hyperkalemia, but are rarely life-threatening if renal function remains intact. Hypertrichosis, which occurs in at least 50% of patients, and gingival hyperplasia are side-effects seen with cyclosporine. Neurotoxic symptoms may also occur; such manifestations include tremor, paresthesias, headache, seizures, mental status changes, visual symptoms, and insomnia. Other possible side effects include nausea, vomiting, cholestasis/cholelithiasis, and long-term, may accelerate the development of osteoporosis (especially in combination with corticosteroids).

Tacrolimus has been noted to exhibit a similar side effect profile to cyclosporine, although the incidence of hyperlipidemia and hypertension are reduced (see Table 10.2) [19], while the incidence of hyperglycemia and neurotoxicity is relatively increased. There is some evidence to suggest that the onset of diabetes may be more common when tacrolimus is given with azathioprine compared to with mycophenolate mofetil [23]. Care must be taken in specific demographic groups, such as African-Americans and females, with regards to high tacrolimus doses and hyperglycemia [24]. In contrast to the side-effect profile seen with cyclosporine, hirsutism and gingival hypertrophy do not occur with tacrolimus. Indeed, alopecia may be a side effect of tacrolimus.

Tacrolimus is frequently used as a substitute for cyclosporine when cyclosporine-related toxic effects occur; the converse is also applicable to tacrolimus-related toxic effects [24].

Drug Interactions

The calcineurin inhibitors and proliferation signal inhibitors are extensively metabolized by the cytochrome P-450 3A4 enzyme pathway in the liver; as a result, their blood levels are affected by drugs that induce or inhibit this pathway. As a result, the nephrotoxic effects of CNIs may be enhanced. The interactions may occur with very commonly used drugs; as such, constant attention is required and vigilance as to potential interactions, and utmost care should be taken when introducing new drugs. Table 10.3 summarizes potential interactions of CNIs with common, everyday medications.

Table 10.3 Overview of common calcineurin inhibitor drug interactions in cardiac transplantation

Drugs that increase cyclosporine/ tacrolimus levels	Drugs that decrease cyclosporine/ tacrolimus levels	Drugs that enhance nephrotoxicity
Calcium channel blockers: Diltiazem, verapamil, nifedipine, nicardipine	Antibiotics: Nafcillin and rifampin	Antibiotics: Aminoglycosides, vancomycin, trimethoprim-sulfamethoxazole
Antibiotics: Erythromycin, clarithromycin, doxycycline (cyclosporine only)	Anticonvulsants: Phenytoin, phenobarbital, carbamazepine	NSAIDs: All formulations, colchicine
Antifungal: Ketoconazole, voriconazole, fluconazole	Miscellaneous: Hypericum perforatum, ticlopidine (cyclosporine only), cholestyramine	Antifungals: Amphotericin B
GI agents: Metoclopramide, cimetidine, omeprazole		GI agents: cimetidine, ranitidine
HIV protease inhibitors		Antivirals: aciclovir
Miscellaneous: Amiodarone, allopurinol, grapefruit, grapefruit juice, methylprednisolone		Antineoplastics: Cisplatin

Adapted with permission from Kobashigawa [107]
Abbreviations: *GI* gastrointestinal, *HIV* human immunodeficiency virus, *NSAIDs* non-steroidal anti-inflammatory drugs

Antiproliferatives

An antiproliferative agent is usually used in current immunosuppressive regimens; azathioprine and mycophenolate mofetil (MMF) are the most commonly used. Early immunosuppressive protocols in the 1970s used azathioprine with prednisone, with relatively poor 1-year survival of 60–65% and 5-year actuarial survival of 35–40% [25, 26]. The introduction of cyclosporine significantly improved survival and somewhat relegated the role of azathioprine to that of an adjunctive agent; with the introduction of MMF in the 1990s, azathioprine has further fallen out of favor. However, it still holds value as a vital component of a low-cost immunosuppressive regimen, or where MMF is unsuitable.

Azathioprine

Mechanism of Action

Azathioprine is a prodrug that is hydrolyzed rapidly in the blood to 6-mercaptopurine, which is subsequently converted to thioinosine monophosphate, a purine analog which is its active metabolite (see Fig. 10.1). This purine analog is incorporated into DNA, thereby inhibiting its synthesis and the consequent proliferation of both T and B lymphocytes.

Adverse Effects

The major side-effects of azathioprine are hematologic, and hence complete blood counts should be regularly monitored. Myelosuppressive adverse effects, including leukopenia, anemia, and thrombocytopenia (see Table 10.2) may occur. Generally, dose-dependent, these events typically resolve after 7–10 days with dose reduction. More rarely, pancreatitis, hepatitis, and hepatic veno-occlusive disease may also occur.

Mycophenolate Mofetil (MMF)

Mechanism of Action

MMF is a reversible inhibitor of inosine monophosphate dehydrogenase, a crucial enzyme in the de novo synthesis of guanine nucleotides. Proliferating lymphocytes are dependent on this pathway because it is their only pathway for the purine synthesis and DNA replication; in contrast, other cells use both de novo and salvage pathways for purine synthesis. Therefore, MMF is a more selective inhibitor of lymphocyte proliferation than azathioprine. In vivo and in vitro mycophenolic acid blocks the proliferation of T and B cells, inhibits antibody formation and inhibits the generation of cytotoxic T cells [27]. Furthermore, MMF down-regulates the expression of adhesion molecules on lymphocytes.

Notes

MMF is largely preferred over azathioprine due to its reduced adverse-effect profile combined with superior efficacy in maintaining survival and preventing rejection. In a multi-center, active-controlled, randomized trial [28], MMF was compared with azathioprine when used in conjunction with cyclosporine and corticosteroids in 650 de novo heart transplant recipients. Because an intravenous form of the study drug was not available at the time of the trial, 11 percent of the patients withdrew before receiving the drug. Survival and rejection were similar in both groups when analyzed in an intention-to-treat manner. However, among treated patients, MMF was associated with a significant reduction in both mortality (6 vs. 11 percent, $p = 0.031$) and in the incidence of treatable rejection (66 vs. 74 percent, $p = 0.026$) at 1 year. These findings are supported by retrospective data from the International Society for Heart and Lung Transplantation (ISHLT) Thoracic Registry [29], which find significantly superior actuarial 1 and 3-year survival in MMF patients compared to azathioprine patients. (1 year, 96% vs. 93%; 3 year, 91% vs. 86%; $p = 0.0012$). MMF has also been demonstrated to be effective in reversing recurrent rejection when used in place of azathioprine [30, 31]. In patients with chronic renal dysfunction, switching from azathioprine to MMF in combination with cyclosporine reduction or withdrawal to improve renal function has also been employed as an effective strategy [32].

Adverse Effects

MMF is considerably less myelosuppressive than azathioprine and is usually well tolerated (see Table 10.2). The most common side-effects include nausea, vomiting, and diarrhea, which

usually respond to dose adjustment. However, the toxicity of MMF may be more closely related to the mycophenolic acid levels than the dose itself. There is also data to suggest that the risk of opportunistic infections may be higher in patients on MMF compared with azathioprine [28].

Proliferation Signal Inhibitors (PSIs): Sirolimus and Everolimus

The proliferation signal inhibitors include sirolimus and everolimus. Sirolimus is a natural product of the actinomycete *Streptomyces hygroscopicus* [33, 34]. Like tacrolimus, sirolimus is a macrolide antibiotic and is structurally related. Everolimus is an analog of sirolimus, with a shorter half-life and identical mechanism of action to sirolimus. In certain cases or scenarios, the proliferation signal inhibitors may be used in place of azathioprine or MMF (see later for a full discussion), but their role is still somewhat unclear; despite their stronger immunosuppressive effects, there appears to be greater potential for adverse events.

Mechanism of Action

Sirolimus and everolimus bind to the same family of immunophilins as tacrolimus, the FKBPs, but instead of blocking calcineurin-dependent T-cell activation, the resultant complex inhibits a key regulatory kinase; mammalian target of rapamycin (mTOR) (see Fig. 10.1). mTOR phosphorylates proteins that play a vital role in cell cycle regulation , in turn connecting signals from the growth factor receptors to the cell nucleus for stimulation of growth and proliferation of T and B lymphocytes [35, 36]. In this way, sirolimus/everolimus is able to specifically inhibit cell division. Notably, sirolimus has also been noted to inhibit arterial smooth muscle and endothelial cell growth via inhibition of mTOR; this has translated to reduced allograft atherosclerosis in animal models [37, 38].

Notes

Sirolimus, which was discovered before everolimus, has been shown to effectively inhibit acute graft rejection and treat refractory acute graft rejection in heart transplant recipients [39]. In randomized, open-label clinical trials, sirolimus has demonstrated reduced rejection compared to azathioprine, though with similar mortality [40]. Furthermore, sirolimus has been shown to decrease the development of cardiac allograft vasculopathy (CAV), as assessed by intravascular ultrasound (IVUS) at 6 months; the benefit was maintained at 2 years [40]. In existing patients with CAV, sirolimus was also demonstrated to slow the progression of CAV as per angiography [41]. Interestingly, sirolimus has also been noted for its antitumor effects; a useful quality in a field where a major cause of death after transplant is malignancy. In a recent study, the switch from cyclosporine to sirolimus in renal transplant recipients who subsequently developed Kaposi's sarcoma was shown to reduce tumor burden significantly [42].

Clinical trials involving everolimus have also demonstrated largely positive results. In a randomized double-blind prospective 634-patient three-arm trial that compared everolimus (1.5 mg or 3 mg) to azathioprine [43], significantly fewer patients on everolimus reached the 6-month composite endpoint of death, graft loss or retransplantation, loss to follow-up, biopsy-proven severe acute rejection, or rejection with hemodynamic compromise (36.4% and 27.0%, compared to 46.0%). Furthermore, a decrease in the development of CAV, as assessed by intravascular ultrasound (IVUS) at 12 months, was observed in the everolimus groups compared to those on azathioprine. These study results are further supported by a recent 721-patient clinical trial in heart transplantation [44] which found no difference between everolimus and MMF in 2-year survival and rejection, and actually found a favorable effect of everolimus in reducing CAV compared to MMF [45]. Interestingly, the rates of cytomegalovirus (CMV) infection have been noted to be significantly lower in everolimus patients compared to azathioprine.

Adverse Effects

When administered alone, sirolimus/everolimus are not noted to adversely affect renal function; however, data from clinical trials shows that everolimus with low-dose cyclosporine has been shown not to worsen [46] and may even improve renal function when compared to standard-dose cyclosporine with MMF—a finding supported in multiple prospective studies [44, 46–49], includ-

ing the more recent NOCTET study by Gullestad et al. and the recent SCHEDULE trial, which showed regular everolimus with no cyclosporine (with MMF) to be superior to cyclosporine with MMF for renal function.

Nevertheless, while potent effective immunosuppressive drugs, use of proliferation signal inhibitors following heart transplantation has remained limited because of evidence from clinical trials regarding worsening CNI nephrotoxicity, delayed wound healing and increased infection and dehiscence [50, 51]. Furthermore, data from the everolimus vs MMF trial showed an increased mortality from infection in the patient group with high-dose everolimus (3.0 mg) [44]. Other major adverse effects of the proliferation signal inhibitors include hyperlipidemia, hypertriglyceridemia with increased LDL cholesterol, mouth ulceration, deep venous thrombosis, proteinuria and more rarely, thrombocytopenia, neutropenia, and anemia (see Table 10.2) [52–56]. Rarely, cases of noninfectious pneumonitis have been reported with sirolimus [52].

Hypercholesterolemia, hypertriglyceridemia, thrombocytopenia and mouth ulcers are generally at least partially responsive to dose reduction [52]. PSI-induced hyperlipidemia also responds to conventional treatment with HMG-CoA reductase inhibitors (statins) and fibric acid derivatives (fibrates) [57].

Drug Interactions

It must be noted that interactions with sirolimus/everolimus and statins or fibrates may occur as a result of competitive metabolism via CYP3A [58]. Thus, heightened awareness is necessary for potential hepatic and muscular toxicity when combining statins or fibrates with sirolimus/everolimus. In a microcosm of immunosuppression, the risk of hyperlipidemia must be balanced against the powerful anti-atherogenic effects.

Statins

The use of statins post-cardiac transplant is now widespread and will be explained fully in Chap. 13. They are typically initiated a week or two after transplant (see Chap. 13 – Outpatient Management).

Major Clinical Trials of Maintenance Immunosuppression Regimens-Which Agent to Use?

Part of the reason that there remains no standardized protocol for immunosuppression is a lack of available evidence. Indeed, relatively few heart transplant procedures occur per year, thus limiting the number of randomized clinical trials available to inform treatment decisions. Consequently, the majority of ISHLT guideline recommendations are class IIa or IIb and based on level B or C evidence [59]. The most commonly used regimen consists of a triple therapy regimen, consisting of a corticosteroid, calcineurin inhibitor, and antiproliferative agent.

Typical major study endpoints of clinical trials of immunosuppression in heart transplantation have included the following, either alone or in combination: survival, rejection, CAV, and adverse events. While survival is the most important endpoint, the low population typical of heart transplant studies means that most studies are not powered to demonstrate a mortality benefit. However, the clinical endpoints of rejection, CAV, and adverse events, which studies are often powered to detect differences in, are noted to either indirectly or directly affect mortality, morbidity and quality of life and thus are considered clinically reasonable endpoints for the purposes of comparison.

Survival appears to be largely comparable in all the randomized clinical trials of immunosuppressants in heart transplantation, and in any case, these studies were not powered to demonstrate survival difference. The other clinical endpoints of rejection, CAV, and adverse events have revealed differences between immunosuppressive regimens across several trials. The major randomized clinical trials of immunosuppressive therapy in heart transplantation are summarized in Table 10.4.

Table 10.4 Overview of results from major randomized multicenter clinical trials comparing efficacy of immunosuppressive drugs in cardiac transplantation

Study	*n*	Follow-up	Survival	Rejection	CAV by IVUS	Renal function	Infections	Cholesterol and triglycerides	Hypertension	Hematologic	GI disorders	Other
Kobashigawa (1998) MMF vs. AZA	650	3 years	[a]MMF = higher survival	MMF = less rejection	NS; [b]MMF = less CAV at 1 year		MMF = more any opportunistic infection			AZA = more leukopenia	MMF = more diarrhea and esophagitis	NS for hyperglycemia treatment
Reichart (1998) TAC vs. CSA	82	1 year	NS	NS		NS	NS		CSA = more hypertension			NS for glucose intolerance
Taylor (1999) TAC vs. CSA	85	1 year	NS	NS		NS	NS	CSA = higher chol & tri	CSA = more hypertension	NS		
Eisen (2003) EVR vs. AZA	634	1 year	NS	EVR groups = less rejection	EVR groups = less CAV	EVR groups = worse renal function	EVR groups = lower viral/ CMV but more bacterial infections	EVR groups = higher chol & tri	NS	NS	NS	NS for wound infection
Keogh (2004) SIR vs. AZA	136	2 years	NS	SIR groups = less rejection at 6 months	SIR groups = less CAV	SIR groups = worse renal function	SIR groups = lower CMV but more pneumonia	NS for chol; SIR groups = higher trig	NS	SIR groups= more anemia & thrombocytopenia	AZA = more nausea; SIR groups = more diarrhea	AZA = more arrhythmia and atrial fibrillation; SIR groups = more mouth ulcers & abnormal healing
Grimm (2006) TAC vs. CSA	314	1.5 years	NS	TAC = less rejection at 6 months		NS	NS	CSA = higher chol & triglycerides	CSA = more hypertension	TAC = more anemia	CYA = more cholelithiasis	TAC = more diabetes mellitus & tremor; CSA = more gum hyperplasia &hirsutism
Kobashigawa (2006) TAC/MMF vs. TAC/ SIR vs. CSA/ MMF	343	1 year	NS	NS; TAC groups = lower any treated rejection		TAC/MMF = best renal function	TAC/SIR = lower viral but more fungal infections	NS for chol; TAC/MMF = lower trig	NS	NS		TAC/SIR = more insulin therapy & impaired wound healing; NS for diabetes mellitus

Study	*n*	Follow-up	Survival	Rejection	CAV by IVUS	Renal function	Infections	Cholesterol and triglycerides	Hypertension	Hematologic	GI disorders	Other
Baran (2007) TAC/MMF vs. TAC	58	1 year	NS	NS	NS	NS	TAC/ MMF = more hospitalized infections			NS		NS for malignancy
Lehmkuhl (2008) EVR/ rd-CSA vs. MMFsd-CSA	176	1 year	NS	NS		NS	EVR = Less CMV infections			MMF = more leukopenia		
Baran (2011) TAC/MMF vs. TAC alone	150	5 years	NS	NS	NS	NS; TAC alone group = numerically better renal function	TAC/MMF = more hospitalized infections			TAC alone = higher mean white blood cell count, but not clinically meaningful		
Eisen (2013) EVR-CSA vs. MMF-CSA	721	2 years	NS	EVR groups = numerically more rejection	EVR groups = less CAV	EVR groups = worse renal function	EVR = Less CMV infections	EVR groups = higher chol & triglycerides	NS	NS	NS	EVR 3.0 mg high dose = higher overall rate of discontinuation due to increased mortality
Andreassen (2014) EVR-rd-CSA followed by EVR only (early CSA withdrawal) vs MMF-CSA	118	3years[c]	NS	More mild rejection in EVR only group, but no difference after 1 year	EVR group- less CAV	EVR group- better renal function	EVR- numerically more infections	EVR groups = higher chol & triglycerides	NS	NS		

Adapted with permission from Costanzo et al. [59]

AZA azathioprine, *CSA* cyclosporine, *EVR* everolimus, *MMF* mycophenolate mofetil, *rd-CSA* reduced-dose cyclosporine, *sd-CSA* standard-dose cyclosporine, *SIR* sirolimus, *TAC* tacrolimus

[a]Treated-patient population (see text)

[b]Reanalysis of MMF IVUS data

[c]Subsequent 3-year follow up study, published 2016

Comparison by Survival

Clinical trials have not demonstrated differences in survival among the various immunosuppressive regimens, primarily due to inadequate statistical power. There is, however, one notable exception; in a multicenter clinical trial of MMF compared to azathioprine, a treated-patient analysis demonstrated significant 1-year survival benefit for patients on MMF [28]. In this case, the intent-to-treat analysis was severely skewed by unusually high rates of perioperative mortality in the MMF group that occurred by chance, with patients having been randomized before transplant. Since this trial, and other subsequent trials confirming a benefit to MMF in not just survival but also CAV [60], MMF has become the antiproliferative of choice over azathioprine. Nevertheless, the randomized clinical trials comparing cyclosporine to tacrolimus [16, 17, 21], everolimus to MMF [44], sirolimus to MMF, sirolimus to azathioprine [40], and everolimus to azathioprine [43] have not shown a survival benefit.

Comparison by Incidence of Rejection

Several immunosuppressive agents have been shown to decrease the incidence of rejection (Table 10.4). However, it must be noted that many of these trials assessing the efficacy of MMF [28], everolimus [43] and sirolimus [40] used azathioprine as the comparator, which itself has fallen out of favor—thus making the comparison less clinically useful. Nevertheless, more recent clinical trials for everolimus have used MMF as a comparator, including the large multicenter everolimus vs MMF trial [44].

A large 2006 European multicenter trial comparing tacrolimus to cyclosporine reported by Grimm et al. [21] revealed a significantly lower rejection rate at 6 months for tacrolimus compared to cyclosporine (both in combination with azathioprine). More recently, a three-arm trial compared regimens of tacrolimus/MMF, tacrolimus/sirolimus, and cyclosporine/MMF [18] (all in combination with corticosteroids) and found that both the tacrolimus regimens had significantly less treated rejection at 6 months than the regimen with cyclosporine/MMF. Furthermore, tacrolimus/MMF when compared only to cyclosporine/MMF had significantly lower incidences of cellular rejection (ISHLT grade > 3A/2R) and any treated rejections.

Therefore, the overall rejection data from the clinical trials suggest that tacrolimus-based regimens may have benefit over cyclosporine-based regimens (class IIb/level B of evidence) [18, 20]. Regarding specific combinations, comparisons of the contemporary immunosuppressive combination regimens of tacrolimus/MMF and cyclosporine/MMF suggest that tacrolimus/MMF may have benefit over cyclosporine/MMF for preventing rejection (class IIb/level B of evidence). Everolimus with reduced-dose cyclosporine has not been compared to tacrolimus/MMF in a randomized trial.

However, the relative advantage of tacrolimus-based therapy for rejection is balanced by an increased incidence of diabetes. Furthermore, the tacrolimus/sirolimus-treated patients in this three-arm trial had lower rejection but increased nephrotoxic events and impaired wound healing, rendering this regimen less desirable compared with tacrolimus/MMF [18].

A recent 721-patient multicenter clinical trial in 2013 recently compared everolimus to MMF; specifically, reduced dose everolimus 1.5 mg with reduced-dose cyclosporine was found to be no different to MMF with standard-dose cyclosporine in terms of 1 and 2-year biopsy-proven acute rejection, although 3-month mortality was found to be higher in everolimus patients who had undergone induction [44]. Other studies comparing everolimus with low-dose cyclosporine to MMF (with or without low-dose cyclosporine) also demonstrated no difference in rates of rejection compared to MMF [47, 48]. However, a Scandinavian trial investigating low-dose everolimus with early cyclosporine withdrawal followed by regular everolimus dosing compared to standard cyclosporine therapy (both groups with MMF and steroids) showed higher asymptomatic rejection in the everolimus group, further supporting the notion that caution is required in the early initiation of everolimus [49].

Comparison by Effect on Cardiac Allograft Vasculopathy (CAV)

In many of the recent randomized trials of immunosuppression, CAV as an endpoint has been assessed through the use of intravascular ultrasound (IVUS) assessment at 1-year post-transplant compared to baseline. Prior studies have established that an increase of 0.5 mm or more in maximal intimal thickness on coronary IVUS within the first year after heart transplant, is associated with a significantly increased risk of 5-year all-cause death, myocardial infarction, and the subsequent development of angiographic severe CAV. Thus, IVUS has served as a surrogate endpoint for CAV in subsequent immunosuppression trials. Furthermore, IVUS is increasingly used to identify patients at high risk for future cardiovascular events, and may aid in allowing therapeutic adjustment of immunosuppression [61].

Several of the recent randomized immunosuppressive trials including the MMF vs azathioprine [28], everolimus vs azathioprine [43] and sirolimus vs azathioprine [40] trials demonstrated benefit compared to azathioprine in the first-year IVUS results, with a lower incidence of patients developing CAV as defined by an increase of 0.5 mm or more in maximal intimal thickness on coronary IVUS within the first year after heart transplant.

The MMF versus azathioprine study showed benefit in CAV retardation using a threshold for first-year change in maximum intimal thickness greater than 0.3 mm, but at 0.5 mm significant benefit was no longer seen. The sirolimus vs azathioprine study [40] showed benefit for sirolimus therapy using the usual 0.5 mm threshold; however, patients were studied at baseline and at 6 months, not 12, after heart transplantation, making IVUS less useful for predictions of subsequent CAV. Nevertheless, in a randomized study of cardiac transplant patients with established CAV, sirolimus has been demonstrated to slow disease progression as determined by angiography (not IVUS) [41].

In particular, the everolimus studies have been the clearest in demonstrating a benefit in CAV retardation over azathioprine and MMF. In the everolimus vs azathioprine trial, this was demonstrated using several IVUS parameters (intimal volume, intimal area, intimal index in addition to maximal intimal thickness >0.5 mm) [43]. Additionally, in the multicenter trial comparing 1.5 mg everolimus as compared to standard MMF, there was significantly reduced proportion of patients on everolimus with CAV as defined by IVUS [44]. Furthermore, while not a direct comparison against MMF, the CAV benefits of everolimus are further supported by IVUS data from a Scandinavian trial investigating low-dose everolimus with early cyclosporine withdrawal followed by regular everolimus dosing compared to standard cyclosporine therapy (both groups with MMF and steroids), which show a lower incidence of 12-month >0.5 mm increase in maximal intimal thickness in the everolimus group [62].

Thus, there is considerable evidence for CAV benefit with MMF, everolimus and sirolimus over azathioprine, and thus these drugs should be considered for inclusion (class IIb, level B) [40, 43, 60]. There is also strong evidence to suggest that everolimus is superior to MMF for CAV retardation [44]. However, there remain concerns with safety, regarding renal dysfunction for everolimus/sirolimus when combined with standard-dose cyclosporine, and thus caution should be exercised; with low-dose cyclosporine, everolimus appears safer in this regard [47–49]. Furthermore, the use of 0.5 mm change in maximal intimal thickness on 12-month IVUS as a surrogate for subsequent CAV and poor outcomes is only strictly applicable to the everolimus vs azathioprine and everolimus vs MMF studies. Overall, the value of everolimus in retarding allograft vasculopathy appears superior to the competition, but this must be balanced against its negative aspects.

Comparison by Adverse Effect Profile

While survival, rejection data and CAV data are comparable amongst the newer agents of MMF, everolimus and sirolimus, adverse events are often the deciding factor regarding the choice to use a specific drug regimen for a certain patient.

Regarding everolimus/sirolimus, the inferior renal function seen when in combination with standard-dose cyclosporine, along with other side effects of hyperlipidemia, edema and impaired wound healing and greater risk of infection, must be considered when seeking to use this combination. Sirolimus is also noted to cause significantly higher rates of anemia, thrombocytopenia, diarrhea and mouth ulceration. There appears to be a general trend for significantly increased serious adverse events in trials comparing everolimus, without affecting the primary endpoint [47, 49, 62]. Nevertheless, from a renal standpoint, the use of everolimus in more recent trials with reduced or even withdrawn cyclosporine has demonstrated either comparable or improved renal function, compared to MMF with standard-dose cyclosporine [44, 46, 47, 49].

Evidence from other, nonrandomized studies has also demonstrated that conversion from CNI-based immunosuppression to sirolimus-based immunosuppression results in improved renal function [63, 64]. A recent multicenter randomized trial demonstrated that conversion to CNI-free immunosuppression (MMF, sirolimus) was superior to CNI-reduced immunosuppression in improving renal failure in late heart transplant recipients (average 5 years post-transplant) with renal insufficiency [65].

Other side effects must also be considered: Patients on cyclosporine had higher cholesterol and triglyceride levels, and more hypertension, cholelithiasis, hirsutism, and gum hyperplasia than tacrolimus-treated patients [19–21]. However, tacrolimus-treated patients had more diabetes mellitus, tremor, and anemia than cyclosporine-treated patients. Comparing regimens [18] the regimen of tacrolimus/MMF compared to tacrolimus/sirolimus and cyclosporine/MMF had the best renal function and lowest triglyceride levels. However, the tacrolimus/sirolimus group had a higher incidence of poor wound healing and the most patients on insulin therapy.

Overall, sirolimus/everolimus is often preferred in patients with CAV, but is generally not used in the first few months due to the drug leading to poor wound healing, increased infection risk, potentiating the calcineurin inhibitor nephrotoxic effects and propensity for other adverse events and side-effects.

Individualizing Immunosuppression

Caution should be exercised in the interpretation of the aforementioned trials. The most appropriate dose of the medications is unknown, so outcomes in clinical trials may be affected by different doses. Adverse effects may result from a drug interaction within a combination (e.g. tacrolimus with sirolimus) rather than a drug by itself. Additionally, randomized clinical trials tend to include a lower risk population with many exclusion criteria (to exclude high risk patients) including renal dysfunction, older age and pre-sensitized patients. Nevertheless, even taking these concerns into account, there are important findings that can be taken from the results of the randomized clinical trials and applied to our practice.

The adverse events observed for specific drugs and combinations in the randomized clinical trials further support need for individualization of immunosuppression. For example, patients with high risk for CMV infection might benefit from everolimus- or sirolimus-based immunosuppression; patients with gingival hyperplasia from a tacrolimus-based regimen; patients with pre-existing diabetes or excess tremors/peripheral neuropathy from a cyclosporine-based regimen. The adverse events listed in Table 10.3 (along with the results of the clinical trials) can be used to determine what immunosuppressive drugs would best serve patients with specific characteristics in the selection of a particular immunosuppression regimen.

Immunosuppression protocols vary by program, and selection of specific agents and combinations is generally based on that center's experience and their interpretation of randomized clinical trials in the literature. As immunosuppressive regimens continue to evolve with newer drugs becoming available, the choice of immunosuppression in heart transplantation will change, depending on the results of future immunosuppressive randomized clinical trials.

Induction Therapy: Strategies

Currently used in approximately 50% of cardiac transplant patients [2], induction therapy consists of intense perioperative immunosuppression administered intravenously, typically starting on the day of transplantation and lasting 3–7 days. The main benefits of this therapy are two-fold: a considerable reduction in rejection in the early postoperative period, when graft dysfunction, especially in sensitized patients [66], and renal dysfunction are problematic. Furthermore, induction therapy also allows delayed introduction of CNIs, therefore avoiding exacerbation of renal dysfunction [67, 68] .

Induction therapy can largely be divided into two categories: depleting antibodies and non-depleting antibodies [69]. Depleting antibodies include both monoclonal (anti-CD3 antibodies [OKT3] and alemtuzumab) and polyclonal (anti-thymocyte globulin, ATG) antibodies. Depleting antibodies reduce alloreactive T cells at the time of transplantation, in turn suppressing host response to the allograft. In contrast, nondepleting antibodies inhibit critical T-cell activities (such as IL-2-driven cell proliferation).

A summary of induction agents can be found in this chapter's Clinical Pearls, which summarizes trade names, pharmacology, necessary adjustments for renal or hepatic dysfunction, and dosing and general monitoring guidelines for commonly used intravenous induction immunosuppressive drugs. Common adverse events of drugs for both induction therapy and maintenance therapy are included in Table 10.1.

Polyclonal Antibodies

Mechanism of Action

Polyclonal anti-lymphocyte antibodies are available in two ATG formulations: Atgam (equine ATG) and Thymoglobulin (rabbit ATG) polyclonal antibodies. ATG is a polyclonal antibody derived from immunization of rabbits or horses with human thymocytes. The final product includes antibodies against CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, and HLA class I heavy chains, and is effective in preventing cellular immune responses against a variety of antigenic stimuli, through substantial lymphocyte depletion [70, 71]. Administration of ATG results in complement-dependent opsonization, eventual cell lysis and apoptosis of these cells, thus preventing rejection.

Notes

While the concept of induction therapy was originally designed to induce tolerance to the graft (i.e. requiring no subsequent immunosuppression) this aim did not materialize. ATG is generally given for 3–7 days postoperatively and is the most commonly used induction agent. With regards to the two formulations, there is limited data comparing Atgam to Thymoglobulin for induction purposes in cardiac transplant recipients. Around 20% of cardiac transplant recipients receive ATG as induction therapy [2].

ATG induction is often reserved for patients at highest risk of rejection or renal failure. Therefore, patients with high levels of circulating antibodies or known donor-specific antibody, African American patients, and patients supported with ventricular assist devices with high levels of pre-formed antibodies, may be the best candidates to undergo induction. It is also used in the early perioperative management of patients with known pre-existing or worsening renal insufficiency, as it enables delayed initiation with CNIs to prevent the development of acute renal failure. As mentioned in Chap. 12, it is also used to treat certain types of rejection episodes.

It is controversial as to whether ATG actually improves cardiac transplant outcomes. To date, no randomized prospective trial has been conducted to assess benefit for ATG induction in terms of survival, rejection or CAV. However, a national retrospective study in the United Kingdom was recently performed [72], encompassing over 2000 patients between 1995 and 2008, 1000 of whom had been inducted with ATG. The study found no significant difference in survival at 10 years between the two groups, but investigators did note lower rates of rejection over the first year. However, this potential benefit was accompanied by increased rates of infection.

Adverse Effects

The xenogeneic (horse/rabbit) origin of ATG may induce a host antibody response leading to acute hypersensitivity response or rarely, serum sickness on subsequent exposure, which is characterized by fevers, chills, tachycardia, hypertension or hypotension, myalgias, and rash, and may occur after the first dose. Flow cytometry to monitor T cells is helpful in assessing effectiveness and adjusting dosing. Rarely, cytokine release syndrome, which is more common with the monoclonal antibody OKT3, can occur. Hypertension, diarrhea, and headache are common. Furthermore, leukopenia and thrombocytopenia may occur, necessitating either a reduction in dose or termination of therapy. There is an increased incidence of either primary or reactivation CMV infections with ATG use; therefore, prophylactic doses of ganciclovir are given during and for up to 3 months after commencing ATG [59].

A major risk of ATG is malignancy, mainly consisting of virally induced cancers. The cumulative load of immunosuppression has been shown to be a primary determinant of non-Hodgkin's lymphoma incidence early after transplantation [73].

Monoclonal Antibodies

OKT3

OKT3 is a murine monoclonal antibody that recognizes and binds to the T cell receptor-CD3 complex on the surface of circulating T cells. The binding of OKT3 to CD3 renders the T cell unable to respond to an antigen challenge or to bind to target cells. In turn, T cells bound to OKT3 are opsonized and removed from the circulation by macrophages in the liver and spleen. Thus, host immune response to the graft is handicapped.

While it has been used to treat steroid-resistant rejection with some success in the cardiac transplant population, its use as a perioperative induction agent has not been promising. In a clinical trial, although the incidence of early cellular rejection was lower than with conventional triple drug therapy alone, there was an increased incidence of late rejection, a higher rate of antibody-mediated rejection, and no overall benefit at 1 year after cardiac transplantation [74]. Due to decreasing use, OKT3 is no longer available in the United States.

Alemtuzumab

Alemtuzumab is a humanized rat monoclonal antibody that targets the CD52 antigen expressed on both T and B cells, and is thus lymphocyte-depleting. The resultant lymphopenia lasts for approximately 6 months and may persist for up to 3 years in some individuals [75]. In kidney transplant recipients, use of alemtuzumab has permitted use of lower intensity maintenance immunosuppression [76]. Use of this drug is under investigation in heart transplantation, and early experience suggests that it may decrease the incidence of early (<12 months) acute cellular rejection while allowing the use of lower intensity, steroid-free maintenance immunosuppression [77]. However, decline in renal function and increase in antibody-mediated rejection has also been noted.

Basiliximab and Daclizumab

Mechanism of Action

Basiliximab is a monoclonal antibody that selectively binds to the IL-2 receptor of T-lymphocytes, blocks binding of IL-2 to the receptor complex, and inhibits IL-2 mediated T-lymphocyte proliferation [78, 79]. A second IL-2 receptor antagonist, daclizumab, is a humanized anti-IL-2R (CD25) monoclonal antibody that has the murine antigen-binding sequences molecularly engrafted onto a human antibody [80]; however, daclizumab has since been discontinued by the manufacturer due to diminishing use.

Notes

Basiliximab is the most commonly used induction agent, with 30% of transplant patients undergoing induction [2]. In renal transplantation, basiliximab is FDA-approved for the prophylaxis of acute organ rejection in patients as part of a

regimen that also includes cyclosporine and corticosteroids. In cardiac transplants, it is generally used in high risk patients similar to how ATG is used; specifically, for those at highest risk of rejection or renal failure. In a double-blind randomized controlled trial comparing daclizumab with placebo in 434 heart transplant recipients, there was a significant increase in infective mortality due to a study design flaw where some patients received double induction with a cytolytic agent in addition to daclizumab [80]. This trial is notable for being the only multicenter randomized clinical trial of induction versus non-induction in cardiac transplantation.

A recent Cochrane meta-analysis of four trials comparing IL-2 receptor antagonists (including the daclizumab study) versus no induction found no significant difference in outcomes except possibly acute rejection [81]. Of note, acute rejection occurred significantly less frequently with IL-2 receptor antagonist versus no induction when a fixed effect model was applied but not when a random-effects model was used.

Adverse Effects

Basiliximab is notable for a significantly lower incidence in drug-related adverse events [82] compared to ATG. Unlike ATG, cytokine release syndrome has not been reported after administration of this type of drug, and there has been no established increased risk of malignancy [78–80, 83]. However, hypersensitivity has been reported with initial exposure and subsequent re-exposure to basiliximab. In such scenarios, the second dose should be withheld [84].

To Use Induction or Not to Use Induction?

From a clinical perspective, the main advantages of induction therapy are to allow delayed initiation of nephrotoxic CNIs in patients with pre-existing or surgery-induced compromised renal function and to provide some flexibility with respect to early steroid weaning or use steroid-free baseline immunosuppression regimens after transplant. Other indications for induction therapy include sensitized patients and those at higher rejection risk. However, despite the common use of induction therapy for nearly 30 years (currently 52%) there is not yet a large and well-designed definitive, prospective randomized clinical trial examining the clinical utility of monoclonal or polyclonal induction therapy, with the exception of daclizumab (which is no longer in use) [80]. Certainly, the data remains unclear with regard to whether there is an actual benefit to induction, notwithstanding the risk of rejection. Thus the disadvantages and benefits of induction therapy following heart transplantation need to be carefully weighed.

Innovative Strategies to Minimize Immunosuppression

Given the numerous adverse effects of long-term maintenance immunosuppressive agents, a general goal in stable patients is to minimize immunosuppression safely while still protecting against the occurrence of rejection.

Steroid Withdrawal

Long-term steroid therapy is known to be associated with a host of adverse effects, including hypertension, osteoporosis, opportunistic infection, dyslipidemia, glucose intolerance. However, completely steroid-free regimens have been associated with poorer long-term outcomes in relation to regimens with steroids; in an early study of this concept, rejection rates were higher and half the patients were forced to resume maintenance steroids [85]. However, more recent studies demonstrate that careful selection of low-risk candidates, and an appropriate time-point for commencement of steroid weaning may yield more success, with no long-term increase in death or rejection. Patients who are withdrawn from steroids and suffer rejection may require resumption of a steroid regimen.

There are two main steroid withdrawal strategies. Early withdrawal of prednisone is typically attempted in first month of transplantation in

combination with peri-operative cytolytic induction. Long-term outcomes in older studies have been variable, with success in 50–70% of patients [86–88]; however, more recent data from the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial demonstrated successful early corticosteroid weaning commencing at 8–12 weeks post-transplant in 100% of the 58 patients enrolled [89, 90]. Nevertheless, given that acute rejection tends to occur during the first 6 months after transplantation, late steroid withdrawal after this period has generally been more successful with steroid withdrawal being achieved in up to 80%, even without the use of induction therapy [91, 92]. A typical technique would be to wean from 5 mg/day at month 6 post-transplant, lowering the dose by 1 mg/day each month. It has proven difficult to demonstrate a clear benefit to patients from steroid withdrawal through avoidance of side-effects, possibly because the patients receiving steroids in this comparison are already on low doses.

Calcineurin Inhibitor Avoidance, Withdrawal and Minimization

The rationale for reducing CNI dosages centers around minimizing the nephrotoxic effects of these drugs. Indeed, the cumulative incidence of chronic renal failure in heart transplant recipients has been reported at 10.9% over 5 years [93], largely attributable to the effects of CNIs. However, care must be taken with this approach, and as with steroid withdrawal, patient characteristics should be taken into account.

In addition to MMF being associated with better survival than azathioprine [28], there is evidence from multiple retrospective multi-center studies that MMF use rather than azathioprine following polyclonal induction therapy allows a lower cyclosporine level, resulting in concomitantly improved renal function, with no difference in rejection [94, 95]. In contrast, the substitution of sirolimus for azathioprine appears to be of limited benefit, given the propensity of sirolimus to combine with CNIs to exacerbate nephrotoxicity.

Furthermore, monitoring of cyclosporine levels 2-h post-administration (C2) as opposed to trough level monitoring (C0) has been observed to allow lower CNI dosing while maintaining efficacy of immunosuppression, i.e. without compromising patient renal function and rejection outcomes. However, these results were in allografts greater than 1 year post-transplant [96]. There are preliminary reports of early C2 monitoring being safely used in heart transplant recipients in combination with basiliximab induction, without increased risk of rejection nor impaired renal function [97]; however, longer term outcomes remain to be seen.

CNI avoidance protocols have also been attempted in small studies, with a regimen of sirolimus, MMF and corticosteroids; side effects included myelosuppression, and hypercholesterolemia and hypertriglyceridemia [98]. Nevertheless, despite acceptable freedom from rejection (75%) and excellent renal function and survival (100%) in the very small cohort there is limited data and a general lack of enthusiasm to explore the concept of avoiding CNIs entirely, despite their nephrotoxic effects.

The majority of studies that seek to minimize the effect of CNI toxicity have focused on initiating an immunosuppressive regimen with CNIs in addition to MMF/azathioprine and corticosteroids, followed by CNI withdrawal and initiation of another agent, typically sirolimus or everolimus.

Landmark Trials in CNI Minimization and Withdrawal

Heart Save the Nephron Trial

Initial studies on CNI withdrawal investigated the effect of withdrawing CNIs late after transplantation (>1 year) and replacing with sirolimus and generally found that patients with moderate renal impairment improved their renal function significantly compared to control groups without increased rates of rejection after this switch [99, 100–103]. The Heart Save the Nephron (STN) trial, a multicenter randomized endeavor, sought to confirm if early CNI withdrawal and

substitution for sirolimus at 12 weeks post-transplant also demonstrated renal improvement without compromising rejection and survival outcomes [103]. In this trial, MMF and prednisone were the adjunctive immunosuppressants. Unfortunately, the study was forced into early termination, as greater than 50% of the 7 patients randomized to sirolimus experienced an ISHLT ≥ 3A/2R rejection episode, with one patient experiencing hemodynamic compromise. One must therefore conclude that early initiation of sirolimus in the absence of CNI may not be safe in the early period following heart transplantation, especially considering how effective CNIs have been in this regard.

NOCTET Trial

The NOrdic Certican (Everolimus) Trial in HEart and lung Transplantation (NOCTET) trial [47] was a 282-patient, 12-month open-label multicenter study comparing standard dose CNI-based immunosuppression to everolimus with reduced-dose CNI in thoracic transplant patients greater than 1 year post-transplant. The primary endpoint of mean change in mGFR from baseline to month 12, was significantly superior in the everolimus group, without a concomitant increase in rejection. However, serious adverse events were significantly higher in the everolimus group. Nevertheless, this was one of the first multicenter data points to suggest that everolimus with reduced-dose CNI was a viable strategy in stable maintenance patients.

SCHEDULE Trial

In the Scandinavian heart transplant everolimus de novo study with early calcineurin inhibitors avoidance (SCHEDULE) randomized open-label trial [49], an interesting approach where low-dose everolimus with low-dose cyclosporine was used initially in addition to MMF and corticosteroids, followed by early cyclosporine withdrawal and increase to regular dose everolimus at 7–11 weeks post-transplant, in contrast to a control group with standard cyclosporine (adjuvant agents were MMF and corticosteroids, and all patients received ATG induction). The primary endpoint of GFR at 12 months post-transplant was significantly increased in the everolimus group, compared to the cyclosporine control group; furthermore, 12-month IVUS showed a significantly lower incidence of CAV in the everolimus group. However, biopsy-proven rejections at 1 year were increased in the everolimus group. Despite this, left ventricular function was considered similar between the two groups. A subsequent followup of the SCHEDULE trial revealed that this renal advantage persisted at 3-years [62]; again, cardiac function remained similar at 3 years, and incidences of rejection after 1 year were not significantly different. However, there was a trend towards increased serious adverse events in the everolimus group. Overall, the results suggest that in patients with induction, early CNI withdrawal after heart transplantation supported by everolimus is acceptably safe at intermediate follow-up, and offers sustained renal benefit.

Calcineurin Inhibitor Monotherapy

While an unusual strategy, there may be special cases where patients are intolerant to antiproliferative medications (myelosuppression), have severe infections, or are pre-disposed or have suffered severe side effects to steroid therapy. Of note, the Tacrolimus In Combination, Tacrolimus Alone Compared (TICTAC trial) [89, 90] was able to demonstrate that tacrolimus monotherapy had comparable rejection compared to tacrolimus/MMF-treated patients. In this prospective randomized trial, induction therapy was not routinely used; patients were randomized to a group where MMF was maintained (control) or to a group where it was discontinued 14 days after transplantation. Furthermore, early steroid weaning was successful in 100% of the patients it was instituted in. Remarkably, there was no significant difference in rejection, survival, and CAV by IVUS between groups, although there was worse 6-month renal function in the monotherapy group due to increased tacrolimus doses. While a population of largely low-risk patients, these findings are nevertheless interesting, suggesting the possibility that early corticosteroid weaning, dual therapy, or even

tacrolimus monotherapy are viable options for select heart transplant patients. However, more data is certainly needed on this topic.

Monitoring of Immunosuppression

Minimization of immunosuppression requires vigilance to avoid the risk of rejection; there is a fine balance to be met. As more drugs are withdrawn, therapeutic monitoring becomes increasingly important. Regular clinical evaluation, endomyocardial biopsy, and echocardiography remain the principal tools for rejection monitoring during drug weaning (see Chap. 12). Furthermore, immunosuppression can be guided by the perceived risk for rejection as determined by serum antibody analyses (see Chap. 12).

The ImmunKnow T-cell assay (Viracor-IBT Laboratories, Inc., Lee's Summit, MO, USA) is a peripheral whole-blood assay which assesses the net state of immunosuppression in transplant recipients. From validation studies in patients [104, 105] with biopsy-proven rejections, a low score has been demonstrated to correlate with infection risk, and a high score indicates a higher chance of suffering rejection, although a definitive association with rejection has not been proven. Thus, the assay is able to provide a target zone for immunosuppression to minimize both infection and rejection. Such a test may be performed serially to compare results over time. According to the manufacturer's guidelines, a low score is considered <225 ng/ml ATP and high is >525 ng/ml; the validation study [104] revealed 280 ng/ml to be the intersection of odds ratio curves for infection and rejection. However, the test may be confounded by an intrinsically low white blood cell count or African American ethnicity, which may lower the score.

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Managing Infections in Cardiac Transplantation

11

Phillip Zakowski

Clinical Pearls

- Pre-transplant screening of the donor should include screening for bacterial/fungal infection, as well as various viral and protozoal serologies.
- Pre-transplant screening of the recipient should include a thorough history of antibiotic allergies, as well as screening for the same bacterial/fungal/viral/protozoal infections as in the donor.
- The vaccination history of the transplant candidate should be reviewed and updated prior to transplant. Vaccination post-transplant is allowed except for the use of live virus vaccines.
- Prophylaxis for bacterial infections should be given just prior to surgery, with drugs selected based on activity against skin flora. Select antibiotics should be administered based on microbiologic sensitivities in the event of an infected VAD or ongoing donor infection.
- Bacterial organisms that may cause infection post-transplant include Staphylococci, Enterococci, Streptocoocci, Listeria, Nocardia, C. difficile, Pseudomonas, H. influenzae and Legionella.
- Prophylaxis against CMV and HSV in all recipients should include valganciclovir or acyclovir immediate post-transplant, dependent on donor and recipient history of infection.
- Common viral infections post-transplant include CMV, HSV, VZV, community respiratory viruses.
- Prophylaxis against Pneumocystis and Candida should include trimethoprim-sulfamethoxazole as first-line treatment.
- Common fungal infections post-transplant include Candida and Aspergillus.
- Clinical features of infection may include fever, wound infection, pulmonary infiltrates, urinary tract infections, CNS infection, or GI/liver infection.
- A clinical approach to infectious features should take into account the time elapsed since transplant, donor/recipient infectious history, current immunosuppression regimen including recent induction, history of rejection and recent exposure history.
- Additional preventive measures against infection include in-hospital handwashing, and minimization of environmental or occupational exposures to potential pathogens, including pet, food and travel-related exposures.

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Introduction

While the prevention of rejection is crucial for long-term survival, the immunosuppressants that prevent rejection also have the side-effect of compromising the immune system of the recipient. As a result, cardiac transplant recipients are at risk for many opportunistic infections, as well as reactivation of latent infections. This chapter aims to provide an overview of the management of infections in cardiac transplantation, including donor and recipient pre-transplant screening, general prophylaxis and infection prevention, an overview of the most common pathogens, and general clinical approaches to infection in the cardiac transplant recipient.

Pre-transplant Screening, Donor and Recipient, Serologic Testing

Because organ donors represent a potential vector of disease transmission to the recipient, appropriate donor serologic screening prior to transplantation is crucial. Serologic testing reduces the risk of exposure to the recipient of various infections without prohibitively limiting the number of available organ donors. Infectious disease screening includes both routine serological testing and screening for potential transmission of bacterial infections.

When a donor heart becomes available, the medical and social history available in the UNOS database should include relevant information on risk factors such as prior hospitalizations, blood transfusions and intravenous drug use. These factors present an increased risk for acute HIV, HBV and HCV infection even in cases where serologic testing may be negative. Furthermore, the OPO provides results from donor microbiology cultures, serum serologies, and history of infections and/or bacteremia. Here, we will cover donor screening for each group of micro-organisms in greater detail.

Donor Screening

Bacterial/Fungal Transmission

Bacterial infections may be transmitted through a contamination of the heart during procurement, transport of the organ or donor bacterial infection. Most commonly, the source is a donor bacterial infection with bloodstream involvement, such as line sepsis, pneumonia, intra-abdominal sepsis from trauma to the bowels, or even post-traumatic cellulitis. Blood cultures should therefore be routinely performed as part of the evaluation process for a potential donor heart.

While isolated cases report transmission of bacteria such as *Staphyloccoccus, Pseudomonas* and *Escherichia coli* from donor to recipient causing serious infective complications and death [1], more recent and comprehensive data suggests that donors who die of severe community-acquired infections (meningitis, pneumonia, septic shock) should not be arbitrarily excluded [2]. With this in mind, the ISHLT criteria [3] specifies that hearts from donors with severe infection can be used, provided that the following criteria are met: donor infection is community-acquired and donor death occurs rapidly (within 96 h); repeat blood cultures before organ procurement are negative; pathogen-specific anti-microbial therapy has been administered to the donor; donor myocardial function is acceptable; and there is no evidence of endocarditis by direct inspection of the donor heart. Additionally, it is recommended that in cases where such hearts are used for transplantation, the recipient should undergo surveillance blood cultures on the first post-operative day and pathogen-specific antimicrobial therapy should be administered for an appropriate duration of time. The guidelines also apply for cases of latent donor-derived *Mycobacterium tuberculosis*, which has previously been a controversial area (donors from patients with active tuberculosis are not recommended) [4].

Viral Transmission

Hepatitis B

While it is approximated that 1/3rd of the global population would have serological evidence of past or current Hepatitis B (HBV) infection, prevalence in the United States is thought to be less than 2% [5]. The current policy of the Organ Procurement Transplant Network (OPTN) requires that all organ procurement organizations (OPOs) perform deceased donor testing for Hepatitis B

surface antigen (HBsAg) and antibodies against Hepatitis B surface antigen (anti-HBs) and core antigen (anti-HBc), although some OPOs may perform additional testing, including IgG/IgM anti-HBc and HBV nucleic acid testing (NAT) [6].

There is relatively little retrospective data on the long-term success of cardiac transplants involving donors with past HBV infection. Studies examining the use of anti-HBc+ donor hearts (both with and without lamivudine prophylaxis) show very low rates of transmission of clinical hepatitis from donor to recipient [7–11], and a post-hoc analysis of UNOS data shows anti-HBc+ donor status to have no negative affect on overall survival in thoracic transplant recipients [12]. Further data from a Taiwanese transplant center assessing the use of HBsAg+ donor hearts also demonstrate relatively low rates of transmission (8%) [11–14]. Despite this, many OPOs and transplant centers within the United States currently do not accept donors who are HBsAg, IgM anti-HBc or HBV NAT positive due to concern for acute, reactivated, or occult chronic HBV infection in the donor with the risk of transmission to the recipient. When the donor is anti-HBc IgG positive alone, some OPOs and transplant centers will accept such organs (as this is indicative of past exposure rather than current exposure) but overall there remains no uniform approach to donor selection nor recipient management. In cases where donors with previous exposures to HBV are accepted, recipient management is detailed below.

Hepatitis C

Screening for Hepatits C (HCV) is typically performed by anti-HCV assays, and more recently, nucleic acid testing. However, data on outcomes of anti-HCV-positive heart donors is generally limited by small sample sizes and missing donor and recipient characteristics. Furthermore, much of the data is somewhat outdated as nucleic acid testing has not been widely used for evaluation of anti-HCV-positive donors. Retrospective data demonstrates that transplantation of anti-Hepatitis C (anti-HCV) positive donor organs into uninfected recipients results in very high rates of chronic HCV infection, with reported transmission rates ranging from 7% to 82% [15–17].

With regard to subsequent outcomes, while earlier studies have suggested that transplantation of anti-HCV-positive donors to HCV-negative recipients led to equivalent outcomes, the majority have reported significantly worse outcomes for patients receiving HCV-positive cardiac allografts, including accelerated cardiac allograft vasculopathy, cirrhotic liver disease, and increased mortality [18]. Consequently, it has traditionally been the policy of many OPOs in the United States not to accept an anti-HCV positive donor. However, with the advent of nucleic acid testing, it may be that carefully selected seropositive donors with low viral load could be transplanted with equivalent outcomes to seronegative donors [19]. Advances in treatment (see below) of hepatitis C may allow transplantation of seropositive donors to become a viable option.

Cytomegalovirus

The prevalence of cytomegalovirus (CMV) in the organ donor population has been reported as high as 90% [20]. Routine screening for CMV-IgG is considered the gold standard [21]; ideally, blood should be drawn from the donor prior to any blood transfusions, but in cases of trauma, this may not be possible. Unlike Hepatitis B and C positive donors, it is generally accepted that CMV-positive donor hearts can be transplanted into CMV-negative recipients, due to the demonstrated success of prophylaxis and treatment [21]. Nevertheless, it is vitally important that all donors have CMV serological status determined, as the combination of donor and recipient CMV status enables risk stratification for prophylaxis and monitoring (which will be covered below).

Human Immunodeficiency Virus

There are several documented cases of Human Immunodeficiency Virus (HIV) transmission from donor to recipient in cardiac transplantation [22], most of which occurred prior to the introduction of routine screening in 1985. Consequently, all potential transplant donors should be tested for antibodies against HIV-1 and HIV-2 through enzyme linked immunosorbent assays (ELISAs). A negative result in the donor is not a guarantee of

freedom from HIV infection, due to the known 3–6 month delay between the time of contraction to the development of detectable anti-HIV antibodies. A fourth generation HIV combined antibody and antigen test markedly decreases the "window period" of seroconversion to less than 1 month. Therefore, a detailed social history assessing for sex work, intravenous drug use, and blood transfusions is of great importance in determining risk factors for donor HIV infection. If a social risk factor for HIV is revealed, then most centers will generally decline the heart unless the patient is in an actively life-threatening situation with transplant as the only option; in this scenario, the recipient should be informed of the possible risk and made aware of the potential consequences.

If the donor heart tests positive for HIV, then it is illegal to transplant that organ into an uninfected recipient. Indeed, any use (either transplant or research) of known HIV-positive donor organs was formerly a federal crime. However, the 2013 HIV Organ Policy Equity Act has since allowed HIV-positive donor organs to be used in HIV-positive recipients, thus expanding the donor pool for this particular subset of patients [23].

Human T-Lymphotropic Virus

Human T-Lymphotropic Virus I (HTLV-1) is more common in individuals from the Caribbean and Japan. There are limited data on transplants from HTLV-1 positive donor hearts; reports from other solid organ transplants demonstrate myelopathy after transplantation [24]. Current UNOS policy recommends against the use of donors with HTLV-1 seropositivity, due to the risk of transmission and subsequent development of adult T-cell leukemia and spastic paraparesis.

Protozoal Transmission

Toxoplasma Gondii

While not a contraindication, *T.gondii* donor seropositivity is important for the purposes of risk stratification and subsequent prophylaxis and treatment. Data from the literature are mixed regarding outcomes from *T.gondii* mismatched cardiac transplants [25].

Recipient Screening

In addition to evaluation for the same diseases as the donor (as mentioned above), evaluation of the potential transplant candidate's infection risk should also include a thorough history of antibiotic allergies (with the nature of the reaction), a dental examination and routine assessment for active infection, including chest radiograph and urine cultures. The candidate should also be evaluated for potential risk of tuberculosis (including PPD skin test or a serum interferon gamma release assay) and a social history of high-risk behavior with respect to blood-borne viruses. Table 11.1 summarizes the routine infection

Table 11.1 Recommended pathogenic screening in transplant candidates

Underlying medical conditions (see Chap. 3)
Antibiotic/medication allergies, adverse reactions
Chest radiograph (to look for infiltrates, granumolas, scarring)
Dental assessment
Social/sexual history; high-risk behaviors, intravenous drug use, sexually transmitted diseases
PPD skin test, history of tuberculosis risk factors
Urine culture
Routine serologic testing:
CMV IgG antibody
EBV antibody panel
HSV IgG antibody
VZV IgG antibody
Hepatitis B screen: HBsAg, anti-HBc, anti-HBs
HCV IgG antibody
HIV-1, HIV-2 antibody
Syphilis screen: rapid plasma regain
Special serologic testing based on epidemiologic risk factors or exposure history:
Coccidioides IgM and IgG antibody
Histoplasma immunodiffusion antibody or urine antigen
HTLV-I/II antibody
Strongyloides antibody
Trypanosoma cruzi antibody

Adapted with permission from Fischer and Lu [57]
Abbreviations: *PPD* purified protein derivative, *CMV* cytomegalovirus, *EBV* epstein-barr virus, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *HBsAg* hepatitis B surface antigen, *anti-HBc* hepatitis B core antibody, *anti-HBs* hepatitis B surface antigen, *HCV* hepatitis C, *IgG* immunoglobulin G, *HIV* human immunodeficiency virus, *IgM* immunoglobulin M, *HTLV* human T-cell lymphotropic virus

screening recommended for a transplant candidate. As discussed in Chap. 3, the presence of a pre-existing infection such as HIV or Hepatitis B/C is not necessarily an absolute contraindication to transplant, but these patients should be treated appropriately prior to transplant and subsequently monitored more carefully for risk management.

Because vaccine-preventable infections are a common source of morbidity post-cardiac transplantation, the vaccination history of the transplant candidate should be reviewed and updated prior to transplant, including those for diphtheria, tetanus, varicella zoster virus, human papillomavirus, hepatitis A/B, influenza A/B, *Hemophilus influenzae* B, polio and meningitis C. measles, mumps and rubella. Vaccines should be administered no later than 4–6 weeks prior to transplantation, in order to avoid the chance of vaccine-caused infection, especially with live attenuated vaccines. Vaccination should be administered prior to any desensitization protocol to preserve the antibody response.

Post-transplant Infectious Agents, Prophylaxis and Specific Treatments

Bacterial Infections

Bacterial infections remain the most common cause of infectious morbidity in immunosuppressed cardiac transplant patients within the early post-transplantation period [26], and can present as wound infections, pneumonias, urinary tract infections (UTIs), bacteremia from venous catheter-associated infections, and rarely, infective endocarditis. Broadly speaking, the pathogens in the early post-transplantation period are similar to those causing infections in non-transplant surgical patients. Here, the most common bacterial organisms and their treatment will be covered.

Peri-operative Prophylaxis

As a general rule, the ISHLT guidelines state with regard to antibiotic therapy [3]: that prophylaxis should be used before the transplant operation; that drugs should be selected based upon their activity against usual skin flora; that in the event of a chronically infected device such as a VAD, that peri-operative antibiotics should be selected based on microbiologic sensitivities; and that in the event that a donor had an ongoing infection, that a course of suitable antibiotics should be considered.

Gram-Positive Organisms

Staphylococci

The *Staphylococcus* species are the most common Gram-positive organisms causing infectious disease in the cardiac transplant patient, especially in the early period post-transplantation [27]. The coagulase-positive *S. aureus* is the most common, and is usually methicillin sensitive if community-acquired; it may manifest as wound infection, line sepsis, pneumonia or a UTI. Rarely, *S. aureus* has been associated with endocarditis shortly after transplant [28]. Hospital-acquired strains are usually methicillin resistant (MRSA). The methicillin-sensitive variant may be treated with oxacillin or nafcillin, or cefazolin as a possible alternative. For MRSA, vancomycin is the preferred first-line drug. In severe staphylococcal infections, rifampin or gentamicin may also be necessary.

The coagulase-negative *S. epidermidis* is another commonly occurring infection in post-cardiac transplant patients [1]. Almost all cases are nosocomially acquired. Because they normally reside on human skin and mucous membranes, they are usually found in wound infections. There is a higher rate of methicillin resistance among the coagulase-negative Gram-positive cocci; these methicillin-resistant coagulase-negative infections tend to occur later in transplant course rather than in the early period. If methicillin-sensitive, oxacillin or nafcillin should be used, but if resistant, vancomycin is the recommended first-line drug. Where applicable, wounds should be debrided.

Enterococci

Enterococci (*E. faecalis, E. faecium, E. durans*) are Gram-positive facultative anaerobes that are part of the normal gut flora, but take on increased significance given an immunocompromised host. Enterococcal infections, like Staphylococcal, most commonly occur in the early period (first 2–3 weeks) after cardiac transplantation, and tend to manifest as wound/line infections, or biliary and urinary tract infections.

Because enterococci engage in synergistic relationships with other gut flora, they are more likely to be involved in polymicrobial infections, and are more difficult to treat. For sensitive enterococci, the treatment of choice is ampicillin or vancomycin. However, in recent years the emergence of vancomycin-resistant *Enterococcus* (VRE) has provided a major source of morbidity and mortality associated with infections [29]. Rates of VRE infection have been reported from 1% to 16% in solid organ transplant recipients, and mostly occur within the first month post-transplantation [29].

VRE that is not sensitive to ampicillin can be managed with linezolid, quinupristin-dalfopristin (*E. faecium* only), daptomycin or tigecycline. Furthermore, infected lines or devices should be removed, fluid collections drained, and any urinary or biliary obstruction should be addressed.

Streptococci

Cardiac transplant recipients are at increased risk of *Streptococcus pneumoniae* infection compared to the normal population, given their immunosuppressed state. *S. pneumonia*e is an alpha-hemolytic, facultative anaerobe, and infection most commonly manifests as bacteremia, meningitis or pneumonia [30]. Pneumococcal infection is more often community acquired and tends to present later after transplantation. The treatment of choice is penicillin; penicillin-resistant strains may be treated with ceftriaxone, and even vancomycin in cephalosporin-resistant strains. In cases of pneumococcal sepsis, vancomycin should be administered empirically in addition pending sensitivities.

Listeria Monocytogenes

A Gram-positive bacillus, *Listeria monocytogenes* is a reasonably common pathogen in the immunocompromised host. Typically presenting early after transplantation or during treatment of rejection when boluses of immunosuppression have just been administered, *Listeria* is a common cause of bacterial meningitis in solid organ transplant recipients [31], and may also cause other central nervous system (CNS) infections, such as encephalitis, brain abcesses and cerebritis; bacteremia also often occurs [32]. Patients displaying meningitic symptoms should undergo prompt lumbar puncture for cerebrospinal fluid analysis and should be treated with broad-spectrum antibiotics empirically. Occasionally, listeriosis may occur later after transplant, as *Listeria* is known to be associated with certain unpasteurized meat and dairy products; thus patients should be told to avoid these. The treatment of choice for *Listeria* is ampicillin; in the penicillin-allergic patient, a carbapenem or trimethoprim/sulfamethoxazole is appropriate.

Nocardia

While decreased due to the advent of trimethoprim-sulfamethoxazole prophylaxis and cyclosporine-based immunosuppression, infectious complications due to *Nocardia* species are still relatively common within the first 6 months post-transplantation, with frequency reported from 0.7% to 3.5% in solid organ transplant recipients [33]. Nocardiosis may occur in a localized or disseminated form, with the most common form localized to the lungs, although hematogenous spread to the brain, skin and subcutaneous tissues, bone and eye have been reported [33]. As localized lung disease is most common, nocardiosis typically presents as a subacute pneumonia with associated symptoms for a week or more. If treated promptly, survival is high, unless there is considerable spread to the CNS [33]. The treatment of choice is trimethoprim-sulfamethoxazole, or alternatively, third generation cephalosporins or imipenem; treatment should last for at least 6 months or

longer, dependent on response. Antibiotic therapy should be guided by sensitivities [33].

Clostridium Difficile

Diarrhea is relatively common in the early period post-transplantation; the most common causes are an infectious agent, or medication. *Clostridium difficile* is the most common infectious cause [34], and is typically acquired nosocomially, with broad spectrum antibiotics often an exacerbating factor. Patients with prolonged hospitalization or who have recently be treated for rejection with monoclonal antibodies may also be at risk. Possible complications of *C. difficile* infection include pseudomembranous colitis, and potentially intestinal perforation and toxic megacolon. These can lead to electrolyte abnormalities and malabsorption of immunosuppressive agents, and thus must be treated promptly. Oral metronidazole with fluid electrolyte replacement is the first line treatment for milder cases of *C. difficile* infection, with vancomycin for severe or metronidazole-resistant disease [34].

Rhodococcus Equi

A Gram-positive aerobic coccobacillus, *R. equi* typically causes infection in animals but can also affect immunocompromised humans, most commonly causing pulmonary infection later after transplantation [35]. It typically presents with a nodular or cavitary necrotizing pneumonia and empyema and is commonly confused with tuberculosis [36]. Suitable treatment includes the quinolones, vancomycin, carbapenems, doxycycline, erythromycin and trimethoprim-sulfamethoxazole; in some cases, surgical drainage of the empyema may be required.

Gram-Negative Bacilli

Aerobic gram-negative bacilli are common causes of infection in the immunosuppressed post-transplant patient, and may cause pneumonia, wound infection, UTIs, intra-abdominal sepsis, bacteremia and rarely endocarditis; infections normally present within the first 1–2 months post-transplant. Multidrug resistance is increasingly a problem in this cohort of pathogens. The usual sources for these pathogens are the gut and the respiratory tract. Respiratory tract gram-negative bacilli include *Haemophilus influenzae, Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas maltophilia;* enteric Gram-negative bacilli include *Escherichia coli, Pseudomonas spp., Enterobacter spp., Serratia spp., Klebsiella spp., Proteus spp.,* and *Citrobacter spp* [37]. Treatment for gram-negative bacilli is typically based on susceptibility patterns per institution, but empiric therapy should typically include a broad-spectrum penicillin and an aminoglycoside such as gentamicin.

Legionella

Legionellosis may be transmitted to the patient via a contaminated water source within the hospital [38]; further risk factors include mechanical ventilation and repeated corticosteroid boluses for rejection. The most common species are *L. pneumophilia* and *L. micdadei*, which usually cause pneumonia, but may also have extrapulmonary involvement. The clinical presentation typically consists of non-specific symptoms such as fever, myalgias, non-productive cough, and pleuritic chest pain, with diarrhea in half of all cases. Subsequent chest radiograph findings are also non-specific, and may consist of segmental, diffuse alveolar or nodular parenchymal lesions; a sputum culture using special media, direct-fluorescent testing of sputum, tissue or bronchoalveolar fluid and urinary antigen testing are the only definitive diagnostic methods. Treatment should be commenced empirically where legionellosis is suspected, as delayed treatment has been shown to correspond with increased mortality; even with treatment, *Legionella* demonstrates high mortality [39]. Azithromycin, a macrolide, or levofloxacin, a quinolone, are the treatments of choice for *Legionella spp*. infections [40]. Importantly, the use of macrolides can affect blood levels of calcineurin inhibitors and so care must be exercised in therapeutic drug monitoring; macrolides will increase blood levels.

Mycobacterial Tuberculosis

Both tuberculosis (TB) and non-tuberculous mycobacteria are potential causes of serious infection in cardiac transplant patients [41]. Those who resided in or visited a country with a high prevalence of TB may be at particular risk, and vigilance for reactivation tuberculosis is necessary. While typical presentation is that of hemoptysis, night sweats and fever, atypical presentations may occur in the transplant population. Disseminated infection, including involvement of skin, bone, and central nervous system may also occur, with granulomas in extrapulmonary biopsy sites a key finding.

Current consensus is that recipients with a history of latent tuberculosis who are actively immunosuppressed should be treated prophylactically to avoid progression to active tuberculosis, with a 9-month course of isoniazid as the mainstay of treatment [41]. Due to the rise of multidrug resistant mycobacteria, treatment for active TB should consist of isoniazid, rifampin, pyrazinamide and ethambutol for at least 2 months, followed by a 4–10-month course of isoniazid and rifampin depending on clinical manifestation [41]. Both isoniazid and rifampin affect the cytochrome P-450 enzyme system; isoniazid increases calcineurin inhibitor levels, while rifampin will decrease them. Thus, immunosuppressant dosage monitoring and adjustments are necessary in this population.

Viral Infections

Viral infections are common complications in cardiac transplant patients, second only to bacterial infections in terms of frequency. They most commonly occur within 1–6 months post-transplantation.

Peri-operative Prophylaxis

The ISHLT guidelines [3] recommend perioperative anti-viral prophylaxis in all transplant recipients against Cytomegalovirus (CMV) and Herpes simplex virus (HSV). Intravenous ganciclovir may be administered to high-risk patients (i.e. CMV seropositive donor to CMV seronegative recipients, or previously CMV seropositive recipients), whereas patients at low risk for CMV infection may only receive anti-HSV prophylaxis with acyclovir. Some centers may also use CMV immunoglobulin in addition to valganciclovir in high risk patients. Dosages of these drugs are given in Table 11.2, while recommendations for viral prophylaxis in heart transplant recipients according to risk category are summarized in Table 11.3.

Cytomegalovirus

Cytomegaloviruses, which are double-stranded DNA viruses, are extremely widespread agents that commonly infect humans; transmission may occur through direct or indirect contact with an infected person, and prevalence has been noted to be as high as 90% in certain regional populations [20]. In the normal host, CMV infection stimulates the development of cellular and antibody-mediated immunity, which controls viral persistence; in the immunocompromised host, latent CMV may become reactivated. During transplant, transmission may occur from a seropositive donor to a seropositive recipient, or via infected blood transfusions. Subsequent risk factors for acquiring CMV in the transplant population include the use of perioperative induction therapy, and dose and duration of immunosuppression. It is estimated that following cardiac transplantation, nearly 20–50% will experience at least one CMV infection in the first 2 years, with the majority of cases occurring within the first 2 months post-transplant [42]. The combination of CMV-positive donor with a CMV-negative recipient, if left untreated, has been demonstrated to result in worse outcomes [43]. This is thought to be related to the known association between CMV infection and immune dysregulation and inflammation [44]. CMV infection has also been demonstrated to result in a predisposition for acquiring other fungal and bacterial diseases in transplant recipients [45].

Table 11.2 Antiviral drugs for CMV prevention and treatment in heart transplant recipients

Drug	Treatment[a]	Prophylaxis	Comments on use and toxicity
Valganciclovir	900-mg[b] p.o. twice daily	900 mg[b] p.o. once daily	Ease of administration
			Leukopenia is major toxicity
Oral Ganciclovir	NOT recommended	1 g p.o. three times daily	Low oral bioavailability
			High pill burden
			Leukopenia and risk of resistance development
			NOT recommended for preemptive therapy
IV Ganciclovir	5-mg/kg IV every 12 h	5 mg/kg IV once daily	Intravenous access and complications
			Leukopenia is major toxicity
Valacyclovir	NOT recommended	2 g p.o. four times daily	Use in kidney transplant recipients only
			NOT recommended for heart, liver, pancreas, lung, intestinal and composite tissue transplant recipients
			High pill burden
			High risk for neurologic adverse effects
			NOT recommended for preemptive therapy
Foscarnet	60 mg/kg IV every 8 h (or 90 mg/kg every 12 h)	NOT recommended	Second-line agent for treatment
			Highly nephrotoxic
			Used for UL97-mutant ganciclovir-resistant CMV disease
			NOT recommended for preemptive therapy
Cidofovir	5 mg/kg once weekly × 2 then every 2 weeks thereafter	NOT recommended	Third-line agent
			Highly nephrotoxic
			Used for UL97-mutant ganciclovir-resistant CMV disease
			NOT recommended for preemptive therapy

Reused with permission from Razonable and Humar et al. [21]
CMV-immune globulin has been used by some centers as an adjunct to antiviral prophylaxis, especially in heart and lung transplant recipients. The efficacy of this approach is debatable
The doses of the antiviral drugs are for adults and should be adjusted based on renal function
Abbreviations: *CMV* cytomegalovirus, *mg* milligrams, *p.o.* per os, *kg* kilogram, *IV* intravenous, *BSA* body surface area
[a]These treatment doses are also recommended for preemptive therapy of asymptomatic CMV replication. Foscarnet, valacyclovir, oral ganciclovir and cidofovir are not recommended for preemptive therapy
[b]Pediatric valganciclovir dose is mg = 7 × BSA × Creatinine clearance

Active CMV infection may be symptomatic, causing a constellation of symptoms including fever, chills, malaise with leukopenia and thrombocytopenia; this is known as CMV syndrome. Alternatively, active CMV infection may be asymptomatic. Primary CMV infection occurs when a CMV-seronegative recipient receives a CMV-positive donor organ, whereas secondary CMV infection represents infection in a previously infected seropositive host, caused by reactivation of latent virus or additional infection with a new viral strain. The term "CMV disease" is used to refer to the clinical symptoms of CMV syndrome as well as features of any invasive CMV disease such as pneumonitis, hepatitis, cholecystitis, or colitis/enteritis. Rarely, invasive CMV disease may also include the myocardium (necrotizing myocarditis) and retinitis.

Where suspected, testing for serum IgG anti-CMV by ELISA is useful to record seroconversion, but has little relevance is diagnosing acute CMV disease. Traditional tissue culture methods may be used, and could still be performed in invasive cases of CMV, but are time consuming and rarely routinely used in transplant recipients. For rapid quantitative diagnosis of acute disease, the CMV pp65 antigenemia test and CMV quan-

Table 11.3 Recommendations for CMV prevention in heart transplant recipients

Risk category	Recommendation/options (see Table 11.3 for dosing)	Evidence
D+/R–	Antiviral prophylaxis is preferred	I (3-month prophylaxis)
	Drugs: valganciclovir, oral ganciclovir or intravenous ganciclovir. Some centers add adjunctive CMV immune globulin	III (6-month prophylaxis)
	Duration: 3–6 months	II-2 (immune globulin)
	Preemptive therapy is an option	
	Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg[a] p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	
R+	Antiviral prophylaxis	II-2
	Drugs: Valganciclovir, oral ganciclovir or intravenous ganciclovir. Some centers add adjunctive CMV immune globulin	
	Duration: 3 months	
	Preemptive therapy	
	Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg[a]p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	

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The above recommendations do not represent an exclusive course of action. Several factors may influence the precise nature and duration of prophylaxis or preemptive therapy
Antiviral prophylaxis should be started as soon as possible, and within 10 days after transplantation. Preemptive therapy is NOT recommended for heart–lung allograft transplantation
Notes: CMV D−/R– heart transplant recipients do not require anti-CMV prophylaxis. Instead, CMV D−/R– should receive anti-Herpes Simplex Virus (HSV) prophylaxis during the early period after transplantation. If blood transfusion is required, CMV D−/R– SOT patients should receive CMV-seronegative or leuko-reduced blood products
Abbreviations: *D+* donor seropositive, *R−* recipient seronegative, *D−* donor seronegative, *R+* recipient seropositive, *CMV* cytomegalovirus, *PCR* polymerase chain reaction, *IV* intravenous, *mg* milligram, *p.o.* per os, *BID* twice a day, *kg* kilogram, *BSA* body surface area
[a]Pediatric valganciclovir Dose is mg = 7 × BSA × Creatinine clearance

titative nucleic acid testing (QNAT) are the tests of choice. Both are highly sensitive in the diagnosis of CMV disease [21] and are useful for monitoring response to antiviral therapies through their quantitative ability, although there has historically been a lack of standardization with QNAT.

While prophylaxis for CMV is addressed above, effective prophylaxis has greatly decreased CMV-associated morbidity and mortality. Treatment for active CMV disease should involve oral valganciclovir, an acyclic guanine nucleoside analog, to clear CMV viremia in mild to moderate cases. In more severe cases intravenous administration of ganciclovir should be performed. Therapy typically lasts 2–3 weeks, with weekly monitoring of blood viral load using QNAT or pp65 antigenemia to assess response [21]. The length of time for which a patient remains on valganciclovir depends on a number of factors, including donor seropositivity and other known risk factors for CMV reinfection. The potential adverse effects of valganciclovir should be noted: these include neutropenia and thrombocytopenia due to the myelosuppressive nature of the drug, as well as fever, rash, nausea, seizures, nausea, and liver enzyme abnormalities. Since CMV disease itself also presents with leukopenia, there can be confusion as to whether it is CMV or drug-induced; persistent leukopenia is likely to be valganciclovir-induced.

The development of valganciclovir-resistant CMV may occur after prolonged courses of administration; genotypic testing for resistance should be performed. Possible solutions include switching to a sirolimus or everlomus based regimen, due to the reportedly lower risk of CMV risk with this regimen; other options may include foscarnet or cidofovir [21].

Herpes Simplex Virus

Herpes simplex virus (HSV) infection generally develops early after transplantation and predominantly affects mucosal surfaces, although in rare cases dissemination to the esophagus, liver and lungs and even brain may occur. In the transplant population, most cases of active HSV infection are caused by reactivation in previously infected patients. Diagnosis is based on the visual appearance of typical vesiculoulcerative lesions and positive immunofluorescent stain specific for HS. For cases of suspected HSV encephalitis, PCR should also be employed. Prophylaxis is typically administered perioperatively, and treatment for active HSV infection typically involves oral or intravenous acyclovir, depending on severity.

Varicella Zoster Virus

Herpes zoster, more commonly known as shingles, is caused by the varicella zoster virus (VZV). VZV also causes chickenpox. In transplant recipients, active infection is often caused by reactivation of latent disease, and typically presents as a dermatomal vesicular rash, although disseminated disease has been known to occur. [46]. Symptoms typically present later (after 3 months) after transplantation and diagnosis can usually be made clinically, with laboratory confirmation where necessary to differentiate between VZV and HSV. While candidates should have been vaccinated against VZV prior to transplant (see above), oral acyclovir is the current agent of choice for milder cases, with intravenous treatment warranted for disseminated zoster.

Epstein-Barr Virus

Epstein-Barr virus is a herpesvirus that is known to cause acute mononucleosis in healthy patients. It is estimated that 90% of the Western population have been exposed to EBV [47]. In the transplant patient, EBV infection may be caused by reactivation of latent virus or donor-to- recipient transmission.

If antiviral therapy is instituted ganciclovir is preferred. Post-transplant EBV infection has a strong association with subsequent development of malignant post-transplantation lymphoproliferative disorder (PTLD), Preemptive therapy consists of reduction of immunosuppression, antivirals and possible immune globulin verses merely reduction of immunosuppression [48].

Community respiratory Viruses

The community respiratory viruses, which include influenza, parainfluenza and respiratory syncytial virus (RSV), have the potential to cause significant morbidity and mortality in cardiac transplant recipients [49]. They are typically transmitted by respiratory droplets and aerosols via direct person-to-person contact or contaminated surfaces. The usual presentation is that of upper respiratory tract symptoms combined with fever, arthralgias and mucosal inflammation. With these viruses, there is the potential for secondary bacterial complications (*S. aureus, Streptococcus*) as well as CMV reactivation.

Diagnosis can be achieved using a combination of serology, viral culture, antigen detection, and nucleic acid testing. All patients with presumed respiratory viral infection should undergo nasopharyngeal swab, wash, or aspirate performed and sent for testing. If upper tract samples cannot prove the cause of the respiratory illness or if there is clinical or radiologic evidence of lower tract involvement, bronchoalveolar lavage (BAL) should be considered and sent for the range of available tests [49].

Regarding treatment, for influenza viruses (A and B), the neuraminidase inhibitors oseltamivir and zanamivir have been demonstrated to be effective if commenced promptly [49]. In cases of RSV infection, ribavirin has been shown to be effective [49]. For parainfluenza, there is no currently proven treatment, but ribavirin has demonstrated in vitro activity and some centers also use intravenous immunoglobulin and corticosteroids [49].

Hepatitis B

While Hepatitis B virus (HBV) is screened for in the donor heart, on occasion, donors have past

exposure to Hepatitis B (anti-HBc positive), and thus transmission may on occasion occur from donor-to-recipient. Alternatively, transmission may occur through blood transfusions during transplant or even endomyocardial biopsy (through an infected probe), as has been reported. Left untreated, there is the potential for serious chronic liver disease. It is recommended that HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely in all recipients regardless of current or prior prophylaxis strategy [5]. Any sign of clinical hepatitis post-transplant should be investigated with HBV DNA PCR or NAT, and HBsAg and anti-HBc testing, to assess the possibility of de novo HBV infection.

In cases where an anti-HBc positive and HBsAg negative donor heart is given to an anti-HBc negative and anti-HBs negative recipient, prophylaxis should be carried out to minimize the risk of transmission and reduce potential disease progression. This consists of up to 1 year course of entecavir or tenofovir (reverse transcriptase inhibitors) for recipients. Antiviral prophylaxis is not recommended if the recipient is anti-HBc positive [5].

Hepatitis C

Because HCV-positive hearts are generally not accepted for transplantation except in particularly urgent cases, there are few data to guide appropriate treatment in heart transplant patients. There is evidence from liver transplant recipients that the combination of ribavirin (a nucleoside inhibitor) and pegylated interferon alfa-2b (IFN) may produce normalization of liver function tests, improve liver histology and reduce circulating serum levels of HCV RNA [18, 50]. Thus, heart transplant recipients should be evaluated for antiviral treatment. However, IFN may exacerbate heart failure or arrhythmias, and ribavirin-induced anemia may lead to coronary ischemia [19]. Because there are few data on Hepatitis C treatment in cardiac transplant patients, the management should be considered on an individual basis with a close monitoring of the adverse events. However, in the new era of direct-acting antivirals, antiviral therapy may allow more liberal use of HCV positive hearts.

Other Viruses

Other viral infections that may rarely occur after transplantation include the human herpesviruses HHV-6 and HHV-8, BK virus, adenovirus, parvovirus B19, human papillomavirus (HPV), and West Nile virus. The approach to treatment for these viruses in the post-transplantation patient is generally no different to the approach in the non-transplant patient.

Fungal Infections

Fungal infections remain a significant cause of morbidity and mortality after cardiac transplantation, and may present as locally invasive or disseminated disease. The frequent breaching of skin and mucosal barriers, as seen with the invasive procedures of urinary catheterization, intra-arterial lines and intubation combined with immunosuppression and administration of broad-spectrum antibiotics provides an opportunistic environment for these pathogens.

Peri-operative Prophylaxis

As per ISHLT guidelines [3], anti-fungal prophylaxis to prevent mucocutaneous candidiasis should be initiated once the recipient is extubated. The agents most commonly used are nystatin or clotrimazole lozenges. Prophylaxis against *Pneumocystis jiroveci* pneumonia should also be initiated in the early post-operative period with trimethoprim/sulfamethoxazole—the most commonly used agent (see Table 11.4 for a summary of recommended treatment, including dosages). In the setting of a sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens can be used, including Dapsone with or without pyrimethamine, atovaquone, and inhaled pentamidine.

Table 11.4 Specific prophylactic agents for prevention of *Pneumocysitis* in heart transplant recipients, listed by preference

Agents	Dosing	Comments
Trimethoprim-sulfamethoxazole (TMP-SMX, cotrimoxazole)	Can be given at 80 mg TMP/400 mg SMX or 160 mg TMP/800 mg SMX po (single or double strength) daily or three times weekly	TMP-SMX remains the *drug of choice f*or PCP prophylaxis
		Daily regimens may be required to have efficacy for other forms of post-transplant infections
Dapsone (4,4′-diaminodiphenyl-sulfone)	50–100 mg po qd	Dapsone is considered a second-line agent for the prophylaxis of PCP
		Side effects may be more common among solid organ transplant recipients
		Avoid in G6PD deficiency, methemoglobin reductase deficiency
		Uncommon allergy to sulfone or sulfa-containing agents
		Generally not recommended in with history of severe sulfa reactions (desquamation, neutropenia, interstitial nephritis or hepatitis)
Atovaquone	1500 mg po qd (as single dose)	Clinical trial data in HIV patients who could not tolerate TMP-SMX showed atovaquone to be equivalent to dapsone in preventing PCP
		Data in solid organ transplant recipients show it to be well-tolerated
		Failures of atovaquone have been reported at doses of 1000 mg or less daily
Pentamidine	300 mg administered through aerosolized nebulizer q 3–4 weeks	Pentamidine requires administration by experienced personnel with a nebulizer producing droplets of 1–3 μ
		Pentamidine is well-tolerated with minimal side effects other than cough and bronchospasm
		There is a higher incidence of breakthrough infection compared to TMP-SMX or dapsone
		Reports of disseminated infection involving the thyroid in HIV cases receiving inhaled pentamidine as prophylaxis
Clindamycin and pyrimethamine	Up to 300 mg of clindamycin po qd with 15 mg of pyrimethamine po qd (some clinicians have administered this regimen three times weekly instead of daily)	Somewhat efficacious in AIDS, though less effective than TMP-SMX or dapsone
		Failure rate higher than for aerosolized pentamidine
		Gastrointestinal intolerance may be limiting

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AIDS acquired immunodeficiency syndrome, *HIV* human immunodeficiency virus, *PCP* Pneumocystis pneumonia, *TMP-SMX* trimethoprim-sulfamethoxazole
Dosing abbreviations: *mg* milligrams, *po* per os, *qd* once a day

Candida Spp.

Candidiasis is the most common invasive fungal infection following cardiac transplantation. Nosocomial in origin, it normally presents within the first month. The sub-species of *C. albicans* and *C. tropicalis* are the most commonly observed in the cardiac transplant population [51]. Local infection may present on a variety of mucosal surfaces, including the mouth, esophagus, vagina, and even the sternal wound. Disseminated candidiasis has the potential to involve all the major organ systems, presenting with generalized fever and symptoms relating to the affected organ.

There are limited diagnostic tools for invasive candidiasis; blood cultures are the only reliable tool, but are not particularly sensitive, and symp-

toms tend to be non-specific making definitive diagnosis difficult [51]. Isolation of *Candida* species from stool, skin surfaces, drains, respiratory secretions and urine does not necessarily indicate infection, but may be a clue to patients at higher risk for developing an infection. However, repeated results showing colonization at multiple sites would be a significant clue for invasive candidiasis. Traditionally, treatment for invasive candidiasis has involved Amphotericin B, but the relative toxicity has led to fluconazole becoming the drug of choice. Other viable alternatives include voriconazole and echinocandins, a new class of antifungals [51].

Aspergillus

Aspergillus species are ubiquitous soil-dwelling molds, of which *A. fumigatus, A. flavus, A. niger* and *A. terreus* are the most common, with 12-month cumulative incidence in heart transplant recipients of 3.4% [52]. Frequently nosocomial, *Aspergillus* is transmitted exclusively via inhalation, and thus commonly presents with pulmonary and sinus symptoms, such as chest pain, hemoptysis, dyspnea and fevers. If invasive, *Aspergillus* most commonly disseminates to the CNS, causing abscesses with potential hemorrhagic infarction and resulting in a clinical picture of altered mental status or stroke-like symptoms.

Diagnosis of invasive aspergillosis is made based on a combination of findings; in additional to the clinical picture, chest radiographic findings may show cavitating nodules with infiltrates, with computerized tomography to confirm their presence, although these findings are non-specific. While blood cultures and serologic assays may be performed, they are rarely helpful; serial measurement of *Aspergillus* galactomannan may aid in diagnosis, although the false positive rate is high. Bronchoalveolar galactomannan is more sensitive [52]. The most confirmatory test is histological evidence of tissue invasion with isolation of *Aspergillus* from involved tissue [52].

Treatment has traditionally consisted of amphotericin B, although recent solid organ transplant studies have demonstrated superior efficacy for voriconazole [52]. Viable alternatives include the echinocandins and itraconazole, which may also be utilized.

Pneumocystis Jiroveci

Well known as an AIDS-defining illness, *Pneumocystits jiroveci* also represents a potential threat in immunocompromised cardiac transplant patients. *P. jiroveci* is an organism of usually relatively low virulence found in the lungs of humans and other animals; the threat posed in the transplant may be a result of reactivation, although this is unclear.

Patients with active *P. jiroveci* infection present with fever, non-productive cough, dyspnea and progressive hypoxemia. Chest radiographs typically demonstrate diffuse interstitial infiltrates, sometimes with cavitary lesions. Histologic diagnosis is definitive; characteristic helmet-shaped organisms are seen on bronchoalveolar lavage, or alternatively lung biopsy [53]. Yield may vary with other methods, including PCR testing and routine sputum smears. Beta-D-glucan may be elevated though it is not specific for *P. jiroveci* [53].

Routine prophylaxis, as detailed above, aims to achieve primary prevention of active *P. jiroveci* infection; however, in cases of active infection, trimethoprim-sulfamethoxazole is also used and is considered the gold standard [53]. In the setting of a sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens can be used, including pentamidine, Dapsone with or without pyrimethamine, atovaquone, and clindamycin and pyrimethamine. It should be noted that active infection in the transplant recipient is now very rare due to effective prophylaxis [53].

Other Fungal Infections

Other less common, but significant fungal infections seen in the cardiac transplant population include *Cryptococcus neoformans, Rhizopus*

spp.-induced zygomycosis, *Histoplasma Capsulatum, Blastomyces Dermatidis,* and *Coccidioides Immitis*. By and large, treatment of these infections is performed with Amphotericin B as an initial treatment followed by fluconazole or itraconazole.

Protozoa

Perioperative Prophylaxis

As per ISHLT guidelines [3], prophylaxis against *Toxoplasma gondii* in high-risk cases (seropositive donor with seronegative recipient or seropositive recipient) should also be initiated in the early post-operative period. The suggested regimen is exactly the same as that used for prophylaxis against *Pneumocystis jiroveci*: trimethoprim/sulfamethoxazole. In the setting of a sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens can be used, including Dapsone with or without pyrimethamine, atovaquone, and clindamycin and pyrimethamine.

Toxoplasma Gondii

Toxoplasma gondii is a common intracellular protozoal parasitic zoonosis that may cause disease in immunocompromised cardiac transplant recipients. Two forms of the disease may occur in this cohort: acute and reactivation disease. Transmission may occur from seropositive donors, or from contact with oocysts in cat feces or tissue cysts in improperly prepared meat [54]. Acute disease tends to occur earlier post-transplant (within the first 6 months), whereas reactivation disease tends to occur later.

The disease most commonly manifests as fever with lymphadenopathy and leukopenia, but encephalitis, pneumonitis and myocarditis are also commonly seen. Cases of *Toxoplasma*-related myocarditis may present similarly to acute rejection, although toxoplasmosis should be distinguished by the eosinophilia seen in the specimen. The presence of ring-enhancing lesions in the cerebrum on brain imaging is sufficient to start presumptive treatment; however, definitive diagnosis is made based on demonstration of the organism by tissue histopathology; serologic assays of IgG and IgM antibodies to *Toxoplasma* are also useful to support the diagnosis. Seroconversion from seronegativity to seropositivity also presents strong evidence for toxoplasmosis. CSF *Toxoplasma* PCR has variable sensitivity but has high specificity.

If left untreated, toxoplasmosis can be fatal in the cardiac transplant recipient. The recommended regimen for solid organ transplant recipients is pyrimethamine with sulfadiazine, combined with folinic acid supplementation. Alternative agents include trimethoprim-sulfamethoxazole, atovaquone and azithromycin [54].

Clinical Approach to Infectious Features

Many of the bacterial, fungal and viral infections described above present with very similar clinical syndromes; as a result, diagnosis can be difficult. A general approach to these clinical aspects is summarized below.

Fever

While there is usually a mild fever in the immediate post-operative period, after this initial period, a fever generally indicates underlying infection of some kind and is frequently the first symptom to present. A systematic clinical approach to fever requires consideration of a number of potential risk factors for infection after transplantation, and may assist in identifying the causative pathogen and hence the initiation of appropriate empirical therapy. Table 11.5 summarizes a systematic approach to fever with regard to narrowing down potential pathogens.

The timing of the fever in relation to the transplantation date should be one of the first factors considered. Most infections occur in the first month after transplantation, especially UTIs, and tend to be related to invasive devices or complications from surgery. From months 1–6, immu-

Table 11.5 Systematic clinical approach to infectious features

Factor for consideration	Relevant information
Timing of symptoms relative to transplant	≤30 days: consider nosocomial sources: wound infection, UTI, pneumonia, venous catheter-associated bacteremia from typical pathogens such as *Staphyloccocus, Enterococcus*. With the exception of candidemia and occasionally aspergillosis, fungal and other classically opportunistic infections are rare
	1–6 months: the period of maximal immunosuppression, allowing classic transplant-associated infections to flourish, e.g. CMV, VZV, *Toxoplasma gondii, Aspergillus*, etc
	>6 months: community-acquired infections are more likely (e.g. pneumonia, gastroenteritis); mycobacterial infections and endemic fungal infections (e.g. cryptococcosis, histoplasmosis). Late viral complications may also occur, e.g. herpes simplex virus
Donor history of infection	Review donor serology for high risk factors, HIV, VDRL (syphilis), *Toxoplasma gondii*, CMV, hepatitis B and C, evidence of active or latent TB in donor; donor history of active infection
Recipient history of infection	Review CMV, *Toxoplasma gondii* serology, look for evidence of mismatch. Consider reactivation tuberculosis or fungal disease, especially if >6 months after transplant
Immunosuppressive regimen	Use of induction agents (e.g ATG, basiliximab) increases risk of infection, especially from CMV. Higher doses of corticosteroids increase risk of invasive fungal disease
History of rejection	Recent rejection necessitating fresh immunosuppressive bolus treatment resets the timeline such that CMV and other opportunistic pathogens are again seen commonly as in the 1–6 month post-transplant interval
Recent exposure history	Review recent occupational, recreational, and travel history. Review potential risk factors for exposure to tuberculosis or other potentially transmissible agents

Reused with permission from Kirklin et al. [58]
Abbreviations: *UTI* urinary tract infection, *CMV* cytomegalovirus, *VDRL* venereal disease research laboratory test, *HIV* human immunodefiency virus, *TB* tuberculosis, *ATG* anti-thymocyte globulin

nosuppression dosages are at their highest and thus there is increased susceptibility to opportunistic infections and reactivation of latent infections. From month 6 onwards, infections are more likely to be community acquired and similar to infections found in the non-transplant population, in addition to viral infections like CMV, EBV, and VZV.

The immunosuppression status of the patient should also be assessed, and any recent history of rejection should be noted; patients who underwent perioperative induction therapy or who have recently received therapy for rejection are at greater risk of infection. This can also be assessed quantitatively by measuring leukocyte, thrombocyte and immunoglobulin levels, as well as T-cell assays. Dosages, duration, and the temporal sequence of immunosuppressant therapy should be reviewed.

The infectious history of both the donor and recipient are also very important; both donor and recipient serologies prior to transplant should be reviewed, with additional tests performed if the clinical picture supports them. The patient's occupational, recreational and travel history should be reviewed in order to ascertain the probability of tuberculosis or other transmissible agents.

Overall, these principles can be used to aid in evaluation of not just fever, but many of the other clinical features of infection post-transplant.

Pulmonary Infiltrates

The appearance of a pulmonary infiltrate in a cardiac transplant patient may be due to numerous bacterial, viral, fungal or protozoal infections, but may also be due to non-infectious causes, such as pulmonary edema, PTLD and primary pulmonary neoplasia. Similar to the consideration of fever, timing of onset is especially important, as well as a full social history from the patient. The nature of onset of pulmonary symptoms may also offer a clue: generally speaking, bacterial and viral

infections tend to present acutely, whereas fungal and parasitic infections are more insidious in onset.

Blood cultures are generally less useful in this scenario. Sputum cultures should be performed, although they are unlikely to be useful, except in the cases of *Legionella*, mycobacteria, and fungi, as these are not normally found in the pharynx. Further investigation should involve chest radiography, and if there are pneumonic signs, computerized tomography (CT), which may be especially useful in determining the location of the lesion prior to biopsy. Definitive diagnosis can subsequently be obtained based on histology from bronchoalveolar lavage and/or transbronchial lung biopsy.

As the process leading to biopsy may take some time, in severe cases of pulmonary infiltrative disease empiric broad-spectrum antibiotic therapy should be initiated in order to avoid a delay in treatment. Milder cases may warrant restraint until the organism is identified.

Wound Infections

Wound infections generally occur within the first month after transplantation, and have the potential to lead to mediastinitis, which has potentially fatal consequences if left untreated. Mediastinitis typically presents with fever, increased wound drainage and sternal instability. Wound cultures should be taken in order to optimize antibiotic therapy; the most common category of pathogens in this setting is Staphylococcus, although other organisms have also been found. The solution to definitive management of mediastinitis remains controversial in the cardiothoracic community, with debridement, rewiring, sternal closure with or without muscle flaps and antibiotic irrigation all viable approaches [55].

Urinary Tract Infections

UTIs are very common in cardiac transplant patients due to perioperative urinary catheterization. The incidence and treatment are identical to that of UTIs observed in the non-transplant surgical population. Urine cultures should be performed to identify the pathogen, and appropriate treatment commenced; colonized catheters should be replaced. Long-term, in the sexually active transplant recipient, a complaint of genitourinary symptoms or disclosure of high-risk behavior should trigger a full evaluation for sexually transmitted infections [3].

CNS Infection

While CNS infection post-cardiac transplantation is relatively rare, it is potentially fatal if left untreated. The usual presentation of CNS infection involves meningitis, focal lesions and/or encephalitis, with overlap between the three main patterns. Typical symptoms would include headache, altered mental state, fever, seizures, confusion, and/or focal symptoms; these may also be caused by non-infectious pathology, such as an ischemic stroke post-transplant, and must be distinguished as such.

The timing of onset of symptoms may also offer clues as to the potential pathogen; focal disease presenting within the first month may be due to a bacterial, *Aspergillus* or *Candida* brain abscess; an encephalitis might also be due to various bacteria, herpes simplex or *Candida*. Later after the first month, focal disease may be due to progressive multifocal leukoencephalopathy secondary to JC virus, *Nocardia* or *Rhizopus* abscesses. Meningoencephalitic symptoms after the first month may be due to *Listeria, Cryptococcus*, VZV, HHV-6, or even CMV [56]. A useful general rule is that an early onset of symptoms is normally bacterial or *Aspergillus/Candida* (due to its ability to invade vascularly), whereas later symptoms tend to be due to opportunistic infections.

Other sites of potential invasion such as the lungs, wound and intra-arterial line sites should also be examined to aid in diagnosis, as the CNS is often not the only site of invasion. Brain imaging with CT and MRI should be performed to determine the nature of the CNS disease; if not contraindicated by mass effect, lumbar puncture should also be performed and cerebrospinal fluid cultured and sent for appropriate other studies.

Gastrointestinal and Liver Infections

Many of the opportunistic infections described above may disseminate to the gastrointestinal (GI) and hepatobiliary systems, but diagnosis is difficult. Symptoms such as abdominal pain, bleeding, and diarrhea are highly non-specific, and may instead suggest a noninfectious cause such as peptic ulceration, pancreatitis, or drug toxicity rather than an infectious cause. CMV commonly causes inflammation of both the GI and hepatobiliary tracts, and HSV may also cause esophagitis; *C. difficile* is another very common cause of diarrhea post-transplant. Patients should undergo endoscopy/colonoscopy with biopsy to aid in identification of the responsible pathogen, if any.

Preventive Measures

In addition to antimicrobial prophylaxis and appropriate vaccination prior to transplantation, which have been mentioned above, the usual infection control measures should be enacted post-transplantation. While an inpatient, the usual hand-washing precautions by both staff and visitors alike is mandatory. Healthcare providers with air-transmissible diseases should also refrain from direct contact with the patient. As outpatients, caution should be exercised to minimize the risk of environmental or occupational exposures to potential pathogens, as well as pet-related exposures; certain types of food should be avoided, and the patient should be aware of possible travel-related exposures. There is disagreement in the need for antibiotic prophylaxis when undergoing dental procedures but in general, antibiotic prophylaxis is supported by many programs [3].

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Cardiac Allograft Rejection, Surveillance and Treatment

12

David Chang and Jon Kobashigawa

Clinical Pearls

- Cardiac allograft rejection is most common in the first 6 months after transplantation, and if left unchecked is associated with increased mortality and development of cardiac allograft vasculopathy.
- Surveillance, diagnosis and grading of rejection is based on histologic examination of regularly scheduled endomyocardial biopsy, the gold standard for rejection surveillance.
- The disadvantages of endomyocardial biopsy are potential procedure-related complications, patient discomfort and interpathologist variability of interpretation.
- Recently, non-invasive methods to detect rejection have emerged such as the gene expression profiling blood test; however, it has not yet gained widespread use.
- Rejection is often asymptomatic; in symptomatic cases the patient may present with dyspnea, edema, syncope, tachyarrhythmias, dizziness or a fever >100 °F.
- Acute cellular rejection (ACR) is the most common form of heart transplant rejection and is characterized by T-cell mediated response against the donor allograft with macrophage and lymphocyte infiltration; it is divided into 3 grades of severity based on histologic criteria: 1R (mild rejection), 2R (moderate rejection) and 3R (severe rejection).
- Antibody mediated rejection (AMR) develops when recipient antibody is directed against donor-HLA antigens (and less so non-HLA antigens) on allograft endothelium, initiating the complement cascade and causing tissue injury via inflammatory pathways; it is divided into 3 grades of severity based on immunologic and histopathologic criteria: pAMR1(H+) or pAMR1(I+), pAMR2, and pAMR3.
- Treatment for rejection proceeds in a step-wise fashion based on severity by biopsy and the patient's clinical presentation; asymptomatic mild ACR (1R) and AMR (AMR 1) typically do not require intervention.

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- Treatment options for ACR2 or greater consist of corticosteroids and maintenance immunosuppression modification; if symptomatic, treatment is empirical and consideration of additional agents such as anti-thymocyte globulin (ATG) is warranted.
- Treatment options for AMR2 or greater consist of corticosteroids and maintenance immunosuppression modification; if symptomatic, treatment is empirical and consideration of additional agents such as intravenous immunoglobulin (IVIG), rituximab, bortezomib or plasmapheresis is warranted.
- Empiric aggressive treatment is required in the scenario of acute cardiogenic shock due to rejection, including corticosteroids, ATG, IVIG, plasmapheresis, inotropes, and potential initiation of short-term mechanical circulatory support.

Introduction

Since the early days of cardiac transplantation, allograft rejection has remained the main barrier to favorable long-term outcomes until the introduction of effective immunosuppression, as detailed in Chap. 10. With the introduction of calcineurin inhibitors rejection rates have sharply declined and improvement in survival rates has permitted cardiac transplantation to become an increasingly practical therapeutic option for end-stage heart disease. While rejection rates continue to decline, the risk of rejection remains significant particularly in the early period following transplantation, necessitating routine surveillance for both acute cellular and antibody-mediated rejection. Left unchecked, acute rejection is known to lead to cardiac allograft vasculopathy (CAV) [1], one of largest barriers to long-term survival, making surveillance and prompt treatment of acute rejection episodes even more crucial. This chapter intends to discuss the major forms of cardiac allograft rejection, methods of diagnosis, surveillance and its treatment.

Pathology and Diagnosis of Cardiac Allograft Rejection

The Endomyocardial Biopsy

The endomyocardial biopsy, first described by Caves in 1973 [2], remains the gold standard method for detection of rejection following heart transplantation (see Fig. 12.1). Indeed, diagnosis and grading of rejection is based on histologic examination of the biopsy, and may be combined with clinical observations, but cannot be made by clinical observations alone.

Procedural Technique

Endomyocardial biopsy is commonly performed by a percutaneous technique using the right internal jugular or femoral vein or femoral artery with fluoroscopic guidance, 2-dimensional echocardiography, or both. Since the introduction of more flexible bioptomes, however, such as the Stanford-Caves Schultz and King's bioptomes, the preferred site of access is now the right internal jugular vein, for access to the right ventricle. Biopsies should be taken from the interventricular septum, given that the right ventricular free wall is thin, and scraping too hard may cause perforation.

Procedural Limitations

Due to its invasive nature, the test may provoke anxiety and discomfort for the patient and remains particularly challenging in the pediatric population, often requiring the use of general anesthesia. A major drawback to the endomyocardial biopsy is that it samples only a limited area of the endocardium. Inflammatory changes may be sporadic through the myocardium, or may predominantly affect the subendomyocardium; in these cases, the biopsy may miss the diagnosis. Thus, diagnosis of rejection also relies on the clinical presentation and echocardiographic findings, which may or may not be supported by

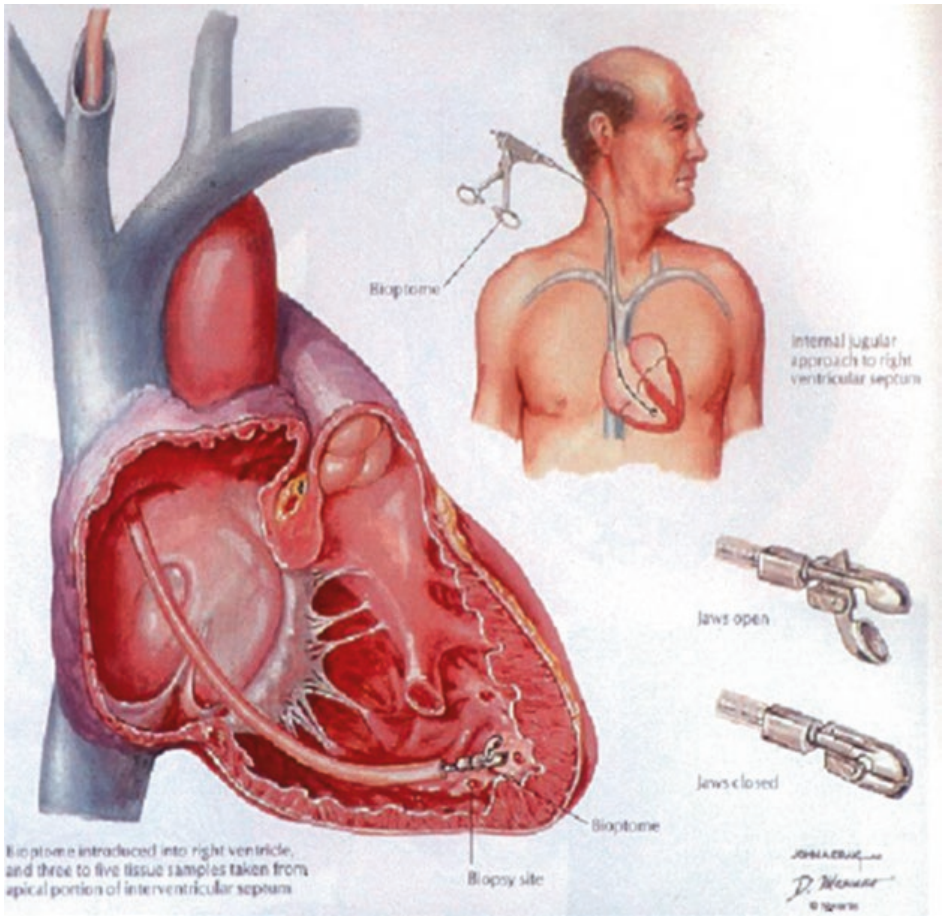

Fig. 12.1 Overview of the endomyocardial biopsy (Image used with permission from Elsevier)

histology [3, 4]. Furthermore, biopsy utilizes significant resources including physician time and is associated with substantial costs.

Potential Complications

Although the procedure is considered safe with a complication rate well below 6% [5], there is a finite risk of injury. Such reported complications include transient right bundle branch block, tricuspid regurgitation, access site hematoma, transient arrhythmias and occult pulmonary embolism [5]. More rarely (<1%), right ventricular perforation has been reported [5]. Generally speaking, only those who undergo repeated biopsy are at risk of long-term complications, which may include severe tricuspid regurgitation and coronary artery to right ventricular fistula.

Scheduling of Endomyocardial Biopsy

As the transplanted heart is denervated, symptoms resulting from graft rejection may remain silent and may not be recognized until late during the course of a rejection episode. Consequently, surveillance biopsies are traditionally performed at standard intervals from the time of transplantation. The recommended frequency for performing surveillance right ventricular biopsy varies by center. There has been a recent trend towards a reduction in the number of procedures being performed as improvements in immunosuppressive therapy and post-transplant management continue to show a decline in the number of rejection episodes. The development of alternative, non-invasive surveillance methods has further decreased the use of biopsy at some centers. A typical biopsy schedule consists of performing the procedure weekly during the first month, every 2 weeks for another month and monthly until 6 months and then every two or 3 months until the end of the first post-operative year, with yearly biopsies thereafter in higher-risk patients. This schedule is intended to reflect the general risk of allograft rejection which is highest in the first 6 months post-transplant. After the first year, any additional protocol biopsies are likely not to be of clinical significance given the very low

rates of rejection observed in this period [6]. However, biopsies are performed anytime in cases of clinically suspected rejection. Repeat biopsies are performed 7–14 days after treatment of rejection in order to confirm resolution.

Clinical Features of Allograft Rejection

Histologically speaking, acute rejection is observed as an inflammatory response of the host to the transplanted organ. Though T-cell mediated mechanisms leading to acute cellular rejection (ACR) were initially described, there is now consensus that host antibody responses play an equally important role, and may result in antibody-mediated rejection (AMR). The diagnosis of AMR remains technically more challenging and a consensus on its definition and management has only recently evolved [7].

As rejection is a histological diagnosis, there are many cases where the patient may remain asymptomatic, especially with milder forms of rejection. In cases where there are clinical features, symptoms of rejection may include palpitations, tachycardia, arrhythmias, edema, dizziness or blackout spells, dyspnea, and a fever of 100 °F or greater.

Hyperacute Rejection

Although now uncommon, the development of hyperacute rejection was the most feared complication prior to the advent of effective immunosuppressive therapy. Hyperacute rejection is mediated by preformed antibodies to the allograft in the recipient. It typically presents following surgical engraftment and restoration of native circulation as an almost immediate, aggressive and inevitably lethal immune attack on the organ. Hyperacute rejection is mediated by preformed antibodies to predominantly HLA antigens, although the phenomenon has also been observed in cases of ABO incompatibility [8]. It is characterized by thrombotic occlusions and hemorrhage of the graft vasculature that begins minutes to hours after the graft is placed. Antigen recognition activates the complement system, along with an influx of neutrophils. Endothelial cells and platelets are induced to shed lipid particles from their membrane that promote coagulation; the resulting inflammation prevents vascularization of the graft, which suffers irreversible damage from ischemia. While this is the most drastic consequence of preformed antibodies to the graft, the presence of donor-specific antibodies is also associated with adverse outcomes even after successful engraftment [9].

The development of the prospective cytotoxic crossmatch, and subsequently the virtual crossmatch (mentioned in Chap. 6) has been a major achievement in avoiding hyperacute rejection in solid organ transplantation [10]. Use of these strategies also helps identify patients who are at high risk of rejection in whom immunosuppression may need to be augmented after transplant. Such advances in perioperative management and improvements in immunosuppression in recent years have led to a general decline in the rates of allograft rejection, though it still remains a significant problem post-transplant.

Acute Cellular Rejection

Acute cellular rejection (ACR), the most common form of rejection in heart transplant, is characterized by a predominantly T-cell mediated response with infiltration of macrophages and lymphocytes, which in turn can lead to myocyte necrosis. Thus, histologically ACR is defined by an inflammatory infiltrate which is typically lymphocyte predominant with associated evidence for myocyte injury (see Table 12.1, Fig. 12.2). Most episodes of ACR occur within the first 6 months post-transplant.

Diagnosis of ACR is made by endomyocardial biopsy; the first standardized grading scale was proposed by Billingham [11] in 1990, which was later revised in 2004 to accommodate for the reporting of AMR [12]. The most recent ACR grading scale, which classifies rejection into mild (1R), moderate (2R) or severe (3R) grades has allowed standardization of reporting, although

variability of interpretation and discordance between pathologists remains, particularly for higher grades of rejection [13]. The main benefit of the new grading scale allows improved guidance for appropriate therapy, in conjunction with clinical assessment. Generally speaking, mild grades of rejection (ISHLT Grade 1R) do not require augmentation of immunosuppressive therapy as the vast majority of these episodes resolve spontaneously, without increased risk of poor subsequent outcomes. However, higher grades (ISHLT ≥2R) invariably require aggressive supplemental immunosuppression (see Sect. 12.4.3).

Table 12.1 Revised 2004 standardized cardiac biopsy grading for acute cellular rejection International Society of Heart and Lung Transplantation (ISHLT)

Rejection grade	Comments
Grade 0R	No rejection
Grade 1R – Mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2R – Moderate	≥2 foci of infiltrate with associated myocyte damage
Grade 3R – Severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis

Adapted from JHLT with permission: Stewart et al. [12]

Frequency and Time Course of ACR

ACR may occur at any time after heart transplantation, especially if there has been a lapse in immunosuppressive therapy (most commonly due to patient non-compliance), but is most frequently seen in the first 6 months post-transplant [1]. The initial risk of allograft rejection rises in the first 1–3 months after transplantation, then

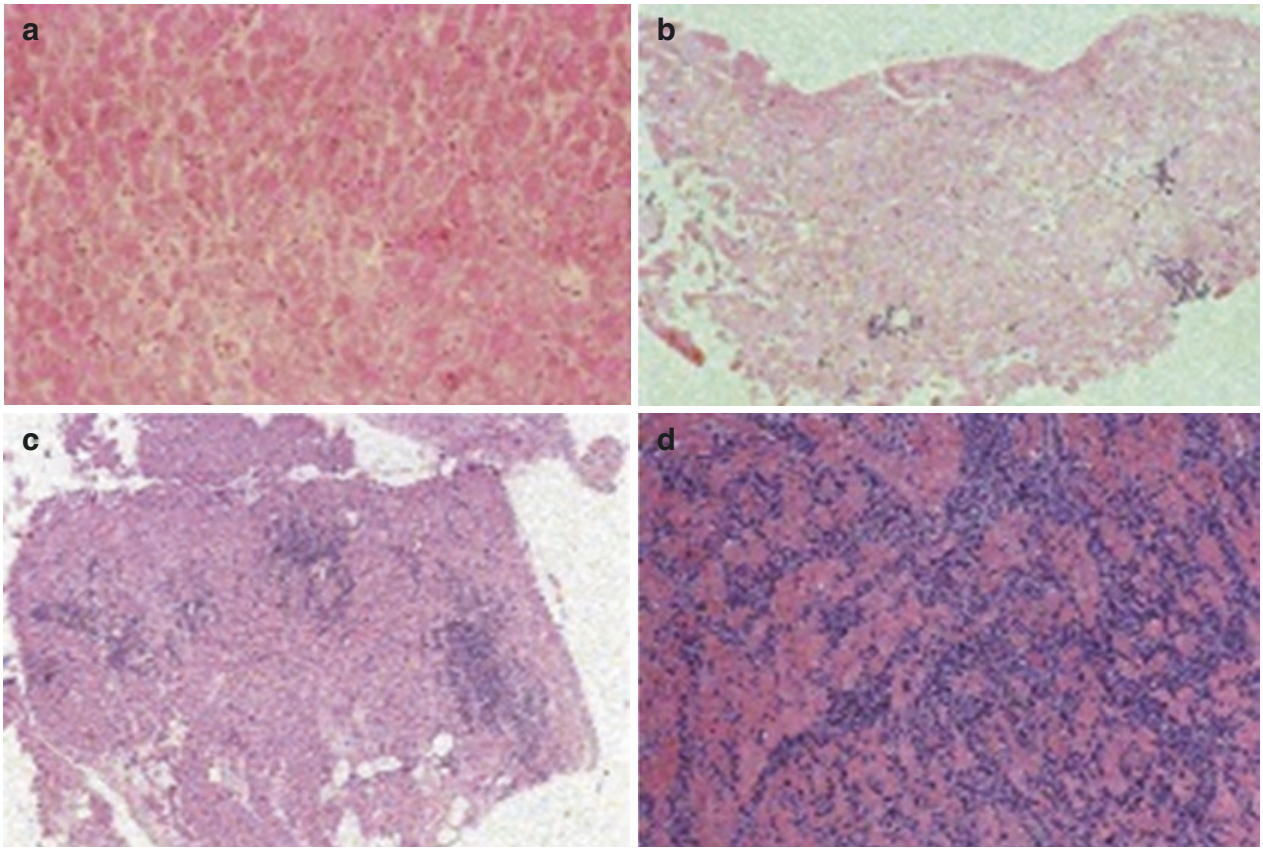

Fig. 12.2 Panel (**a**) Grade 0R: Normal endomyocardial biopsy showing no evidence of cellular infiltration (H&E stain). Panel (**b**) Grade 1R: Low power view of endomyocardial biopsy showing three focal, perivascular infiltrates without myocyte damage (H&E). Panel (**c**) Grade 2R: Low power view showing three foci of damaging mononuclear cell infiltrate with normal myocardium intervening (H&E). Panel (**d**): Grade 3R: Diffuse damaging infiltrates with encroachment of myocytes and disruption of normal architecture (H&E) (Adapted with permission from Stewart et al. [12])

rapidly decreases thereafter, merging with a low constant risk of rejection after 1 year. Nearly 40% of adult heart transplant patients have one or more acute rejection episodes of any degree within the first month, and over 60% experience one or more rejection of any grade within 6 months [1]. Indeed, at 1 year only one third of patients have not experienced rejection. Overall, approximately 30% of patients will have rejection that requires adjustment of immunosuppressive therapy within the first year (see Chap. 10).

Risk Factors for ACR

A number of risk factors have been identified for acute cellular rejection: younger age of recipients, female gender (donors and recipients), higher number of HLA mismatches, black recipients and induction therapy [4, 14]. The development of acute rejection requiring treatment leads to a higher incidence of CAV and mortality [15].

Antibody-Mediated Rejection

While the role of antibodies in mediating acute myocardial injury has been appreciated since the early days of cardiac transplantation when suboptimal immunosuppressive regimens and unidentified preformed circulating antibodies led to early post-operative graft failure from hyperacute rejection, only in recent years has there been official acknowledgement of the role of humoral (antibody) responses in causing allograft rejection in the later phases post-transplantation [16].

It is now known that AMR develops when recipient antibody is directed against donor-HLA antigens on the donor heart endothelium. The recipient antibody initiates fixation and activation of the complement cascade, resulting in donor tissue injury. This complement activation results in activation of the innate and adaptive immune responses. Complement and immunoglobulin are deposited within the allograft microvasculature, resulting in an inflammatory process characterized by endothelial cell activation, macrophage infiltration, cytokine upregulation, increased vascular permeability, and microvascular thrombosis [17]. This process ultimately manifests clinically as allograft dysfunction.

In 2005, the ISHLT revised the 1990 working formulation for the standardization of heart transplant rejection to officially recognize AMR as a distinct rejection entity alongside ACR. The new scale established immunohistologic criteria for the reporting of AMR [12]. It was defined by histopathological changes consisting of capillary endothelial changes, macrophage (in particular CD68-expressing) and neutrophil infiltration, interstitial edema, and linear accumulations of immunoglobulins and complement, especially complement component C4d (see Table 12.2, Fig. 12.3). Additional clinical and serological

Table 12.2 The 2013 ISHLT working formulation for pathology diagnosis of cardiac antibody-mediated rejection

Grade	Definition	Substrates
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+)
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with profound hemodynamic dysfunction and poor clinical outcomes

Adapted with permission from Berry et al. [7]
Abbreviations: *pAMR* pathology antibody-mediated rejection, *CD* cluster of differentiation

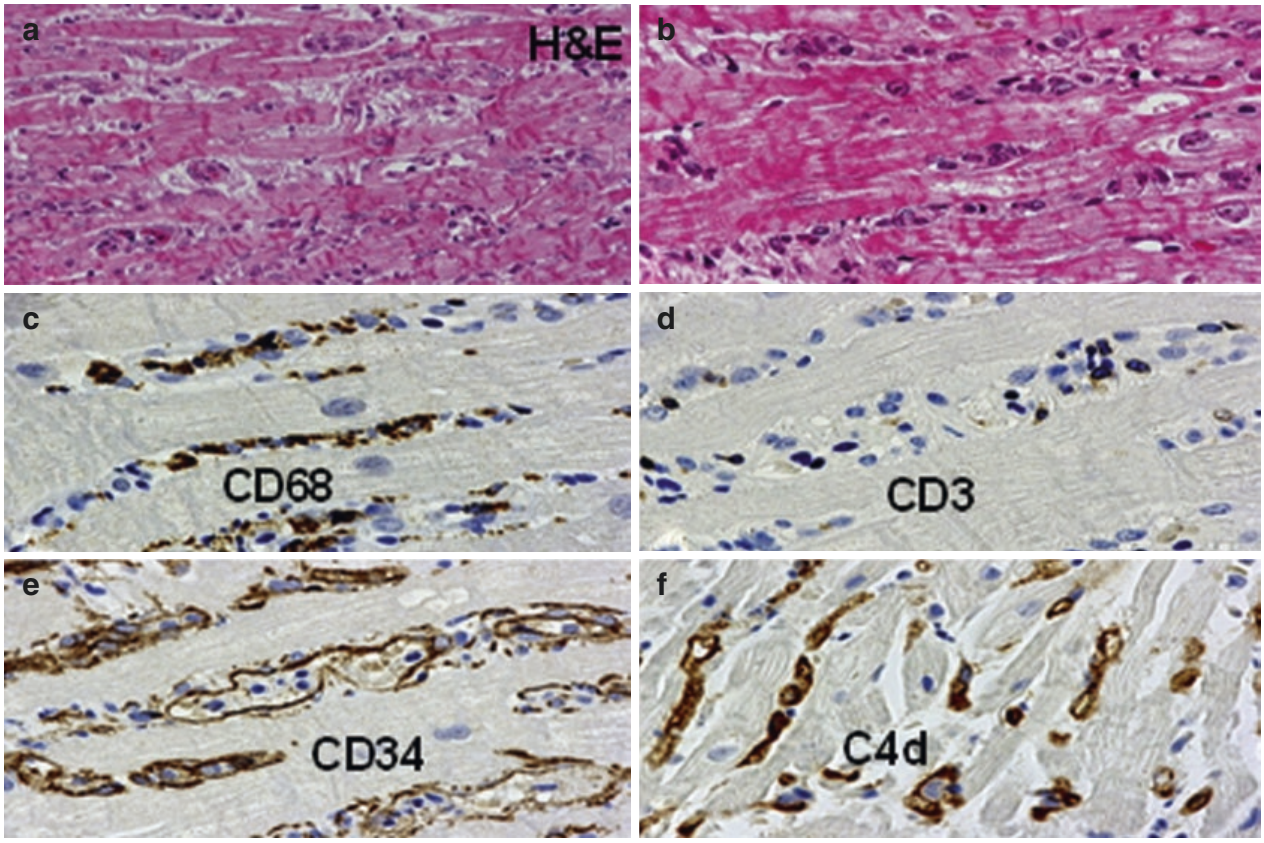

Fig. 12.3 Histologic findings of AMR are typified by the presence of macrophages (CD68+) within capillaries with a relative paucity of lymphocytes (CD3+). Additionally there is evidence of myocyte degeneration on hematoxylin and eosin (H&E) stain and complement deposition (C4D+). (**a**, **b**, **h**, **e**) stain, **c** = CD68 (macrophages), **d** = CD3 (T cells), **e** = CD34 (endothelial cells), **f** = C4d (Complement) (Adapted with permission from Patel et al. [63])

findings of donor-specific antibodies supported the diagnosis of AMR [18].

However, in subsequent years, the phenomenon of asymptomatic AMR associated with worse outcomes was raised [19–21], and the sensitivity and specificity of the immunohistologic features and C4d staining was questioned [22–27]. Furthermore, surveys revealed a variety of approaches to the biopsy specimen investigation and considerable discordance between pathologists in the diagnosis of AMR, with opinion growing that AMR should be classified by severity analogous to ACR [23, 28–30].

Thus, in 2013, following expert discussions and consensus of expert opinion [31], further revisions were made by the ISHLT to the diagnostic criteria for AMR, in an attempt to further standardize diagnosis, and acknowledge that AMR evolves along a worsening spectrum of pathologic changes similar to ACR [7]. The new system specifies that AMR is divided into 3 degrees of severity (see Table 12.2) and is diagnosed from combined histologic and immunopathologic review of the endomyocardial biopsy.

The histopathologic features of AMR include intravascular macrophage accumulation within distended capillaries/venules, and enlarged nuclei and expanded cytoplasmic projections within endothelial cells that may narrow or even occlude the vessel lumen. For more severe cases, there may be signs of hemorrhage, interstitial edema, myocyte degeneration and necrosis, mixed inflammatory infiltrates, and endothelial cell pyknosis/karyorrhexis. The immunopathologic component of AMR comprises of the application of a panel for various antibodies (including C4d, CD68 and anti-HLA-DR) using immunohistochemistry from paraffin sections or immunofluorescence from frozen graft sections. Based on the combination of these findings, an overall pAMR grade is assigned to the biopsy (Table 12.2).

Mixed ACR and AMR

Mixed rejection is a recognized phenomenon defined as the simultaneous presence of cellular infiltrates of ACR and the histopathologic and/or immunopathologic characteristics of AMR [7]. It is not uncommon to find both AMR and low-grade (1R) ACR; however, specimens displaying both moderate to severe (≥2R) ACR and AMR are rare.

Frequency and Time Course of AMR

AMR manifests in up to 15% of heart transplant patients and has overall been associated with poor outcome due to the risk of hemodynamic compromised rejection, greater development of CAV, and increased mortality [16, 32–34].

Clinically, AMR most frequently presents during the first 1–2 months after transplantation, and is accompanied by a rise in donor-specific antibodies [32]. In cases where AMR occurs within the first week post-transplant, the recipient usually has evidence of pre-sensitization to donor HLA antigens [32]. In these early cases of AMR, the patient usually has accompanying graft dysfunction. When AMR occurs late (defined as greater than 1 year after transplantation), typically due to de novo donor-specific antibody, prognosis is poor, with increased mortality and association with fulminant CAV in these cases [35].

For patients where AMR is suspected, with clinical symptoms of heart failure or evidence of left ventricular dysfunction (which may be asymptomatic) without cellular infiltrates, prompt treatment is required (see Sect. 12.4.3). Asymptomatic patients may have incidental findings of AMR on their protocol biopsies and the current consensus is that these patients generally do not warrant treatment if cardiac function is preserved, however this has not been definitively established. Although long-term survival is comparable in these patients to those asymptomatic patients without AMR, it has been demonstrated that they possess greater risk for the subsequent development of CAV and death [19, 20].

Risk Factors for AMR

Risk factors associated with the development of AMR include elevated pre-transplant panel-reactive antibodies (PRAs), positive donor-specific crossmatch, development of de novo donor-specific antibody post-transplant, female gender, prior sensitization to OKT3 (now rarely used), cytomegalovirus (CMV) seropositivity, prior implantation of ventricular assist device, and/or retransplantation [16, 18, 36–39].

Biopsy-Negative Rejection

Prior to the acknowledgement and standardization of diagnosis of AMR as a distinct entity, hemodynamic compromise in the absence of evidence of acute cellular rejection was termed "biopsy-negative rejection". While the prevalence of this so-called "biopsy-negative rejection" has substantially decreased with clear criteria for AMR diagnosis, there continue to be incidences of patients who present with LVEF <45% but have no biopsy findings of ACR or AMR. Nevertheless, these are exceedingly rare [40]. Due to the inherent flaws with the endomyocardial biopsy, the existence of BNR is questioned in some circles. Cases of BNR tend to respond favorably to appropriate rejection therapy.

Non-invasive Diagnostic Methods in Cardiac Allograft Rejection

While endomyocardial biopsy-derived histology remains the gold standard for rejection diagnosis, the potential complications and disadvantages—in particular patient discomfort, sampling error and poor inter-pathologist concordance—are notable. Furthermore, the pathological finding of rejection is a relatively late phenomenon, with diagnosis only made once myocardial damage has already taken place. An ideal test would be non-invasive, utilize less economic resources (biopsy requires radiologists, anesthesiologists, cardiologists, pathologists, associated technical staff) and allow early detection for the onset of rejection before any significant myocardial necrosis has occurred. Many non-invasive modalities have been investigated for this purpose, with the aim of minimizing biopsies if possible.

Clinical Evaluation and Antibody Surveillance

The patient is clinically evaluated for symptoms of rejection at every biopsy appointment, ensuring regular surveillance schedule. In addition to clinical evaluation and in the light of emergent knowledge of the mechanisms of AMR, many centers now regularly assess post-transplant circulating antibodies, given their increased association with incidence of AMR and poor subsequent outcomes, including CAV [32]. The ISHLT now recommends solid-phase assays and/or cell-based assays to assess for presence of DSA, along with quantification if antibody is present. Quantification may further help stratify risk in patients with circulating antibodies. The recommended schedule starts at 2 weeks post-transplant, and then at 1, 3, 6 and 12 months then annually after transplantation, or when AMR is clinically suspected [17].

Gene Expression Profiling

This innovative technique involves screening for genetic markers to determine a gene expression profile that may be representative of the process of ACR. Microarray technology was used to screen for a number of candidate genes that were expressed in cardiac allograft cellular rejection as determined by routine endomyocardial biopsy. The selected genes were then examined in peripheral leucocytes using polymerase chain reaction from blood samples obtained at the time of endomyocardial biopsy [13]. An algorithm that factors in the level of expression in each of these genes is used to produce a score (0–40) that predicts rejection. In general, a score of ≥34 at 6-months or more post-transplant or ≥30 at 2–6 months post-transplant is considered predictive.

In the multicenter IMAGE (Invasive Monitoring Attenuation through Gene Expression) trial [41], 602 patients between 6 months and 5 years post-transplant were randomized to either routine surveillance endomyocardial biopsy or gene expression profiling, with the study powered to determine non-inferiority between the two groups. The study concluded that a strategy of monitoring for rejection that involved gene expression profiling, as compared with routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies. A subsequent, 60-patient follow up study—the EIMAGE (*Early* Invasive Monitoring Attenuation through Gene Expression) trial—initiated gene expression profiling starting at 2 months post-transplant [42], also demonstrating similar outcomes, with no difference in 12-month death, hemodynamic compromise or intimal thickening between the biopsy and gene expression groups. The technique was shown to have a high negative predictive value for the diagnosis of ACR, but low positive predictive value. That a low score was highly associated with a low risk of rejection, demonstrates that the test may be useful in identifying low-risk patients who may safely avoid the need for surveillance biopsy.

However, both these studies demonstrated a selection bias towards stable, low-risk patients, with most of those in the IMAGE trial greater than 1-year post-transplant. Indeed, many centers typically do not perform routine surveillance endomyocardial biopsies after the first year in such patients as the risk of allograft rejection is very low. However, gene expression profiling is now used at many centers in low-risk patients in lieu of biopsy, starting at 2 months post-transplant.

Thus, while there is evidence that gene expression profiling can be used in low-risk patients starting at 2-months post-transplant while using biopsy only sparingly, the test is only validated with regard to ACR and is not applicable for the monitoring of AMR, which can occur in up to 15% of patients. Thus, in high-risk sensitized populations, gene expression profiling is not considered a viable strategy. Nevertheless, to date, it remains the only non-invasive test for the detection of cardiac allograft rejection that has reached routine clinical use and that is approved by the Food and Drug Administration (FDA) in the United States and included in the ISHLT patient care guidelines.

Electrocardiogram (ECG)

Electrical conduction abnormalities have been noted during rejection, but the role of the ECG in diagnosing acute rejection is controversial, and frequently non-specific. In some, mainly European centers, the observation of these electrical abnormalities has led to the development of devices implanted at the time of cardiac transplantation, which allow subsequent monitoring by telemetry of intramyocardial electrocardiograms. Studies demonstrate that changes in amplitude obtained during ventricular pacing are correlated with rejection [43–45]. This modality has a high negative predictive value which may allow a significant reduction in the number of protocol biopsies required to be performed [45–47]. At many European centers, use of intramyocardial ECG monitoring is combined with echocardiography to identify those with reduced need for endomyocardial biopsy.

Echocardiography

While echocardiography remains a vital tool for assessment of graft function in routine management of transplant patients, systolic dysfunction is generally detected relatively late in the course of allograft rejection. Other echocardiographic parameters, such as diastolic function and tissue Doppler imaging have also been investigated to determine their potential utility in detecting rejection earlier during the course of disease [48, 49]. Studies have demonstrated low specificity but high negative predictive value, which may allow a significant reduction in the number of biopsies needing to be performed

Cardiac Magnetic Resonance Imaging

More recently, cardiac MRI has been investigated, and shows promise for the detection of allograft rejection with high sensitivity [50, 51]. In various single-center studies, the separate combinations of myocardial contrast enhancement/edema and right ventricular end-diastolic volume index (RVEDVI)/T2 relaxation time have been found to correlate with biopsy-proven rejection with good accuracy, and high sensitivity and specificity. In fact, one study even showed the combination of RVEDV/T2 relaxation time to be more sensitive than biopsy at predicting clinical rejection [52]. Overall, this technique has the potential of detecting early changes which accompany allograft rejection, and may be helpful in cases where biopsy is negative, but much larger studies are needed for validation.

Biomarkers

Predictably, the traditional biomarkers used in myocardial infarction (troponin) and congestive heart failure (B-type natriuretic peptide) have also been investigated for the purposes of rejection detection post-transplant. Logically, myocardial necrosis may be a consequence of the inflammation accompanying allograft rejection resulting in the release of ultra-structural proteins, including creatine phosphokinase and cardiac troponin. However, in practice, troponin has been found to be non-specific and only detected in episodes of severe rejection [39, 53]. Similarly, while natriuretic peptides are produced in response to cardiac stress, as is reasonably expected to occur during rejection, the significant variability of BNP levels in the early post-transplant period limits its utility in detecting rejecting patients or identifying those at low risk of rejection, although BNP changes over longer periods of time can predict significant rejection [54–56].

Treatment of Cardiac Allograft Rejection

Initial Treatments for Rejection Episodes

There are no definitive protocols in treatment, partly due to the difficulties of designing definitive trials in heart transplant with such small patient populations, but based on the available evidence,

Table 12.3 Treatment options for acute cellular and antibody- mediated rejection

	Asymptomatic	Reduced EF	Heart Failure/Shock
Cellular Rejection (ACR grade ≥2R)	Target higher CNI levels Oral steroid bolus + taper MMF → PSI	Oral steroid bolus/taper *or* IV pulse steroids	*Treat based on clinical presentation; do not await biopsy findings* IV pulse steroids Cytolytic therapy (ATG) Plasmapheresis (before ATG dose) IV immune globulin Inotropic therapy IV heparin IABP or ECMO support
Antibody-Mediated Rejection (AMR grade ≥2) with no/↓ DSA	Target higher CNI levels MMF → PSI	IV pulse steroids consider IV immune globulin	
Antibody-Mediated Rejection (AMR grade ≥2) with ↑DSA	Oral steroid bolus + taper MMF → PSI	IV pulse steroids IV immune globulin Consider ATG, rituximab, bortezomib	

Adapted with permission from Chang et al. [66]
Abbreviations: *DSA* donor-specific antibody, *CNI* calcineurin inhibitor, *MMF* mycophenolate mofetil, *PSI* proliferation signal inhibitor, *ATG* anti-thymocyte globulin, *IV* intravenous, *IABP* intra-aortic balloon pump, *ECMO* extra-corporeal membrane oxygenation

there are a number of guidelines (of level of evidence C) for treatment of both ACR and AMR from the heart transplant community [1, 17].

The management of rejection proceeds in a step-wise fashion based on a combination of severity of rejection detected on biopsy and the patient's presentation (Table 12.3). In general, biopsies with mild grade 1R or AMR1 rejection in the absence of clinical or hemodynamic compromise, do not require further intervention.

Higher grades of rejection, including Grade 2R or higher and AMR2 or higher warrant immediate treatment. The intensity of treatment depends on the patient's presentation; in the asymptomatic patient (i.e. no heart failure symptoms and normal LVEF), treatment options include oral pulse steroids, aiming for higher levels of immunosuppression, and switching from cyclosporine to tacrolimus [57, 58] or from MMF to a proliferation signal inhibitor such as sirolimus/everolimus. In the asymptomatic outpatient with moderate rejection (2R or AMR2 or higher), an oral course of steroids will generally be the first option, given its equivalent efficacy to IV steroid regimens [58].

Asymptomatic AMR1 presents a conundrum; while it may be associated with poor outcomes [19, 20, 33], it is unclear whether treatment affects outcomes. Some centers may choose not to treat; other centers consider it prudent to administer an oral corticosteroid bolus, consider a course of intravenous immune globulin, and initiate monitoring of DSA.

For patients with heart failure symptoms or reduced ejection fraction, regardless of rejection grade, treatment is required to be more aggressive, with intravenous corticosteroids and cytolytic therapy with anti-thymocyte globulin. In cases of AMR2 or higher, patients should also receive intravenous immune globulin (IVIg). If donor-specific anti-HLA antibodies are present in the setting of AMR, patients may receive more intensive therapy with rituximab or bortezomib.

In the scenario of acute cardiogenic shock, empiric aggressive treatment is necessitated. This includes intravenous corticosteroids, cytolytic therapy, plasmapheresis, IVIg, heparin (patients have frequently demonstrated thrombotic occlusion of the cardiac microvasculature on post-mortem examination [59, 60]), and hemodynamic support with intra-aortic balloon pump or even extracorporeal membrane oxygenation as salvage therapy [61].

Treatment of Recurrent Rejection

For recurrent acute or corticosteroid-resistant episodes of cellular rejection, cytolytic therapy with anti-thymocyte globulin should be considered. Furthermore, maintenance immunosuppression should be re-evaluated and a switch

from MMF to sirolimus or everolimus considered [1]. These patients should be frequently monitored by echocardiography even if persistently asymptomatic. Further therapeutic options that may be considered include methotrexate pulse therapy and photophoresis (in which the patient's blood is treated with a photosensitizing agent and subsequently irradiated with specified wavelengths of light to alter the function of T cells) [1]. Total lymphoid irradiation has also been demonstrated to be effective in quelling recurrent rejection, and thus may be considered [1, 62].

Long-Term Treatment of Rejection in AMR Patients

While ACR is often successfully treated with corticosteroids and cytolytic therapy, resulting in a resolution of heart failure and normalization of the ejection fraction [63], AMR often follows a more complicated course after initial treatment. Patients may display a persistent reduction in left ventricular ejection fraction, restrictive physiology combined with recurrent heart failure, and accelerated progression of transplant coronary artery disease [63]. There remains a lack of consensus as to how to best manage these patients; currently, research is investigating the efficacy of therapies to reduce the levels of donor-specific anti-HLA antibodies using agents such as rituximab and bortezomib as well as photopheresis, with promising early results [64, 65]. However, many of these patients subsequently require redo heart transplantation.

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13 Outpatient Management and Long-Term Complications in Heart Transplantation

David Chang, Jon Kobashigawa, and Minh Luu

Clinical Pearls

- Frequent clinical evaluation is required post-transplant, especially in the first year, to monitor for allograft rejection and/or potential infection. A suggested evaluation schedule: Weekly during the first month, every 2 weeks during month 2, monthly until month 6, and every 2 months until a year; thereafter, at least semi-annual evaluation is recommended.
- Cardiac allograft vasculopathy (CAV), best characterized as a diffuse immune-mediated pan-arteritis with concentric, longitudinal intimal thickening of the coronary arteries, remains a major cause of long-term morbidity and mortality after transplantation.
- Risk factors for CAV include history of rejection, older donor age, the presence of donor-specific anti-HLA antibodies, ischemia-reperfusion injury and traditional risk factors for coronary atherosclerosis.
- CAV often remains asymptomatic due to denervation of the donor heart, which blunts angina pain. Symptomatic CAV may present with dyspnea, left ventricular dysfunction, restrictive physiology, or even sudden cardiac death.
- The gold standard for diagnosis of CAV is the coronary angiogram, which can be performed annually. However, maximal intimal thickness as measured by intravascular ultrasound at 1-year compared to baseline is a predictor for subsequent angiographic development of CAV and other poor long-term outcomes.
- Medical strategies to abrogate CAV include the administration of statins and targeted use of proliferation signal inhibitors (PSIs) such as sirolimus/everolimus.
- Interventional options for CAV include the placement of drug-eluting stents, but these are usually temporary measures;

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the only definitive solution is retransplantation.
- Malignancy due to chronic immunosuppression is another major limitation to long-term survival and is more than twice as common compared to the non-transplant population; common malignancies post-heart transplant include post-transplant lymphoproliferative disease (PTLD), skin cancer, lung cancer and Kaposi's sarcoma.
- Common medical problems after transplantation include calcineurin inhibitor-induced hypertension and renal dysfunction, steroid-induced diabetes and osteoporosis, peptic ulcer disease, and hyperlipidemia.

Introduction

Outpatient management after heart transplantation requires longitudinal follow-up to monitor for potential complications. Frequent follow-up is required post-heart transplant to monitor for allograft rejection (Chap. 12) or potential infection (Chap. 11). The focus of this chapter is the diagnosis and management of additional potential long term complications including cardiac allograft vasculopathy, malignancy, hypertension, renal dysfunction, hyperlipidemia, endocrine and bone complications, gastrointestinal complications, heart rhythm disorders, and other cardiac structural problems.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV), known as chronic allograft rejection, remains a main cause of morbidity and mortality after heart transplant. CAV is generally thought to be a diffuse panarteritis with concentric, longitudinal intimal thickening of the epicardial coronary arteries. It likely involves the coronary microvasculature as well. The mechanisms of native coronary artery disease may contribute to CAV development. While CAV is generally a diffuse process, it can manifest in ways similar to native coronary artery disease with focal stenosis.

Pathophysiology

The pathophysiology and molecular basis for CAV include contributions from atherosclerotic mechanisms, ischemia-reperfusion injury, immune responses, and particular infections [1] (see Fig. 13.1). Non-immune mechanisms include atherosclerotic mechanisms and traditional risk-factors for coronary atherosclerosis. Traditional risk factors for coronary atherosclerosis are prevalent after heart transplant and include hypertension, hyperlipidemia, renal dysfunction, and glucose intolerance (diabetes). Older donor age has been associated with the development of CAV [2]. In one study, donors over age 50 were noted to have higher prevalence of traditional cardiac risk factors. In this study, risk of CAV was higher at 5 and 10 year follow-ups [3]. Tissue damage may occur during the process of heart transplant and include physiologic changes at the donor level due to the process of brain death, cardiac arrest of the donor heart, the process of organ procurement, and ischemia-reperfusion at the time of organ implantation. Elements of the adaptive and innate immune systems likely contribute to the development of CAV. Human leukocyte antigen (HLA) shedding during heart implantation can lead to indirect allorecognition with internalization and processing of donor soluble HLA by recipient antigen presenting cells. Presentation of these donor antigens may lead to T cell stimulation. Heat shock proteins may be detected by toll-like receptors and promote maturation of dendritic cells. Complement deposition, namely C3d deposition, is associated with antibody-mediated rejection and CAV [4]. Alloimmune interactions will lead to T and B cell stimulation, the release of pro-inflammatory cytokines, and a state of vascular inflammation. Endothelial cells that line transplanted coronary arteries may be the primary antigenic stimulus for the initiation and progression of CAV as this is a main point of contact and communication of recipient blood and the transplanted graft. For example,

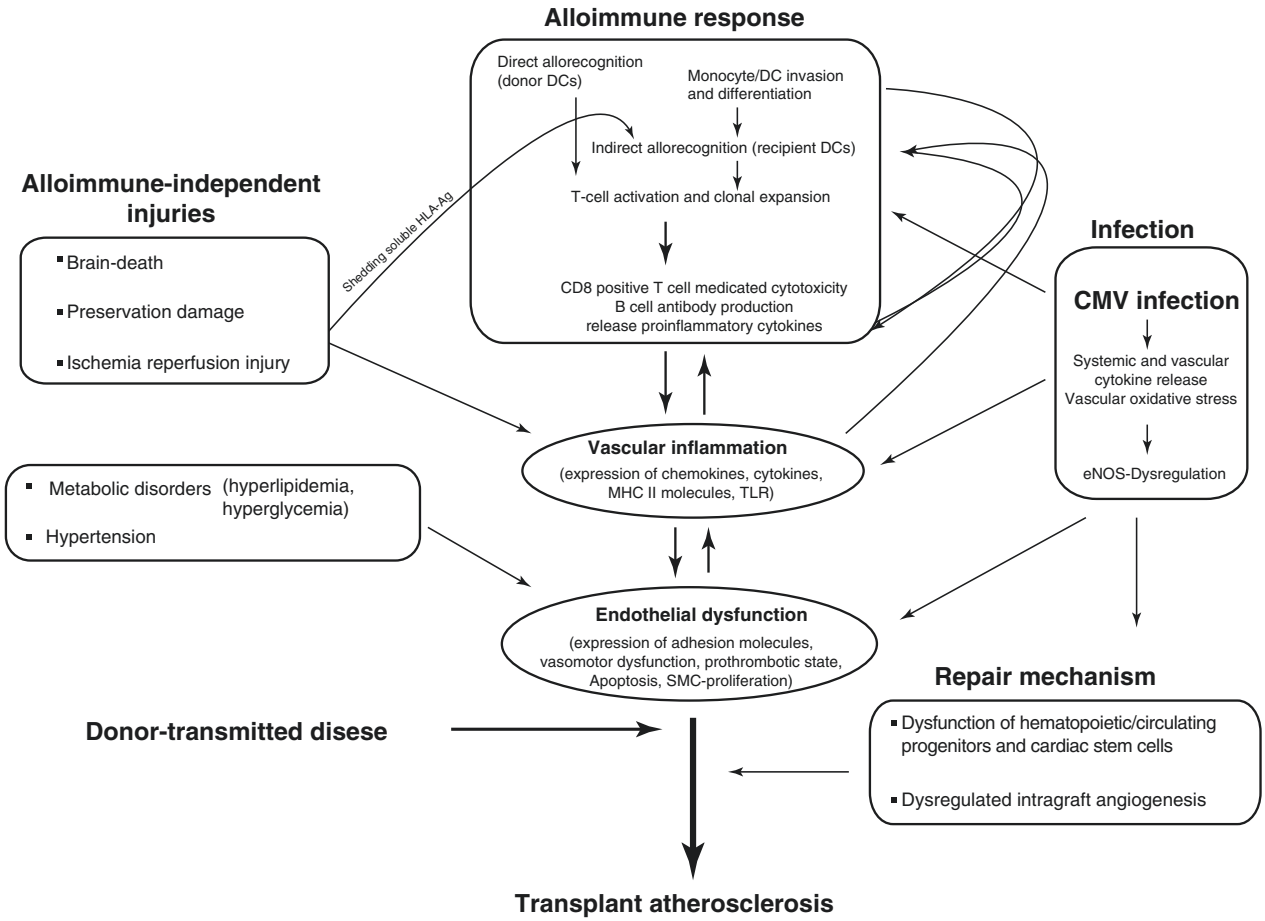

Fig. 13.1 A diagram demonstrating the collaboration and interaction of alloimmune-dependent and independent factors that influence the pathogenesis of transplant vasculopathy. Abbreviations: *Ag* antigen, *CD* cluster of differentiation, *eNOS* endothelial nitric oxide synthase, and *SMC* smooth muscle cell (Reused with permission from Schmauss and Weis [1])

vimentin is expressed on endothelial cells and anti-vimentin antibodies have been associated with CAV [5]. Donor specific antibodies (DSA) can develop to the transplanted graft, particularly after episodes of cellular and/or antibody-mediated rejection. The presence of DSA, particularly to major histocompatibility complex (MHC) type II antigens, is associated with CAV and poor outcomes after heart transplant [6–8]. In addition to DSA, non-HLA antibodies, many of which are expressed on endothelial cells are likely involved in the development of CAV. Non-HLA antibodies associated with CAV include anti-angiotensin II type I receptor [9], anti-MHC class I chain-related A [10], anti-MHC class I chain-related B, as well as adhesion and trafficking receptors. Moreover, inflammatory modulators may influence cytokine signaling and the development of CAV [11, 12]. Infections, such as cytomegalovirus (CMV), may also influence the development of CAV [13, 14]

Clinical Features

The process of heart transplant causes denervation of the transplanted graft. Due to cardiac denervation, CAV may present insidiously. Cardiac angina is typically absent due to lack of cardiac afferent nerves. Shortness of breath or atypical symptoms may accompany CAV, but CAV may be asymptomatic. CAV may present with left ventricular systolic dysfunction, but even with severe CAV, left ventricular systolic function may be preserved. Significant CAV is often accompanied by restrictive allograft physiology. Restrictive physiology is defined as symptomatic heart failure with either echocardiographic

Table 13.1 The International Society for Heart and Lung Transplantation nomenclature of cardiac allograft vasculopathy

Grade of CAV	Disease severity	Angiographic findings
CAV0	No disease	No detectable angiographic lesion
CAV1	Mild	Angiographic LM <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
CAV2	Intermediate	Angiographic LM <50%; a single primary vessel >70%, or isolated branch stenosis >70% in branches of two systems, without allograft dysfunction
CAV3	Severe	Angiographic LM >50%, or ≥2 primary vessels >70% stenosis, or isolated branch stenosis >70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF <45%, usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology

Adapted with permission from Mehra et al. [15]
Abbreviations: *CAV* cardiac allograft vasculopathy, *ISHLT* International Society of Heart and Lung Transplantation, *LM* left main, *LVEF* left ventricular ejection fraction

or hemodynamic abnormalities on right heart catheterization. Echocardiographic parameters consistent with restrictive allograft physiology in adults include E/A velocity ratio > 2, decreased isovolumic relaxation time <60 ms, shortened mitral valve deceleration time <150 msec. Restrictive hemodynamics on right heart catheterization include right atrial pressure > 12 mmHg, pulmonary capillary wedge pressure >25 mmHg, and cardiac index < 2 L/min/m^2. A consensus statement was published in 2011 by the International Society for Heart and Lung Transplantation (ISHLT) that established a working formulation of standardized nomenclature for CAV (Table 13.1). By this form of classification, CAV can be separated into not significant (CAV0), mild (CAV1), moderate (CAV2), and severe (CAV3) disease [15].

Epidemiology

The incidence of CAV increases temporally in a progressive manner. Per the latest registry report from the ISHLT [16], for adult heart transplant recipients, the prevalence of CAV is 7.8% at 1 year post-transplant, 30% at 5 years post-transplant, and 50% 10 years following heart transplant. CAV is the third leading cause of death for heart transplant recipients who are more than 3 years post-transplant. In one early study, mortality was over 50% at 2 years after diagnosis of CAV [17]. Graft failure, which may reflect undiagnosed CAV, is another main cause of mortality post-transplant. In the pediatric population, CAV rates are reduced compared to adult heart transplant recipients with the prevalence of CAV primarily dependent on recipient age at time of heart transplant. In infants and young children (ages 1–5), 31% of heart transplant recipients will have CAV within 11 years post-transplant. For children age 6–10, 43% of transplant recipients will have CAV within 11 years post-transplant. For children age 11–17, 45% of recipients will have CAV within 11 years post-transplant. In the pediatric population, survival was 42–48% in the 6 years after diagnosis of CAV [18].

Diagnosis

Due to the morbidity and mortality associated with CAV, diagnosis of this disease process is critical. The gold standard test for diagnosis of CAV continues to be the conventional coronary angiogram. Interpretation of lumen patency by conventional coronary angiography may give a false sense of security as the lumen of the coronary artery may not be compromised until intimal thickening encroaches and causes focal stenosis (Fig. 13.2). For this reason, many institutions utilize intravascular ultrasound (IVUS) in addition to conventional coronary angiography for assessment of CAV. CAV that presents early post-transplant portends a poor outcome

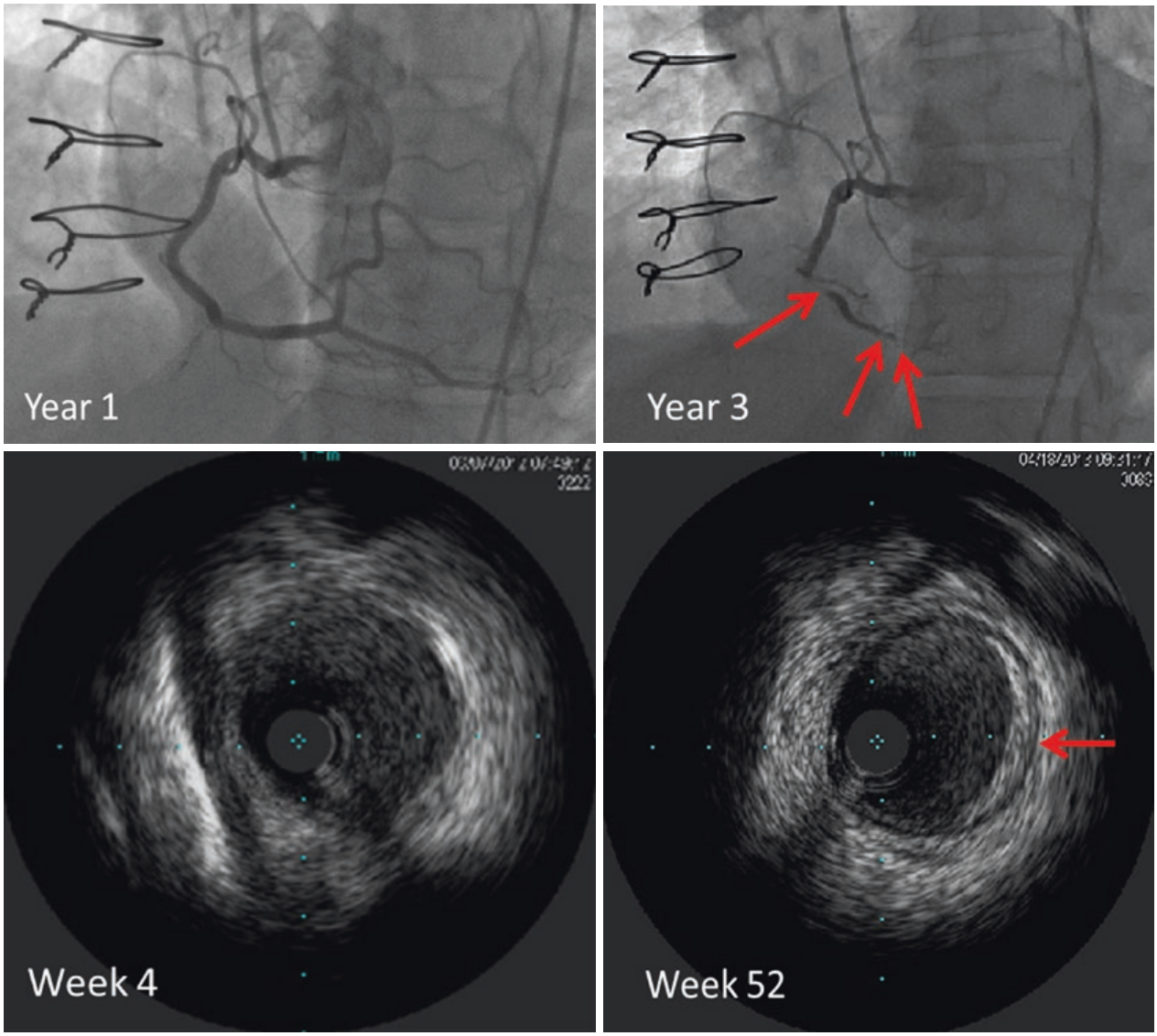

Fig. 13.2 The *top* half demonstrates the progression of cardiac allograft vasculopathy as demonstrated by right coronary artery angiogram at year 3 post-transplant compared to year 1. Note the multiple, diffuse stenoses (*red arrows*). The bottom half demonstrates the progression of intimal thickness (*red arrow*) as demonstrated by intravascular ultrasound at 52 weeks (1 year) post-transplant compared to baseline (week 4 post-transplant). There was a difference of greater than 0.5 mm change between baseline and 1 year. Such a finding is highly prognostic for poor long-term outcomes

[19, 20]. Although a number of IVUS based parameters have been analyzed post-transplant, change in maximal intimal thickness (MIT) of a matched cross-sectional area of a coronary artery from baseline (approximately 6 weeks post-transplant) to 1 year post-transplant was a reliable surrogate marker for subsequent mortality, nonfatal major adverse cardiac events (MACE), and development of angiographic CAV through 5 years post heart transplant. Patients with MIT increase of 0.5 mm or greater in any matched site of a coronary artery had significantly higher incidence of death or graft loss, nonfatal MACE, and higher incidence of new angiographic CAV [21, 22].

Procedures such as conventional coronary angiography and IVUS pose risks that accompany invasive tests. These risks include bleeding, infection, contrast induced nephropathy, peripheral vascular disease, risk of myocardial infarction, dissection or damage of the coronary artery, stroke, and potentially death from the invasive test(s). Due to patient discomfort and the inherent risks of invasive testing,

non-invasive tests can be used to assess for CAV. Non-invasive tests for CAV include exercise or pharmacologic-based stress tests, positive emission tomography (PET) testing with coronary flow reserve (CFR), and coronary computed tomographic angiography (CCTA). A normal dobutamine stress echocardiogram predicted an uneventful clinical course [23]. Patients undergoing regadenoson perfusion scans with fixed or reversible perfusion defects had significantly higher risk for death, left ventricular dysfunction, and increased rates of percutaneous intervention within 1 year of abnormal stress test compared to patients with normal perfusion on regadenoson perfusion scan [24]. Patients undergoing PET testing with CFR measurements that had CFR <2 showed higher incidence of left ventricular dysfunction and left ventricular enlargement with stress [25]. Abnormal CFR likely represents microvascular dysfunction not necessarily reflective of epicardial CAV. Although there are limitations of CCTA, it may be a reasonable alternative in patients who have had complications from conventional coronary angiography or for assessment of variant coronary anatomy. As denervation generally leads to higher resting heart rate post-transplant (due to lack of parasympathetic nervous system tone), CCTA can still yield technically adequate results in the post-heart transplant population [26, 27].

Management

Medical

Prevention and treatment options for CAV include medical therapies, modulation of the immune system, mechanical therapies including percutaneous intervention, and redo-heart transplant. The 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitor, pravastatin, was shown in a prospective clinical trial to reduce the incidence of CAV, reduce cholesterol levels, reduce cardiac rejection with hemodynamic compromise and increase survival at 1 year post-transplant [28]. This study was supported by another prospective trial of simvastatin, a similar drug, which demonstrated superior 8-year survival and freedom from CAV compared to a control group [29]. In another trial, use of vitamins C and E showed no progression of CAV (compared to placebo treated control patients) [30]. Given risk of development of CAV and likely contribution of traditional risk factors to development of CAV, low dose aspirin is generally advised post-transplant. The use of induction agents at time of heart transplant, including T cell depleting agents and interleukin (IL)-2 receptor antagonists, may lead to reduced rates of CAV. Anti-thymocyte globulin (ATG), a commonly used T cell depleting agent, has shown delayed onset of CAV [31] and decreased CAV progression by IVUS parameters between baseline and 1-year post-transplant [32]. Different approaches to maintenance immunosuppression have shown differences in the development of CAV. The purine inhibitor mycophenolate mofetil (MMF) in combination with the calcineurin inhibitor (CNI) cyclosporine showed decreased incidence of CAV [33]. Clinical trials using the proliferation signal inhibitors (PSI) sirolimus or everolimus in conjunction with CNIs have shown reduced rates of CAV compared to maintenance immunosuppressive regimens with CNI in combination with purine antagonist. Everolimus in combination with cyclosporine showed lower rates of CAV compared to cyclosporine with azathioprine [34]. Sirolimus in combination with cyclosporine showed lower rates of CAV compared to cyclosporine in combination with azathioprine [35]. High-dose everolimus in combination with cyclosporine showed harm in one trial, but low-dose everolimus with cyclosporine showed similar mortality compared to cyclosporine with MMF [36]. Everolimus showed efficacy over MMF for CAV in subpopulations including women, diabetics, patients over age 60, and patients with higher cholesterol levels [37]. A more recent study examined low-dose everolimus with reduced-dose cyclosporine versus standard-dose cyclosporine with MMF. Low-dose CNI was withdrawn and PSI dose increased to target levels 7–11 weeks post-transplant. This study also demonstrated lower CAV burden in the PSI arm [38].

Immunomodulation with photopheresis may reduce rates of CAV due to reduction of rejection episodes. Photopheresis involves removal of approximately 5% of peripheral blood lymphocytes. These cells are treated with ultraviolet-A light and methoxsalen. Treated cells are reinfused into the patient [39]. This treatment is thought to cause apoptosis of T cells and creation of regulatory T cells that, in theory, reduce the inflammatory state. Benefit from photopheresis was demonstrated when used empirically post-transplant [40] and for treatment of post-heart transplant rejection with hemodynamic compromise or recurrent heart transplant rejection [41]. Patients treated empirically with photopheresis for the first 6 months post-transplant had reduced rates of acute rejection without increased risk of infection. Using photopheresis in the treatment of patients with rejection with hemodynamic compromise or recurrent rejection decreased the risk of subsequent significant rejection episodes. Reduction of rejection and the inflammatory state may lead to decreased rates of CAV, although this has not formally been studied in a clinical trial format.

Surgical

CAV is generally a pan-arteritis, but it can present with focal stenosis. Percutaneous intervention and stent placement is generally a temporizing measure for CAV. One study showed equivalent outcomes following placement of sirolimus drug eluting stents (DES) compared to bare metal stents for significant CAV [42]. Data with newer everolimus DES suggest durability of stented segments with low rates of target lesion revascularization [43]. Prior attempts at revascularization by coronary artery bypass grafting (CABG) surgery resulted in high post-surgical mortality and low rates of survival 1 year after CABG [44, 45]. CAV is the main cause of need for redo-heart transplant. Annually, 2–4% of heart transplant recipients are redo heart transplant recipients. Unfortunately, survival after redo heart transplant is reduced compared to index heart transplant. For adult recipients, 1 year survival after redo heart transplant is approximately 70% and 10 year survival is 38% [16].

Outpatient Management

CAV diagnosis and treatment is important to the long term management of patients post heart transplant. There are a number of additional factors important to long-term management. Generally, maintenance immunosuppression is most intense in the first month after transplant. The risk for rejection and infection is highest in this time point and outpatient follow-up is most intense in this time period. Patients generally require involvement of one or two caregivers to assist with medication administration, medication adherence, and transportation to frequent clinic visits. Target trough levels of immunosuppressant medications are lowered in time. Decrement in cardiac function may be asymptomatic and therefore cardiac function and lab work, including renal function, are frequently assessed during follow-up. Many programs use a combination of two immunosuppressant medications and prednisone. If a patient avoids rejection, maintains normal LV systolic function, and does not develop DSA, she or he can potentially wean off prednisone in time. After surgery, a patient's functional status oftentimes improves with cardiac rehabilitation.

Malignancy

The main limitations to long-term survival after heart transplant are CAV, graft failure, and malignancy. The use of chronic immunosuppression after transplant to prevent allograft rejection increases the risk of malignancy in the long term. Recipients of heart transplant may have a pre-existing history of malignancy that, after transplant and on immunosuppression, predisposes them to recurrence of their primary malignancy. For patients with history of low-risk tumors, potential heart transplant recipients need not be delayed in evaluation for heart transplant. For patients with pre-existing cancer with a high risk of recurrence, heart transplant should be delayed for an adequate time as opined by oncology to ensure patients remain free from cancer recurrence. High-risk cancers include melanoma,

breast, and colorectal cancer. Although data is limited, there is possible transmission of malignant oncogenic cells from donor to recipient. Caution should be considered in donors with history of renal cell carcinoma with vascular invasion, melanoma, choriocarcinoma, and central nervous system tumors [46]. Malignancy may be discovered in organ donors after the process of organ transplant or may be known at the time of organ transplant. The rate of de novo malignancy is approximately twofold higher in transplant recipients compared to the general population [47]. Proposed mechanisms for increased rates of de novo malignancy include direct effects of immunosuppression, reduced immune surveillance, and expansion of atypical cells. In addition, oncogenic viruses may proliferate in the setting of immunosuppression and contribute to the development of malignancy. Viruses including Epstein-Barr virus (EBV), human herpes virus 8 (HHV-8), human papillomavirus (HPV), human T-cell lymphotropic virus 1 (HTLV-1), and Merkel cell polyomavirus (MCV) have association with particular malignancies. Survival after diagnosis of malignancy depends on many factors including size of tumor, local or distant spread of the tumor, aggressiveness of the tumor, and ability of the patient to tolerate treatments directed against the tumor.

Cardiac transplant may require more intense immunosuppression because of the risk of death with graft loss. Animal studies suggest CNI may promote cancer through increased production of transforming growth factor (TGF) beta [48]. Common malignancies after heart transplant include post-transplant lymphoproliferative disease (PTLD), Kaposi's sarcoma, skin cancer, lung cancer, and anogenital cancer. PTLD represents a heterogeneous group of lymphoproliferative disorders. EBV infection is associated with PTLD. EBV-seronegative recipients receiving transplants from EBV-seropositive donors are at elevated risk for development of PTLD. With EBV infection, B cells incorporate EBV DNA into the cellular genome, decreasing the rate of apoptosis and leading to cellular proliferation. EBV DNA load is suggestive in the right clinical context for PTLD. Imaging studies including fluorodeoxyglucose (FDG)-positron emission tomography can assess hyper metabolic tissue, but ultimately, diagnosis of PTLD is made on histopathology. Risk of PTLD is highest in the first year after transplant when immunosuppression is most intense. Common sites of PTLD in heart transplant recipients include lung, GI tract, liver, lymph nodes, and disseminated disease. In heart-lung transplant recipients, PTLD is primarily found in the lung. Symptoms are variable with PTLD. PTLD can present with fever, fatigue, malaise, recurrent infections that do not respond to antibiotic therapy, lymphadenopathy, or with significant organ dysfunction. PTLD is generally treated with significant reduction of immunosuppressive therapies. Reduction of EBV can be attempted with the antiviral agent acyclovir or gancyclovir. In high-risk patients, prophylaxis with anti-viral agents can be considered. For treatment of neoplastic B cells, a number of approaches are possible including use of chemotherapy, anti-B cell therapy with Rituximab, use of PSI (and withdrawal of one immunosuppressant agent), and tumor resection [49]. When reduction or withdrawal of immunosuppressant therapies is not effective, mortality from PTLD is high. Kaposi's sarcoma is associated with HHV-8 and occurs in men at rates threefold higher than is seen in women. Lesions typically affect the legs and cause lymphedema. Skin cancers include squamous cell and basal cell carcinomas, melanoma, and Merkel cell carcinoma. Factors that mitigate risk of skin cancer development include ultraviolet radiation, fair skin, pre-transplant history of skin cancer or actinic keratosis, geographic location, and intensity, duration, and type of immunosuppressant therapy. Use of voriconazole for treatment of fungal infections has been associated with the development of aggressive squamous cell carcinomas [50]. Lung cancer, particularly in patients with prior significant tobacco exposure, is increased in heart transplant recipients. Anogenital cancer occurs in 2–3% of transplant recipients. Lesions may be multiple and extensive and may resemble genital warts. Screening for the presence of malignancy after heart transplant is critical. Dermatologic evaluation should be done to screen for skin cancer.

Table 13.2 Indications for changing to proliferation signal inhibitors

Instead of mycophenolatemofetil (MMF):
Rejection
Cardiac Allograft Vasculopathy
Malignancy
Cytomegalovirus infection
Instead of calcineurin inhibitors:
Renal dysfunction

Reused with permission from Chang et al. [52]

There are no formal guidelines for cancer screening after heart transplant, but regular health maintenance screening would be appropriate.

As with CAV, use of PSIs instead of antimetabolites may be favorable in the context of malignancy. Transition to PSIs may decrease the risk of development of subsequent malignancies after heart transplant [51]. Additional indications for use of PSIs in this context include history of heart transplant rejection and viral infection with CMV. Although PSIs can cause proteinuria kidney disease, it can be used instead of CNI in a renal sparing effort [52] (see Table 13.2 for a summary of indications). PSI use should be made on an individual basis. Potential risks of PSIs include increased risk of fungal infection, fluid retention, risk of venous thromboembolism, hypertriglyceridemia, oral ulcers, proteinuria renal disease, nausea, diarrhea, leukopenia, and pneumonitis.

General Medical Management

Cardiovascular

Risk factors for the development of heart disease are quite prevalent after heart transplant. Per the latest ISHLT registry report [16], within 5 years post-transplant, hypertension occurs in 92% of patients, renal dysfunction occurs in 52% of patients with 15% on chronic dialysis, and hyperlipidemia occurs in 88% of patients. Hypertension is a known side-effect of treatment with CNIs [53] and steroids. Salt restriction is advisable, particularly earlier post-transplant when steroid doses and CNI target trough levels are highest. Hypertension management to standard guideline directed targets can be done with a number of different anti-hypertensive agents. Calcium channel blockers in combination with angiotensin converting enzyme inhibitors showed benefit by IVUS-based parameters of CAV assessment at 1 year post-transplant [54]. As with hypertension, CNI is known to lead to gradual reduction of glomerular filtration rate and lead to renal dysfunction with long-term use. CNI toxicity can lead to acute renal dysfunction, so trough levels of CNI are monitored closely. While the mainstay of chronic immunosuppressant therapy remains use of CNIs, usually in combination with an antimetabolite immunosuppressant, CNI-free immunosuppressant regimens can be carefully used to avoid the long-term nephrotoxic effects of CNIs. Nephrotoxins, in particular NSAIDS, should be avoided, if possible, post-transplant. Use of colchicine for treatment of gout should be done with caution. As previously mentioned, statin therapy is recommended post-transplant, in part for treatment of hyperlipidemia. Due to drug-drug interactions, high-dose, high-intensity statin therapy is avoided. Hypertriglyceridemia can be caused by PSI therapy, at times requiring cessation of PSI therapy. Hypertriglyceridemia can usually be managed by agents including fenofibrate or fish oil.

Endocrine

Another common risk factor present prior to and post-heart transplant is glucose intolerance and diabetes. Many patients will have diabetes as a risk prior to diabetes. Need for steroid use post-transplant requires adequate control of diabetes prior to listing for heart transplant. Use of high-dose steroids post-transplant leads to diabetes in many patients after transplant. Between 30% and 40% of patients will develop diabetes post-transplant. Screening for ocular, renal, and podiatric complications of diabetes should continue per usual recommendation. Early high-dose steroids are weaned such that, in one approach, patients are reduced to 10 mg prednisone by 3 months post-transplant, 5 mg by 6 months post-transplant, and if possible, weaned off prednisone by 1 year post-transplant. Many patients will experience symptoms of steroid withdrawal, most often manifest by muscle or joint aches or

fatigue. Rarely will steroid withdrawal symptoms prevent steroid weaning. At times, patients with autoimmune disease may require higher than usual maintenance doses prednisone. The presence of autoimmune disease does not appear to effect long-term outcomes after heart transplant [55].

Bone complications after heart transplant include osteoporosis, fracture, and osteonecrosis [avascular necrosis (AVN)]. Risk factors for osteoporosis include pre-transplant bone state and post-transplant bone loss. Advanced heart failure, chronic heparin or loop diuretic use, chronic kidney disease, vitamin D deficiency, hyperparathyroidism, hypogonadism, and reduced physical activity can lead to low bone mineral density (BMD) prior to transplant [56]. Post-transplant, bone loss is greatest in the first year due to higher doses of steroids and possibly due to higher CNI target trough levels (when cyclosporine is used in maintenance immunosuppression). Steroids cause reduced bone formation and increased bone resorption. In one study of patients who had annual spinal radiographs, vertebral fracture was reported in 27% of patient in the first 2 years after transplant [57]. Predictors of fracture included age and pre-transplant BMD. In another study, women with lowest BMD pre-transplant were at highest risk of fracture, with most fracture occurring in the first 6 months post-transplant [58]. Prevention of falls, smoking cessation, early mobilization after transplant, and regular weight-bearing exercise are recommended. Treatment with vitamin D (particularly in those with vitamin D deficiency) and calcium is recommended prior to and post-transplant. Bisphosphonate therapy to prevent bone loss should be considered in patients over age 65, patients with a history of prior fragility fracture, and BMD T score below negative 1.0. If bisphosphonate therapy is not tolerated or if the patient has significant renal insufficiency, calcitriol is an alternate option. If calcitriol is prescribed, serum and urine calcium levels should be monitored [59]. Treatment with bisphosphonate therapy for osteoporosis may not be required for more than 1 year after transplant. Use of chronic steroids post-transplant is also associated with osteonecrosis. Risk of AVN is <3% in patients maintained on doses of prednisone less than 15 mg/day. Other risk factors for development of AVN include excess alcohol intake, systemic lupus erythematosus, anti-phospholipid antibodies, trauma, sickle cell disease, Gaucher disease, and decompression disease. AVN often presents with weight-bearing pain, but can occur at rest or with night symptoms. Plain films may yield the diagnosis, but magnetic resonance imaging (MRI) is the most sensitive test for diagnoses of AVN. Treatment options include non-operative and operative options. Early stage AVN may benefit from medical therapy with bisphosphonates, statin therapy to reduce transition of bone marrow pluripotent cells into fat cells, iloprost (prostacyclin) vasodilator therapy, and anticoagulation when AVN is related to thrombophilia. For early stage AVN, electrical stimulation and hyperbaric oxygen have been used. Operative approaches include joint preserving procedures or joint replacement.

Gastrointestinal

Gastrointestinal issues can occur post-heart transplant. Early post-transplant, with use of higher doses of steroids, peptic ulcer disease and gastritis symptoms can be reduced by use of proton pump inhibitors (PPIs). PPI use is generally not required long-term. Patients using PSIs for maintenance immunosuppression are at risk for hypertriglyceridemia. Although rare, extreme elevation of triglycerides places patients at risk for development of pancreatitis. Patients maintained on azathioprine are also at risk for pancreatitis. Patients post-transplant are at risk for cholelithiasis and diverticular disease.

General Notes

Additional cardiac complications can arise both early and late post-heart transplant. Routine protocol-based endomyocardial biopsies are done early post-transplant when risk for rejection is highest. In one approach, protocol-based biopsies end 1 year post-transplant. Thereafter, endomyocardial biopsy is done based on patient symptoms or new onset cardiac dysfunction. The process of obtaining tissue for analysis involves

venous access and placement of a bioptome into the right ventricle. Damage to the tricuspid valve is rare, but can cause significant tricuspid regurgitation and, potentially, symptomatic right heart failure. Pericardial effusion related to endomyocardial biopsy can potentially lead to cardiac tamponade. Post-biopsy, assessment for tricuspid regurgitation and pericardial effusion by transthoracic echocardiogram are important to ensure that iatrogenic complications are appropriately managed. Rhythm issues post-transplant include junctional and sinus bradycardia, supraventricular tachycardia (SVT) and ventricular tachycardia (VT). Early post-transplant, approximately 10% of patients will require placement of a permanent pacemaker for atrioventricular (AV) nodal disease. Due to denervation and loss of parasympathetic tone, resting heart rates post-transplant are generally 100 +/− 10 beats per minute. In time, heart rates may decrease as partial re-innervation may occur. Maintenance of cardiac output post-transplant is heart rate dependent. Patients with symptomatic sinus bradycardia would require pacemaker placement. As a late finding, new onset sinus bradycardia may relate to AV nodal disease, requiring pacemaker. Sinus bradycardia as a presentation of rejection or cardiac dysfunction may represent an ominous pre-terminal rhythm when found late post-transplant. Atropine will not be effective in treatment of bradycardia post-transplant. Chronotropic agents, such as isoproterenol, or transvenous pacing may be needed to maintain adequate heart rate and cardiac output. The most common rhythm disturbances post-transplant manifested by patients with rejection include atrial fibrillation and atrial flutter. Treatment for rejection and anti-coagulation may resolve the rhythm disturbance. If not, cardioversion post-transesophageal echocardiogram (when needed) can restore sinus rhythm. Intravenous adenosine or intravenous beta-blockers in the treatment of SVT should be used with caution post-transplant. SVT not related to rejection or CAV are most commonly related to surgical suture lines and may be amenable to electrophysiological ablation techniques [60]. VT can occur post-transplant as a manifestation of donor acquired dysrhythmia or other cardiac dysfunction. Rarely, VT is the cause of arrhythmic death post death. Pulseless electrical activity and asystole are the predominant terminal rhythms seen post-transplant.

Summary

Major complications after heart transplant include infection, rejection, CAV, malignancy, hypertension, hyperlipidemia, renal disease, glucose intolerance, bone, gastrointestinal, and additional cardiac issues. Improvement in post-heart transplant immunosuppression and care will lead to improved quality of life and longevity after transplant. Investigations into other types of immunosuppressants, including targeting of interleukin (IL)-6, down-regulation of the immune system by impairing T cell co-stimulation, and targeting components of the innate immune system may augment the current regimen of agents used in induction and maintenance immunosuppression. Biologic agents used by oncologists in the treatment of malignancy may have a role in immunosuppression-related malignancy. Finally, insights into immune mechanisms of CAV may have an impact on native atherosclerosis as there may be an immune component to the development of native atherosclerosis in non-transplant patients.

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Quality of Life After Heart Transplantation

14

Jon Kobashigawa and Michael Olymbios

Clinical Pearls

- In general, quality of life following heart transplantation has been acceptable.
- Mental health appears to improve over time but can be affected by post-transplant complications.
- There are issues that prevent complete physiologic exercise recovery including immunosuppressive medications, cardiac denervation and deconditioning.
- In some patients, return to work has been limited by possible loss of health insurance termed "insurance disabled".
- Social functioning may largely be dependent on support personnel while sexual intimacy may be affected by both psychological and physiological factors.
- Reproductive health is possible but not encouraged due to potential morbidity and mortality issues following heart transplantation.

Introduction

Patient outcomes after cardiac transplantation have historically been quantified with measures such as survival, freedom from infection, and rates of rejection. In today's era of increased survival, quality of life is now seen as an important outcome measure. The World Health Organization defines quality of life as, "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [1]. In the context of cardiac transplantation, quality of life may be interpreted as the patient's perception of their heart failure, including any therapies, on their ability to live a satisfying life.

The typical heart transplant recipient often endures a poor quality of life prior to transplantation due to the sequelae of heart failure. A principal aim of transplantation is to attain an improved quality of life in addition to prolonging survival. Potential improvements in quality of life are frequently assessed when evaluating end-stage heart failure patients for transplantation. Quality of life can be measured both qualitatively and quantitatively, as will be discussed in this chapter.

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Aspects of Quality of Life

Assessing Quality of Life

Quality of life is assessed across various domains, which are often subjective and involve considerable overlap. Physical wellbeing, functional status, mental health and social standing are all established markers of quality of life in the post-transplant population. There are numerous methods for both assessing and presenting quality of life data. Often, a questionnaire is submitted to the patient and a score is generated from the answers given. The topics covered in a questionnaire may be generic to all individuals or focus on the patient's particular disease and therapies—in this case heart failure, cardiac transplantation and immunosuppression. Questions will often range from the overtly objective, such as whether a patient is currently in paid employment, to the subtly subjective, such as how many days he or she has felt depressed in the past month. Although the patient is the primary source for quality of life data, caregivers and relatives can be useful for supplementing or validating responses.

The hallmark of a good question is one that yields answers that are reliable, valid and sensitive. Reliability refers to the frequency with which the same response is given, by the same patient, at different times. Validity means that a question evokes a response that correlates with the outcome measure. Sensitivity is the likelihood of a question discovering an outcome attributable to the patient. After constructing a questionnaire, subjects are selected. Care is needed to ensure that the sample is representative of the population. Those declining a questionnaire on the basis of being too unwell or too preoccupied represent important parts of the quality of life spectrum. Being unwell may refer to a hospitalization or it may refer to depression or anxiety. Conversely, being preoccupied may be due to a patient having regained employment or enjoying leisure activities. Every effort must be made to recruit a broad spectrum of patients for quality of life studies.

Determining whether variables are dependent on one another and establishing risk factors for outcome variables is a challenging task in the setting of quality of life. Studies often employ multivariate analysis. This means looking at the collective relationships between measured variables and outcomes. For example, determining whether a transplant recipient has returned to work or whether a patient is depressed, may depend on many other factors or even be co-dependent. A patient may not return to work because he or she is depressed or may be depressed because he or she cannot return to work. In turn, a patient may not be able to return to work because of health issues. These relationships can be subtle but identifying the determinants of outcomes is important for allowing patients to attain the highest possible quality of life.

Physical Wellbeing

Barring severe complications, there is a universal improvement in physical status for heart transplant patients when compared with end-stage heart failure. The NYHA Heart Failure scale mentioned in Chapter 1 serves as the traditional measure of functional status in heart failure. After transplantation, over 90% of patients self-classify themselves as NYHA class I [2], in stark contrast to classes III or IV where patients are classified prior to transplantation. In theory these patients are able to return to their "normal" lives. In reality, however, the patient's psyche is tainted by the harrowing experience of an involved and lengthy surgical procedure. Fear of rejection, dealing with hospitalizations from infections, and persevering with lifelong medication can weigh gravely on the patient's mind and thus on their perceptions of their own physical status.

In quality of life studies assessing physical status, patients have consistently reported substantial improvement [3]. Symptoms of heart failure are dramatically reduced in nearly all patients. A prospective study demonstrated that 90% of patients reported minimal or no symptoms of heart disease [4]. Furthermore, exercise capacity as measured by oxygen uptake, maximum heart rate, and anaerobic threshold

significantly improves post-transplant [5], although it rarely returns to normal due to denervation and physiologic derangement. As addressed previously, the greatest improvements typically occur during the first year post-transplantation [5]; however, rehabilitation programs and targeted exercise protocols are often able to achieve further incremental gains [6, 7].

Functional Status

A heart transplant recipient's functional standing encompasses all the activities of daily living such as grooming, mobilizing freely, performing domestic chores, participating in paid employment, attending school and partaking in leisure activities. Patients report improvements in all functional areas after transplantation. While on the wait list, only 8% of patients classify their quality of life as high, and 84% of patients complain of difficulties at work or at school [8]. This compares with two-thirds of patients who report a high quality of life after transplantation. However, half of patients still report being unable to perform one or more work or school related tasks [4]. Although there is a marked improvement in all the functional areas post-transplantation, a significant proportion of patients report a deficit of some kind in one or several of the areas. Two-thirds of patients complain of limitations to desired physical activities [4]. As time since transplantation increases, functional impairment is derived from the chronic use of immunosuppressive therapy. Patients can suffer from muscle atrophy, myalgia, osteopenia or the sequelae associated with renal impairment. These complications can deter patients from activities involving physical exertion.

Employment

Returning to work benefits patients and society at large. Individuals who resume employment not only gain financial independence, but also increase their self-esteem and allows personal goals to be attained and improves socialization [9]. A detached economic analysis of the impact of heart transplantation holds a negative view of the procedure when return-to-work rates are low. An example of cost-benefit analysis for transplantation occurred in Oregon in 1987 where the state legislature denied Medicaid funding for heart (and other organ) transplantation. Over the course of 2 years, 34 individuals were denied Medicaid-funded transplants at an estimated cost of $2.2 million. These funds were, instead, used to provide perinatal care for approximately 1500 low-income women and infants [10]. Several factors influence a patient's likelihood of returning to work. These include age at time of transplant, education, length of disability and the patient's perception of their own health [9, 11, 12]. Recipients who are younger, have a higher level of education, feel confident in their health, and are encouraged by their physicians have a higher chance of gaining employment.

The number of patients who return to work varies widely across centers, ranging from 22 to 86% of heart transplant recipients [11–15]. These figures come from centers across the world. Large studies in the United States show rates of approximated 45% [9, 12, 13]. This contrasts with 69% of patients 1 year after transplantation in the UK [11]. One possible explanation for this difference is that a large proportion of those who did not return to work in the US were "insurance disabled". "Insurance disabled" refers to transplant recipients who would have liked to return to work and were medically fit enough to do so. They could not, however, because working would have resulted in a loss of Medicare health insurance and private medical insurance was either unobtainable or prohibitively expensive. One study [14] found that 36% of patients fell into this category. Legislative changes such as lifelong Medicaid funding for immunosuppression, the Social Security Administration's "Ticket to Work" program, and the Affordable Care Act, will likely mean that heart transplant recipients can more easily gain employment post-operatively. Therefore, future studies could show higher numbers of patients returning to work.

A dilemma facing transplant patients is the loss of disability benefits that may occur upon returning to work. Some patients will lose disability compensation upon starting a paid job. This is

often anxiety-provoking since many are concerned that their health is in a fragile state and a sudden deterioration could put them in financial difficulties. Self-perception plays a significant role in employment rates amongst transplant patients. Paris et al. [12] found that of the 61% of heart transplant recipients who were unemployed, a mere 13% were deemed medically unable to work by their physicians.

More patients who have white-collar jobs return to work than patients who have blue-collar jobs prior to transplantation [16]. This is due to the physical demands required by many blue-collar jobs. Other jobs, such as operators of heavy machinery or airline pilots, require health certification. Unfortunately, concerns over CAV and sudden death often mean patients fail health checks and therefore are denied employment.

The ISHLT guidelines [17] recommend that returning to work should be discussed prior to heart transplantation as a goal of post-operative rehabilitation. The guidelines advise that patients should be encouraged to keep their jobs for as long as possible pre-operatively and that returning to work should be proactively facilitated by a healthcare professional.

Although there is scope for improving the employment rate for heart transplant recipients, it should be noted that the rate is significantly higher when compared with employment rates for those on the wait list. Patients who did find employment worked more hours, missed fewer days and had a higher performance rating when compared to before their surgeries. These outcomes highlight the positive effects of heart transplantation for society as a whole as well as for the patient.

Operating Vehicles

In the initial postoperative period, sternotomy precautions must be taken. The motion of turning a steering wheel can impede healing and therefore a minimum 6–8-week abstention from driving is needed. Patients should be pain-free ideally. When riding as a passenger in a car with airbags, patients should refrain from sitting in the front during the first postoperative weeks.

Actual driving laws vary by geographic region. If a patient has had any episodes of syncope, then they must not drive until they have been free from an episode for a minimum of 6 months. A full neurological assessment should be done looking for tremors, adequate visual acuity and a stable gait. In addition, symptomatic bradycardia requires a permanent pacemaker to be implanted before driving is permissible. Piloting aircraft comes under heavy scrutiny from most aviation authorities owing to the high incidence of CAV and the potential for sudden death.

Mental Health

Patients suffer psychological sequelae as part of their end-stage heart failure and while awaiting transplantation. Anxiety, feelings of hopelessness about the future, a loss of control and an increased dependency on others are frequently experienced by the patient [18, 22]. Although physical symptoms abate quickly after transplantation, anxiety and depression often persist. Psychiatric morbidity has been reported in 39% of patients assessed for transplantation [18]. Patients with a longer duration of illness and patients who are unemployed are more likely to have pre-transplant morbidities. Major depressive disorder was most common followed by generalized anxiety disorder. Sexual dysfunction, mostly in men, is also prevalent.

In the post-transplant population there is actually an increase in the number of patients suffering from depression and anxiety during the first postoperative year [19]. Some patients report feelings of euphoria, guilt and changes in body image [20]. It is known that corticosteroids, as part of the immunosuppression regimen, contribute to anxiety and mood swings. Patients who suffer from postoperative complications experience anger and resentment. Psychiatric morbidities usually resolve after the first year post-transplantation. Interestingly, patients who have psychiatric disorders pre-transplantation also show a resolution of symptoms [21]. Therefore, depression or anxiety should not be a contraindication to listing a

patient. They are usually the result of chronic illness and normally do not progress to post-operative adjustment disorders. Unfortunately, patients who do show persistent signs of psychological morbidities have a reduced quality of life and more physical morbidities [23].

After 5 post-transplant years, recipients generally have good psychological outcomes. Depression and anxiety is lessened or absent, body image improves, and overall quality of life measures are higher [24]. The levels of stress and the ability to cope with stress do not decrease over time. Clinicians should be aware of this and consider therapies focusing on stress-management for the long term.

Social Functioning

Although there are significant improvements in many areas of a patient's life, social relationships tend to suffer. Immediate family members often endure financial hardships and act as caregivers. Increased stress and anxiety from the patients can also strain relationships further. The physical and psychological sequelae of end-stage heart disease often prevent social relationships outside the family unit from being maintained. Family members should be acknowledged as an import part of the transplant process. Healthcare professionals should be mindful of making family members feel included where permitted by the patient themselves [25].

Support networks are important for the patient. Recipients with strong relationships are more likely to be compliant with their long-term management plans. Measures of socialization increase during the first 5 years after transplantation [5]. Relationships are an important part of quality of life. Support should be given to assist in maintaining these interpersonal bonds.

Reproductive Health

With improved survival and decreased morbidities, heart transplant patients are increasingly pursuing romantic relationships, sometimes wishing to begin a family. The data on pregnancy after heart transplantation are limited, with most clinical guidelines derived from studies relating to kidney and liver recipients. There are important genetic and ethical considerations particularly for patients with hereditary heart disease.

Male patients frequently suffer from erectile dysfunction after transplantation. Psychological causes should be excluded before commencing medical therapy. Initially, medical therapy with a phosphodiesterase (PDE) 5 inhibitor can be attempted. As with the general population, concomitant use of nitrates is contraindicated. If PDE inhibitors are ineffective or contraindicated, then a referral to an ED specialist with a view to administering intracarvenous injections of prostaglandin E1 can be considered [17].

Sexually active patients should have routine monitoring for sexually transmitted infections (STIs). A sexual history is useful, particularly in adolescent patients. If warranted, ano-genital exams may also be included in the routine follow up to screen for lesions indicative of HSV, HPV and molluscum contagiosum. Female transplant candidates should receive the HPV vaccine preoperatively. There are no contraindications to postoperative administration, but the effectiveness in unproven.

Contraceptive choices should balance the risks against the benefits of preventing an unintentional pregnancy that may have far-reaching consequences for the mother and child. Although highly effective, hormonal methods of contraception have side-effects to consider. Combined hormonal contraception may impact the levels of immunosuppressants by inhibiting the CYP-3A4 pathway. Hypercoagulable states preclude the use of hormonal methods. Patients with significant hypertension, CAV, estrogen-sensitive malignancies or liver disease should also avoid hormonal contraception. Depo-medroxyprogesterone is not recommended in heart transplant patients because it is associated with decreased bone density. Intrauterine devices are contraindicated because of the risk of infection. Barrier contraceptives should be recommended in adolescents and patients with multiple sexual partners to prevent STIs. They should be used adjunct with other

methods for pregnancy prevention as, on their own, failure rates are too high, risking a potentially detrimental pregnancy.

Patients wishing to have children should receive adequate counseling to discuss genetic and ethical considerations. Although survival has improved, it is still significantly lessened when compared to those of reproductive age in the normal population. Patients should be aware of the distinct possibility that children will have lost a natural parent by their teenage years. For female patients, a multidisciplinary team of cardiologists, fetal medicine specialists, anesthesiologists, neonatologists, geneticists and psychiatrists is needed for a full evaluation. Generally, pregnancy is discouraged in the first year after transplantation. The evaluation should begin by excluding any signs of graft dysfunction which may include an EMB. Renal and hepatic function should be assessed and monitored closely during pregnancy. Any pre-existing nephrotoxicity from CNIs may be exacerbated by pregnancy. The blood pressure should be measured frequently to monitor for hypertension and pre-eclampsia. Immunosuppressive therapy does not appear to impact the immune system of the fetus, although mycophenolate mofetil is teratogenic (class D) and should be discontinued. The plasma volume expansion of pregnancy often causes fluctuations in CNI levels so these should be reviewed frequently, adjusting the dose accordingly. The premature delivery rate has been reported up to 30% and the surgical delivery rate up to 33% in transplant patients [26]. Cyclosporine and azathioprine are detectable in breast milk. There is no evidence to determine whether this effects the fetus but given the potential risks, breastfeeding should probably be avoided.

In general, quality of life following heart transplantation has been acceptable. Mental and physical health appears to improve over time but can be affected by post-transplant complications and medications. Social functioning may largely be dependent on support personnel while sexual intimacy may be affected by both psychological and physiological factors. Finally, reproductive health is possible but not encouraged due to potential morbidity and mortality issues following heart transplantation.

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Pediatric Heart Transplantation: Special Considerations

15

Jon Kobashigawa and Michael Olymbios

Clinical Pearls

- Wait list mortality is worse than in the adult population for heart transplantation due to donor shortages and the limited availability of VADs.
- Contrary to the adult population, ABO-incompatible heart transplantation is possible in infants and younger children with good outcomes.
- Children can be transplanted safely with a pre-operative pulmonary vascular resistance index of up to 9 Wood units/m^2.
- Infants and young children enjoy coronary artery "privilege" that affords them some degree of protection from CAV.
- Heart transplantation for children with CHD often requires additional tissue from the donor for repairing and reversing previous palliative procedures.
- Steroid-avoidance immunosuppressive regimens show good outcomes in children who are not sensitized.
- Survival after heart transplantation is greater in the pediatric population.

Introduction

The first pediatric heart transplant was performed by Adrian Kantrowitz at Maimonides Medical Center in Brooklyn, New York on December 6, 1967 (Fig. 15.1). This was the first human heart transplant in the United States and followed the first ever human heart transplant by only 3 days. The recipient was an 18-day-old male with Ebstein's anomaly and pulmonary atresia. The donor was an infant with anencephaly (Fig. 15.2). Interestingly, the operation was performed under hypothermia rather than cardiopulmonary bypass. The patient survived for only 6 h [1]. Poor survival and a lack of donors resulted in enthusiasm for pediatric heart transplantation waning for over a decade until the success of immunosuppression in adults revived

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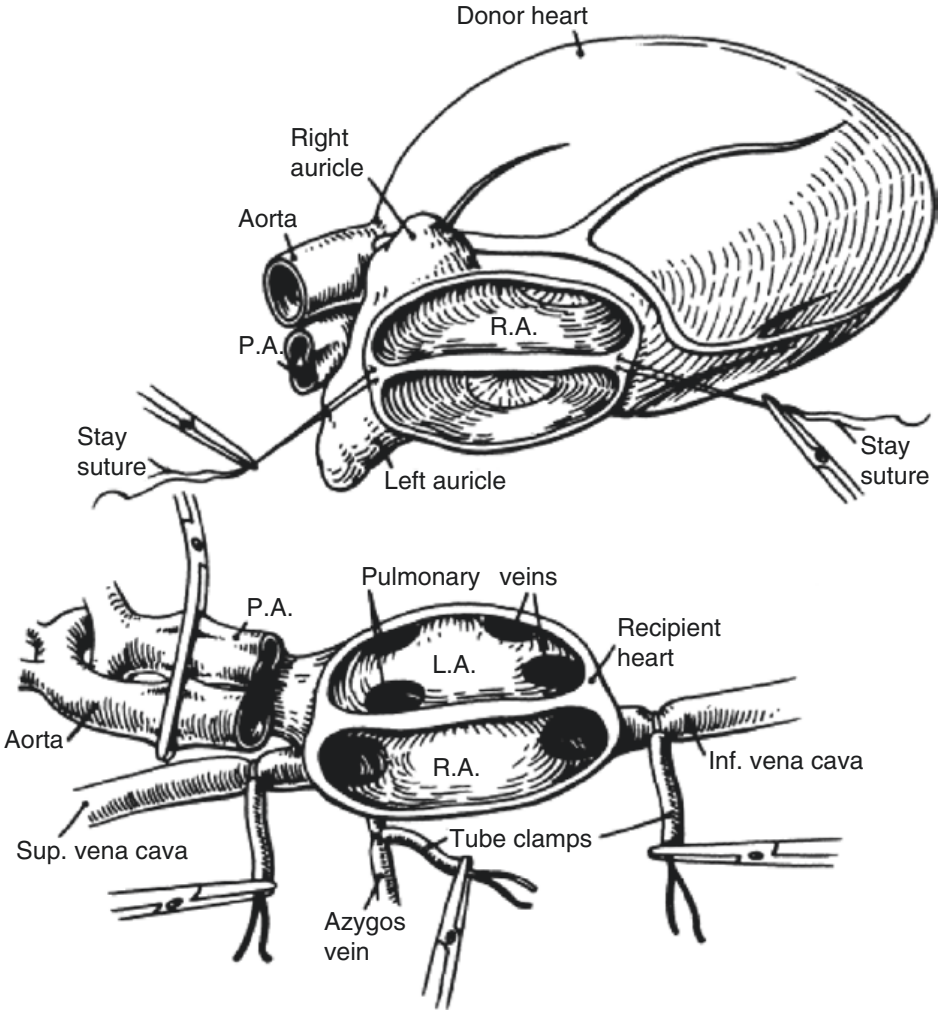

Fig. 15.1 Operative details of the first pediatric heart transplant (Reused with permission from Mendeloff [69])

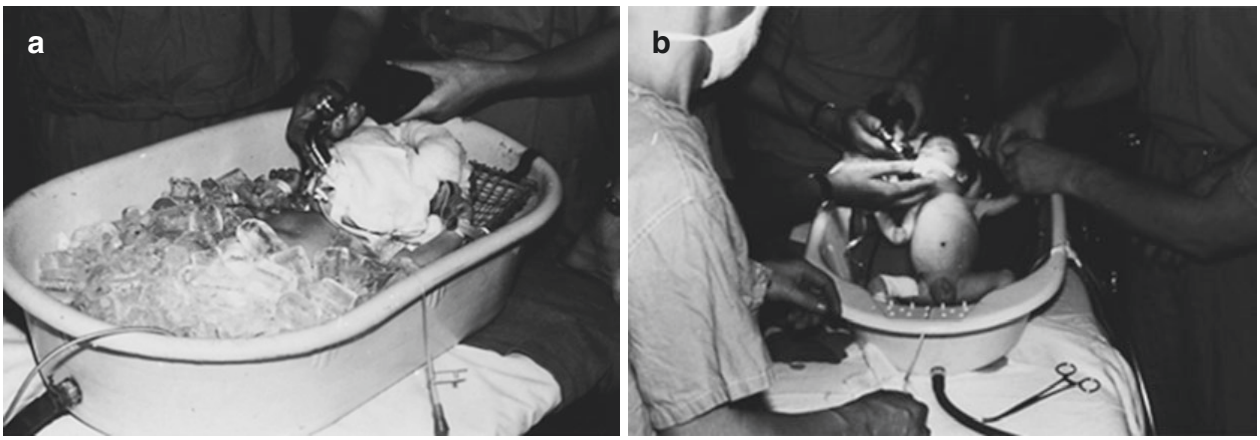

Fig. 15.2 The first pediatric heart transplant: (**a**) the donor (**b**) the recipient (Reused with permission from Mendeloff [69])

interest in the field. In 1983, Leonard Bailey and his colleagues at Loma Linda attempted a xenotransplant between a baboon and a 12-day-old girl. The procedure was technically successful although the recipient suffered severe acute rejection and died 20 days later [2]. The case was highly publicized and helped increase the availability of donor organs in the pediatric population. Bailey went on to perform human-to-human neonatal orthotopic heart transplants. Their first patient, a 4-day old infant with hypoplastic left heart syndrome (HLHS), was operated on in 1985 [3] and survived to adulthood. HLHS was, at the time, a fatal condition treated with a palliative operation known as the Norwood procedure. This pioneering work helped propagate the field.

Children who undergo heart transplantation show excellent outcomes. The median life expectancy is over 15 years after the first year post-transplantation [4]. Despite this, wait list mortality is higher than for any other solid organ. Infant risk of death has been reported as high as 25% [4]. This is, in part, due to the lack of available mechanical circulatory support devices for this age-group.

The Pediatric Heart Transplant Study (PHTS) was established in 1993 by six centers with the objective of advancing our understanding of the specialty by keeping an event-driven database that could be used for clinical research. The organization continues and notably produces data on outcomes and risk factors.

Indications for Heart Transplantation

Cardiomyopathies and congenital heart defects are the most common indications for pediatric heart transplantation. The proportions vary by age, with approximately half of surgeries done for congenital heart disease (CHD) and slightly less than half for cardiomyopathy in children under 11. In children 11–17 years old, two-thirds of patients have cardiomyopathy and a quarter have CHD pre-transplant. The number of pediatric heart transplants recorded by the registry of the International Society for Heart and Lung Transplantation (ISHLT) in the United States has remained relatively constant at between 400 and 600 from 1991 to 2013. The figure from 2013 represented 13% of total heart transplants, including adults, reported to the registry [4]. Donor shortages and the lack of mechanical circulatory support in the infant population are factors impeding the number of operations taking place. The Pediatric Committee of the American Society of Transplantation [5] and a consensus group of the American Heart Association (AHA) [6] broadly agree on the indications of heart transplantation in children. The procedure is considered when life expectancy is less than 2 years or when quality of life is poor. Controversy surrounds HLHS as an indication given wait list times result in high mortality [7]. Many centers advocate palliative surgical techniques such as the Norwood and Fontan procedures instead [8].

Cardiomyopathies

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common cardiomyopathy in children, accounting for more than half of cases. DCM is characterized by left ventricular or biventricular dilation with impaired contraction. It can be congenital or acquired. Familial causes were previously thought to be rare but it is now known that up to 50% of cases involve patients with an underlying genetic abnormality [9]. The causative genes encode for proteins found in the cytoskeleton and sarcomere. Viruses, and in particular adenoviruses, are a significant etiology [10]. Of note is DCM secondary to Adriamycin given that malignancy can be a contraindication to transplantation. The incidence of DCM in the pediatric population is 0.57 per 100,000 per year with boys being slightly more susceptible than girls [11].

The dilated ventricle increases the stress exerted on the chamber wall. Mitral regurgitation and arrhythmias are common. Children may develop heart failure and present with anorexia and weight loss. Clinical signs include tachycardia, jugular venous distention, hepatomegaly and a systolic murmur consistent with mitral regurgitation. The echocardiograph findings include left ventricular dilation with either a low ejection fraction or fractional shortening. There may be mitral regurgitation or a pericardial effusion. The electrocardiograph (ECG) may show sinus tachycardia, pathological Q waves, bundle-branch block, heightened QRS complexes, atrial fibrillation or ventricular arrhythmias (see Fig. 15.3). The biomarker brain natriuretic peptide (BNP) can be useful when trying to distinguish lung disease from heart failure or for monitoring disease progression. An endomyocardial biopsy (EMB) is done to determine the etiology of DCM. This is necessary for identifying underlying pathologies that require different management plans such as sarcoidosis or the glycogen storage diseases. The biopsy sample can be used to detect viral genetic material with PCR (Table 15.1).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the second most common cardiomyopathy seen in

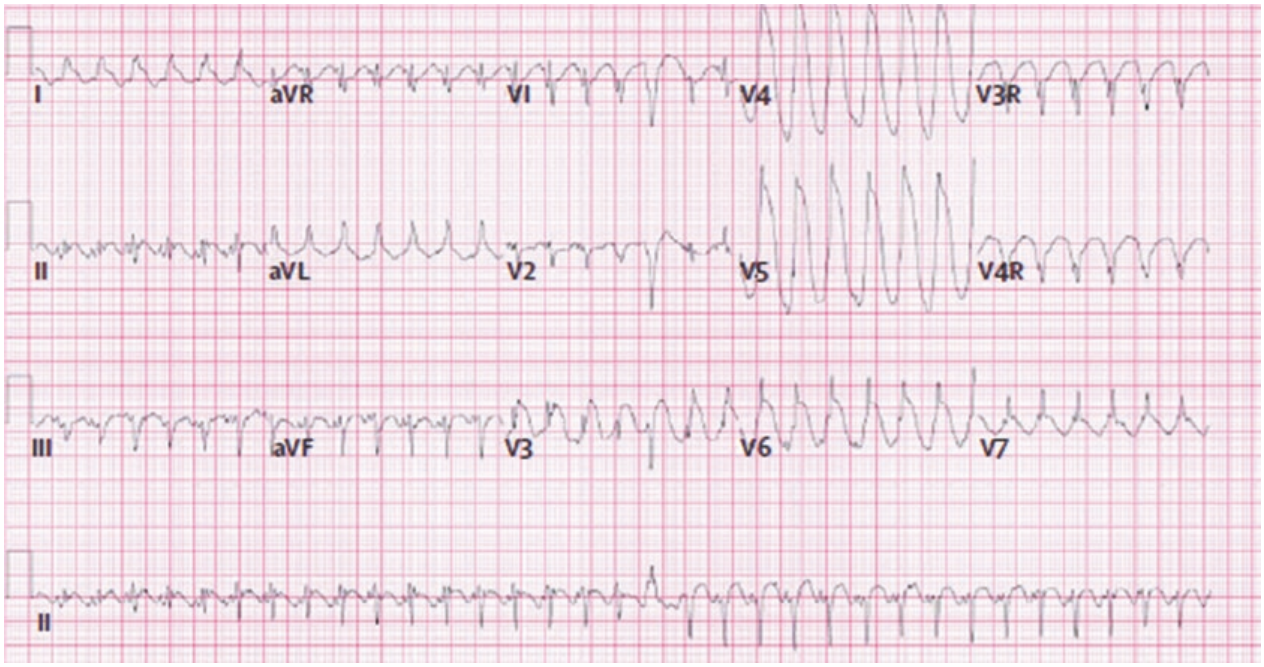

Fig. 15.3 ECG of a patient with DCM and decompensated heart failure (Reused with permission from Jefferies and Towbin [70])

Table 15.1 Genetic causes of dilated cardiomyopathy by chromosome locus

Locus	Gene	Protein	Protein location
Xp21.2	DMD	Dystrophin	Cytoskeleton/SL
Xq28	G4.5	Tafazzin	Phospholipid
1q12	TNNI1	Cardiac troponin I	Sarcomere
1q32	TNNT2	Cardiac troponin type 2	Sarcomere
2q31	TTN	Titin	Sarcomere
2q35	DES	Desmin	Cytoskeleton
5q34	SGCD	δ-sarcoglycan	Cytoskeleton/SL
6q12–q16	CMD1K	Unknown	Unknown
6q22.1	PLN	Phospholamban	Calcium
9q13-q22	CMD1B	Unknown	Unknown
9q22-q31	SEMA4D	Unknown	Unknown
10q22.1	MYPN	Myopalladin	Sarcomere
10q22.3–23.2	ZASP/Cypher (LDB3)	LIM domain binding protein 3	Sarcomere
1q42–q43	α2-actinin	ACTN	Sarcomere
10q22.1–q23	VCL	Metavinculin	Cytoskeleton
10q23.22	ANKRD1	CARP	Sarcomere
10q25.3	RBM20	RNA binding motif protein 20	Unknown
11p11.2	MYBPC3	Myosin binding protein C	Sarcomere
11p15.1	CSRP3	Muscle-LIM protein	Sarcomere
14q11.2–q13	MYH7	β-myosin heavy chain	Sarcomere
15q11–q14	ACTC1	Cardiac actin	Sarcomere
15q22.1	TPM1	α-tropomyosin	Sarcomere

Reused with permission from Jefferies and Towbin [70]

children. It is the most common form of Mendelian inherited heart disease, and it is often found to be the underlying pathology in young people who suffer from sudden cardiac death [12]. Several gene mutations have been described, with most encoding for proteins found in the sarcomere. Unlike DCM and restrictive cardiomyopathy there are no acquired forms of the disease. HCM less often leads to transplantation, with only 5% of patients carrying the diagnosis pre-operatively [6].

HCM is characterized by asymmetric, concentric rings of hypertrophy. There is gross hypertrophying of the heart, predominantly occurring at the inter-ventricular septum. On a microscopic level, cardiac myocytes are in disarray. The anatomical changes may result in left ventricular outflow obstruction, termed hypertrophic obstructive cardiomyopathy.

The clinical presentation of HCM is highly variable. Most patients are asymptomatic with some experiencing chest pain and dyspnea. Palpitations and pre-syncopal episodes can occur. Syncope is rare but is a risk factor for sudden cardiac death (SCD) [13]. Children under the age of 1 often present with congestive heart failure. HCM is infamous for its insidiousness and its tendency to present with SCD in young athletes. The ECG may show atrial fibrillation or a supraventricular arrhythmia. HCM is benign relative to other indications for transplantation with only a 1% annual mortality rate [14]. Holter monitoring is useful for identifying arrhythmias which carry an increased risk of SCD. Genetic testing for inborn errors of metabolism may be warranted to exclude them as a cause of cardiac hypertrophy. Given the autosomal dominance of HCM, screening of siblings is advisable.

Treatment depends on the severity of symptoms and the presence of risk factors for SCD. Patients with chest pain and dyspnea are treated medically with beta-blockers and calcium channel antagonists. The detection of ventricular arrhythmias warrants the placement of an implantable cardioverter defibrillator (ICD). Patients with severe left ventricular outflow obstruction may undergo myomectomy, although this is only for symptom relief and does not slow disease progression, nor does it prevent potentially fatal arrhythmias. Heart transplantation is not a first-line therapy for HCM and is only considered when there are ventricular arrhythmias refractory to treatment or when features of DCM or restrictive cardiomyopathy develop.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is the least common cardiomyopathy seen in children and represents only 3% of pediatric cases [15]. It is characterized by diastolic dysfunction due to restrictive filling with a normal ventricle wall thickness and a normal-sized chamber. RCM often lacks symptoms early on and can present with a decreased exercise tolerance, exertional chest pain and syncope. Physical findings include jugular venous distension (possibly with Kussmaul sign), hepatomegaly, a prominent S_2 heart sound, a gallop rhythm, peripheral edema and ascites. Echocardiography generally shows dilated atria and normal ventricles. With disease progression, the estimated pulmonary artery pressure will be elevated. The electrocardiograph shows low voltage QRS complexes, non-specific ST-T segment changes and sometimes atrial arrhythmias or AV block. Cardiac catheterization is useful for confirming elevated pulmonary pressures seen on the echo. An endomyocardial biopsy (EMB) is only done to exclude etiologies such as amyloidosis or sarcoidosis which more commonly cause RCM in adults. Once the diagnosis is established, first-degree relatives should be screened.

Pharmacological treatments for RCM are principally for palliative symptom relief. Diuretics are used to reduce venous congestion. Caution should be exercised, however, to ensure cardiac output is not compromised. Beta-blockers provide relief to patients by prolonging the diastolic interval, allowing for better filling. Anticoagulants are sometimes used prophylactically to prevent mural thrombi from forming. Given that RCM is refractory to other therapies, patients are more likely to be considered for transplantation. Despite being the rarest cardiomyopathy in children, 12% of cardiomyopathy transplant recipients have RCM [16]. In the

Unites States many centers advocate immediate listing for transplantation because of the rapid development of pulmonary hypertension, the high risk of thromboembolisms and a mean survival of approximately 2 years [17].

Doxorubicin-Induced Cardiomyopathy

The chemotherapy agent doxorubicin (Adriamycin) has long been used in the treatment of neoplasms such as Hodgkin's and non-Hodgkin's lymphomas and sarcomas. One of the most detrimental side-effects of the drug is the development of cardiomyopathy [19]. The mechanism of action is thought to be free radical-induced oxidative damage to cardiac myocytes [20]. There is a dose-dependent relationship between doxorubicin use and cardiotoxicity. At very high doses, cardiomyopathy develops in 36% of patients [19]. This number is negligible at the lowest doses. There can be a delay of up to 20 years after the completion of chemotherapy before cardiomyopathy becomes clinically apparent [21].

Endomyocardial biopsy is the best diagnostic tool available for its detection [22]. The best non-invasive tests are an echo or radionuclide imaging showing a decrease in left-ventricular ejection fraction and should be done in the primary follow-up after doxorubicin therapy. ECG changes are non-specific and include sinus tachycardia, a flattened T wave or a prolonged QT interval. Treatment options are limited. Doxorubicin-induced cardiomyopathy is refractory to usual regimens. Symptom relief can be provided by beta blockers but there is no improvement in mortality. Heart transplantation remains the only therapeutic option.

Congenital Heart Disease

Congenital heart disease remains the most common pre-operative diagnosis in the pediatric heart transplant population in the United States, although it is in decline due to advances in palliative surgery and a lack of available donors [4]. During the advent of pediatric heart transplantation in the 1980s, the overwhelming majority of recipients had hypoplastic left heart syndrome (HLHS). At the time, the palliative Norwood procedure had much worse outcomes than cardiac transplantation. Improvements in the management of patients undergoing palliative procedures saw post-operative survival rise to more than 80% while waiting-list mortality rose to 25% because of donor shortages [7]. Now, therefore, heart transplantation is rarely performed as a first-line treatment for HLHS. Instead, children are being listed once refractory heart failure develops after previous palliative procedures.

The most common forms of congenital heart disease listed for transplantation are non-HLHS single-ventricle abnormalities (36%) followed by conditions in which the right ventricle functions as the systemic pump (20%) [18].

Candidate Evaluation

Evaluating pediatric candidates for heart transplantation is similar to the process used for adults (see Chap. 4). This chapter will examine considerations unique to children. Generally, potential recipients are evaluated for life expectancy, morbidity and weighing the relative advantages and disadvantages of alternative treatments. Due to the diverse pathologies leading to transplantation, special consideration must be given to the anatomy and hemodynamics. An assessment looking for chronic disease and the involvement of other organ systems is of particular importance in the pediatric population given that heart failure etiologies such as inborn errors of metabolism will often have widespread effects. The issue of compatibility is somewhat different in children as sensitization is not always preclusive.

Anatomy

The most important anatomical considerations relate to the systemic and pulmonary vasculature. Adequately developed, appropriately sized and confluent pulmonary arteries are essential for successful transplantation. Any anomalies of the venous return to the heart will also require special attention. If transplantation is being performed after previous palliative surgery, then caution is required in dealing with adhesions and

anatomical distortions such as enlarged atria resulting from the Fontan procedure. The visceral anatomy of the heart is of minimal significance given that it will be almost entirely removed. Magnetic resonance imagining and computer tomography can delineate the anatomy as part of the pre-operative assessment. Further surgical considerations are discussed later.

Pulmonary Vascular Resistance

An increase in pulmonary vascular resistance features in many forms of pediatric heart disease. Congenital heart disease is more strongly associated with pulmonary hypertension, particularly fixed forms. As mentioned previously, in the adult population, when the pulmonary vascular resistance index (PVRI) exceeds 6 Wood units/m^2 or when the transpulmonary gradient exceeds 15 mmHg, heart transplantation is contraindicated. This is due to concerns over acute right-sided failure of the donor heart. The adult guideline is overly restrictive in the pediatric population and patients with a PVRI of up to 9 Wood units/m^2 can safely undergo heart transplantation [24] (see Fig. 15.4). In patients with a high PVRI, inotropes and vasodilators can be used intensively to reduce the PVRI pre-operatively. Inhaled nitric oxide, milrinone and vasodilators may also be

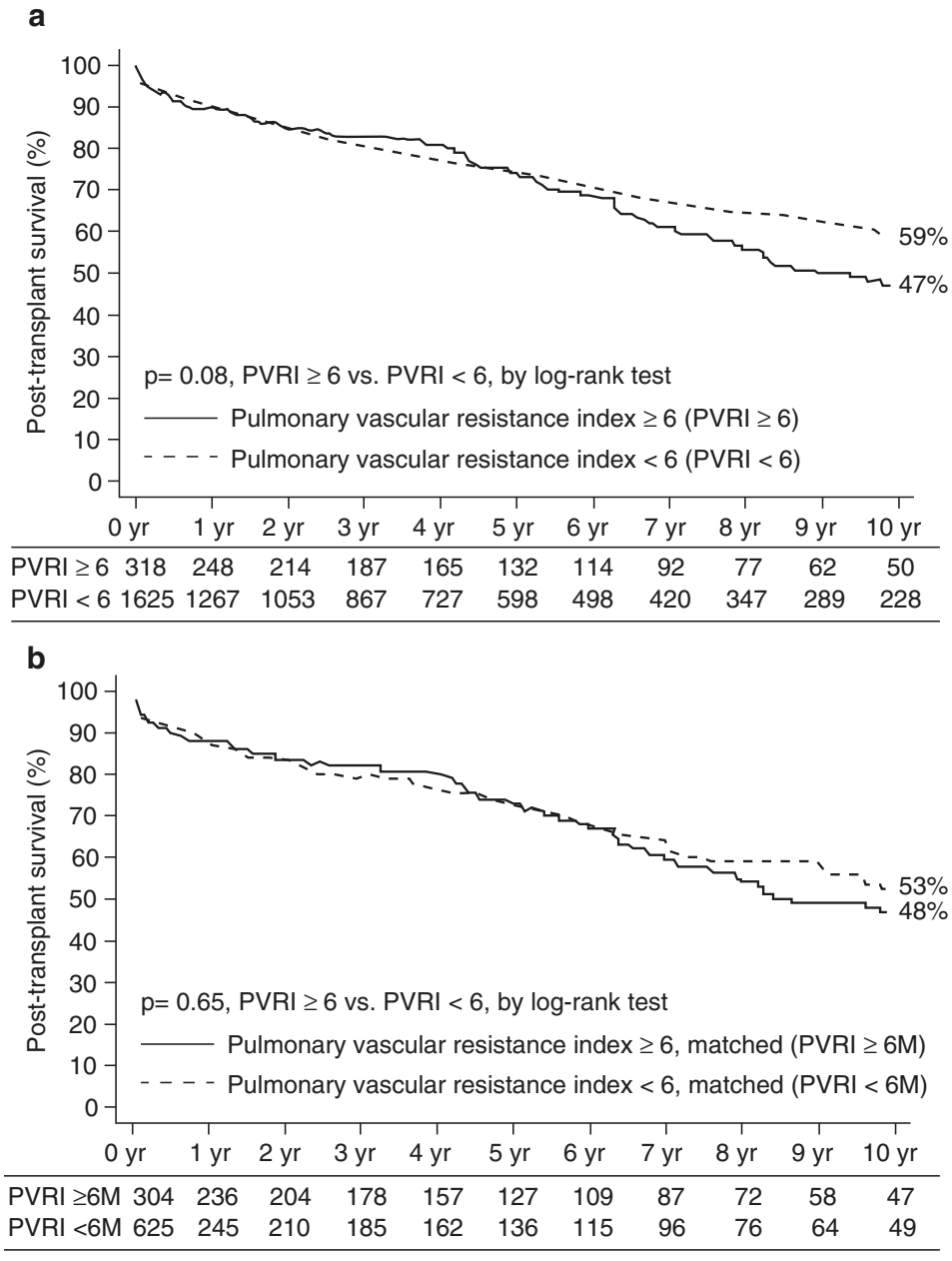

Fig. 15.4 Kaplan-Meier curves showing survival of pediatric heart transplant recipients with a PVRI of less than 6 WU versus greater than 6 WU (**a**) unmatched (**b**) propensity matched (Reused with permission from Chiu et al. [23])

considered intra-operatively. A period of prolonged sedation and intubation may be warranted immediately following surgery. Patients can be weaned onto oral agents—such as nifedipine, digoxin and sildenafil [24]—to maintain a lower PVRI. Ventricular assist devices (VADs) are increasingly being used in the pediatric population as a bridge-to-transplant after their successful use in adults. Adults with previously "fixed" pulmonary hypertension have seen a reduction in PVRI after being on a VAD, allowing for successful orthotopic heart transplantation [25]. A number of case reports show similar findings in children. More extensive evaluation is required.

A recent retrospective study of the UNOS database by Chiu et al. [23] demonstrated that pulmonary vascular resistance was not an independent predictor of post-operative mortality in the pediatric population. Further work is needed, but patients previously excluded on the basis of irreversible elevated PVRI are now being considered for single orthotopic heart transplantation. With improvements in perioperative management, an elevated PVRI may be removed as an absolute contraindication in the future.

Compatibility

Heart transplantation usually mandates that the recipient and donor are ABO-compatible because there is a high probability that preformed anti-A or anti-B antibodies (isohemagglutinins) will precipitate hyperacute rejection. The shortage of donors in the infant population led to ABO-incompatible (ABOi) transplantation on the basis that the immune system is underdeveloped in this age-group. Infants with isohemagglutinin titers that show absent or low levels of antibodies can receive a heart from an ABOi donor with results comparable to ABO-compatible heart transplantation [26]. Most recipients do not go on to form antibodies later in life despite no enhancements to their immunosuppressive therapy [27]. Even recipients who do form antibodies still have good outcomes [27]. More recently, older children have been successfully ABOi transplanted [28]. The lack of B-cells with receptors for donor blood groups and antibody titers of less than 1:4 allow for safe ABOi transplantation [27]. Survival in this patient group is reported at 100% 1-year, 96% 5-years and 69% 10-years post-transplant with the oldest child being 7.5 years old at the time of surgery [27]. An important perioperative consideration for patients where ABOi is likely is the avoidance of blood products that contain isohemagglutinins. ABOi heart transplantation in the pediatric population has had positive effects by reducing wait list mortality and wait list times [27].

Sensitivity to human leukocyte antigen (HLA) and non-HLA donor antigens remain a significant factor in the already high wait list mortality for children awaiting heart transplantation. The presence of donor-specific antibodies (DSAs) carries the risk of allograft rejection and/or cardiac allograft vasculopathy (CAV) [29]. Sensitization can occur from blood products (especially platelets), palliative procedures for congenital heart disease, and the use of mechanical circulatory support devices (MCSDs). The latter has increased in recent times and is the reason for more children being sensitized prior to transplantation.

Potential recipients are tested for panel reactive antibodies (PRA). Testing demonstrates preformed anti-HLA antibodies. Historically this was done using a complement dependent cytotoxicity (CDC) assay on T-lymphocytes from individuals in the donor area. Most centers now use Luminex® solid-phase flow cytometry to detect alloantibodies. The newer test is able to distinguish IgG specificities whereas older tests would indiscriminately test for any antibodies [31]. The result is expressed as a percentage. Patients with a PRA > 10% are considered sensitized and are at increased risk of graft loss [30]. Not all antibodies are of clinical significance. Antibodies that bind C1q complement result in worse outcomes than antibodies that do not [32]. Many centers perform HLA typing so that "virtual" cross-matching can be done once a potential donor is found.

Infection

All potential recipients require serological evaluation for Epstein-Barr virus (EBV), cytomegalovirus (CMV), *Toxoplasma gondii*, HIV, varicella zoster virus (VZV), measles, hepatitis and HIV. Positive results are now rarely an absolute contraindication for heart transplantation but help determine necessary prophylactic treatments and perioperative management plans. HIV was once considered an absolute contraindication owing to concerns that organs were "wasted" on those with a terminal illness, and concerns that immunosuppression would result in further deterioration of CD4 T-lymphocytes. With newer anti-retroviral therapies, survival is now over 90% at 10-years [33]. Good outcomes have been realized for HIV-positive adults who are compliant and have low or undetectable viral loads at the time of transplantation [34]. Outcomes in the pediatric HIV-positive population have yet to be evaluated. Heart transplant recipients who are seropositive for hepatitis B show similar survival rates to those who are seronegative, however, the majority of deaths in seropositive patients are due to hepatitis [35]. Reactivation of hepatitis B after transplantation is controlled with lamivudine [36]. EBV infection either preoperatively or postoperatively (usually from donor tissue) puts the patient at risk for post-transplant lymphoproliferative disease (PTLD). Patients must be vaccinated against measles, mumps, rubella, *Hemophilus influenzae*, VZV, pneumococcus and hepatitis A and B prior to transplantation.

Other Organ Systems

Severe and irreversible end-organ damage, including kidney and liver failure, are usually considered contraindications to single orthotopic heart transplantation. Multisystem organ failure carries a 1-year post-transplant mortality of 16.6% [4] in children. Requiring dialysis prior to transplantation is the second worst risk factor for 1-year mortality [4]. Given that immunosuppressive agents are highly nephrotoxic, children with moderate to severe renal impairment should be considered for combined heart-kidney transplantation [40].

Diabetes mellitus is rarer in the pediatric population and is not considered an absolute contraindication. Due to the scarcity of donors and the desire to allocate organs to those with the best chances of survival, patients with diabetes are less often listed for transplantation. In the adult population patients with diabetes have significantly worse survival overall, but when stratified according to those with or without diabetic complications, those without complications have survival rates that are similar to non-diabetic patients [41].

Obesity is a relative contraindication in adults owing to concerns over poor wound healing, an increased risk of infection and an increased risk of deep vein thrombosis and pulmonary emboli [42]. Similar concerns translate over to the pediatric population, although little data exists. A review of the PHTS database showed few children were listed for transplantation when their BMI was more than 2 standard deviations above normal [43].

Psychosocial Factors

Family support is paramount to successful transplantation and long-term survival. A full assessment of the psychosocial state of the family should be made. This includes access to transportation, compliance and whether the family is able to make informed decisions. These factors should not exclude a child from being listed but instead act as a guide for providing adequate support from allied medical professionals. Developmental delay is a feature of some diseases and syndromes associated with congenital heart disease. Children should be assessed on a case-by-case basis for suitability. A common example is Down's syndrome (trisomy 21). Down's syndrome is associated with congenital heart defects and developmental delay. There is a broad spectrum, with patients having varying degrees of both developmental delay and other comorbidities. Although rarely listed for heart transplantation, Down's syndrome patients have shown reasonable

outcomes after both renal and bone marrow transplantation [37, 38] highlighting the need to comprehensively assess each case.

Donor Selection

The number and quality of donor hearts remain significant limiting factors in pediatric heart transplantation. A study of the UNOS database from July 2000 to December 2008 found that only 65.7% of potential pediatric donor hearts were transplanted [39]. Common reasons for declining an organ included the prolonged use of cardiopulmonary resuscitation (CPR), the use of high-dose inotropes, blunt trauma to the chest wall and prolonged ischemia time [39]. The lack of studies means clinicians rely on experience or data from the adult population. The donor pool may be unnecessarily narrow as a result.

As with adults, vital organ donation from children can only occur after a diagnosis of brain death has been established. The criteria for diagnosing brain death are the same as in adults. There are also additional criteria that vary according to age [45]. In addition, an interval of between 12 and 48 h between two evaluations is required [45].

Donor evaluation should include gender, age, weight, height, the cause of death, a review of any chest trauma, inotrope use and hemodynamic status. Donor hearts have been declined in the past because of CPR use but it has been shown to have no impact on outcomes [44]. Allograft ischemic time is a risk factor for survival in older children, particularly those 11–17 years old, and has almost no impact on the survival of infants < 1 year old [4].

An echocardiogram should be done to exclude structural and functional abnormalities. A reduction in ejection fraction to below 50% after inotrope use will normally preclude a heart's use. Some regurgitation of the mitral and tricuspid valves is normal after brain death. Prior chest trauma may result in a pericardial effusion being visualized. The ECG normally shows nonspecific changes that are due to hemostatic disturbances resulting from brain death. Donor troponin I levels were thought to be predictive of outcomes but recent analysis shows no difference in children who received a heart from a donor with elevated troponin I levels [46].

The donor-to-recipient weight ratio is used for size matching. An undersized donor with a ratio below 0.6 is associated with worse outcomes and most centers avoid going below 0.75 [47]. This is especially the case if the recipient suffers from pulmonary hypertension. Oversizing the donor can be done safely up to a weight ratio of 3 [48]. This is helpful for dealing with shortages particularly in the infant population. In older children, 25% of recipients received adult hearts [4]. Patients with cardiomyopathy often have significant cardiomegaly that creates a cavity amenable to oversizing the donor.

Donors should have serological screening for infectious agents, including, HIV, hepatitis, human T-cell lymphotrophic virus (HTLV), CMV, EBV, syphilis and *Toxoplasma gondii*. A positive result for HIV, HTLV or hepatitis B precludes organ use. Finding antibodies for *T. gondii*, CMV or EBV do not contraindicate transplantation but guide post-operative management.

Adequate donor support is important for organ preservation. Extreme metabolic changes occur after brain death. There is an upsurge in catecholamines that causes vasoconstriction, increasing the afterload and therefore the metabolic demands of the heart. Thyroxin, cortisol and insulin become depleted. Potential donors must be closely monitored, ensuring that the CVP, pO_2, pCO_2 and pH are within normal limits. Supportive hormonal and circulatory support should be given as needed.

Wait List Management

The decision to list a child for heart transplantation should consider the implications of transplanting too early versus transplanting too late. Transplantation carries serious risks and lifelong immunosuppression, however, postponing too long may result in death before a donor heart becomes available or result in the worsening of

co-morbidities such as renal dysfunction and pulmonary hypertension.

Although as a group, children awaiting heart transplantation have the worst survival of all solid organ wait lists, when stratified, subgroups show large variabilities in mortality. Needing hemodynamic support puts patients most at risk of death, with extracorporeal membrane oxygenation (ECMO) being the worst predictive factor followed by mechanical ventilation and then inotrope use. Other factors include having a pre-transplant diagnosis of congenital heart disease, mechanical ventilation, dialysis and being of non-white ethnicity [49]. Interestingly, hemodynamic support more reliably predicts wait list mortality than UNOS listing status [49]. The heterogeneity of patients in the same status group is likely due to greater numbers of less sick children listed as 1A because of less stringent guidelines than for adults (children do not need to undergo pulmonary artery catheterization) and because of fewer contraindications to transplantation [6]. The UNOS allocation algorithm was revised in 2006 to allow donor hearts to be made available across geographic regions to status 1A and 1B patients [50]. The change has had a positive effect in reducing both mortality and wait times [51]. One-year mortality now stands at 8% compared with 16% for patients listed between 1999 and 2004 [52]. In addition to changes to the listing algorithm, the increased availability and use of mechanical circulatory support devices (MCSDs) has helped increase survival.

Bridge to Transplant

Progression of heart failure despite maximal medical therapy is an indication for mechanical circulatory support with either ECMO or a ventricular assist device (VAD). Children, and especially infants, were once limited in their treatment options for bridging to transplant due to a lack of VADs for those under 30 kg (the lower weight limit for adult devices). Since the introduction of VADs aimed at children, such as the Berlin Heart EXCOR®, use has significantly increased, with 29% of children receiving VADs or total artificial hearts (TAH). ECMO use has dropped to 5% in all children but is still 30% in the infant age group [4]. Biventricular VAD use now exceeds ECMO use [4]. Transplantation or recovery occurred in 75% of children with the EXCOR®. Mortality was 25% and the leading cause of death was thromboembolic stroke [52]. Decreased renal function, smaller patient size and elevated total bilirubin were additional risk factors for death when on EXOR® VAD therapy [52]. Post-transplant survival was equal to that of patients not on mechanical circulatory support pre-operatively and was greater than for patients who had ECMO support [53].

Surgical Techniques

Pediatric heart transplantation may require the surgeon to make modifications to the standard biatrial or bicaval techniques used in adults. The anatomical distortions that may be present in congenital heart disease or from previous palliative surgery can make the procedure technically challenging. As is the case in the adult population, centers are now favoring the bicaval method. This is amid concerns that the enlarged atria resulting from the biatrial method lead to complications such as tricuspid regurgitation, reduced right ventricular function and arrhythmias [54]. There are also advantages in using the bicaval method for patients who have already had Mustard or Senning procedures for CHD. However, superior vena cava (SVC) stenosis has been associated with bicaval anastomoses, especially in infants [55].

Transplantation for CHD involving the great arteries is generally straightforward, whereas anomalies of the systemic veins pose the biggest challenges. Careful planning is required when excising the donor heart in these cases. Sometimes extra portions of the vena cava and inclusion of the brachiocephalic vein are needed. This is necessary for recipients who have left-sided venae cavae (see Fig. 15.5 for an example of the surgical technique used for a patient with *situs inversus*). Other special considerations include patients who have shunts formed as part of previous palliative

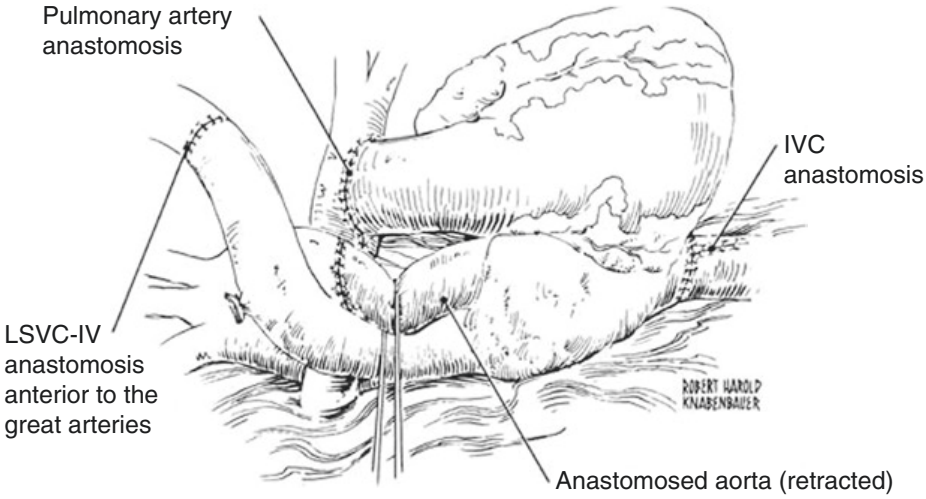

Fig. 15.5 Technique for recipient with situs inversus. A conduit is formed using the donor SVC and barchiocephalic vein (Reused with permission from Razzouk and Bailey [71])

operations such as the Fontan procedure. The donor pulmonary artery must be preserved for these recipients. Occasionally, additional graft material is needed to patch anastomoses after the removal of shunts. Donor or recipient tissue is normally used, however, bovine pericardium can be substituted if necessary.

Post-operative Management and Complications

Cardiovascular System

Maintaining cardiac output (CO) post-operatively is the most significant management objective. The donor heart will have suffered some degree of ischemic injury during transplantation. Added to this are the effects of denervation and the lack of sympathetic control over the heart. Support with inotropes is recommended for the first 72 h. In the pediatric setting, dobutamine or isoproterenol (isoprenaline) are usually selected. Where the CO continues to fall or there is evidence of systemic or pulmonary hypertension, milrinone, which has both positive inotropic and vasodilator effects, can be added. In infants who received an oversized heart, delayed closure can assist in supporting CO. If the CO cannot be maintained without the continuous infusion of inotropes after 3 days, or if the patient was not even able to be weaned off cardiopulmonary bypass, then primary graft dysfunction (PGD) should be suspected. PGD is of concern owing to the very high mortality rate. If the underlying cause of PGD is rejection then this should be treated accordingly, otherwise ECMO supportive therapy can bridge the patient to recovery.

Arrhythmias can occur after transplantation. Sinus tachycardia and sinus bradycardia, caused by sinoatrial node pathology, are common. Ventricular arrhythmias, especially ventricular ectopic beats and non-sustained ventricular tachycardia, are seen early on post-operatively but usually do not require any treatment.

Hypertension is a common complication owing to several contributory factors. Changes to the systemic vasculature in heart failure, cyclosporine, and an oversized donor can all cause systemic hypertension. As a preventative measure, patients with good allograft function demonstrated on echo should be weaned off inotropes. If needed, vasodilators should be used.

Respiratory System

Early extubation should be attempted where possible. Some recipients will have had mechanical ventilation for a prolonged period of time prior to transplantation. These patients need to retrain their respiratory muscles and require additional support. Pulmonary hypertension was once regarded as a contraindication to early extubation but now appears safe in children who have undergone cardiac surgery [56].

Pre-existing pulmonary hypertension is treated with nitric oxide intraoperatively once the patient is on cardiopulmonary bypass. In addition, mechanical hyperventilation with a high fraction of inspired oxygen is used to prevent acidosis. The right ventricle must be supported with catecholamines in addition to the usual post-operative regimen of positive inotropes. This allows time for the donor heart to adapt to the higher pressures.

Other Organ Systems

Renal Function

Deranged renal function is a common complication. The kidney is susceptible to damage from underperfusion that can occur in heart failure, cardiopulmonary bypass, post-operative hypotension and immunosuppressants. Although some degree of oliguria tends to occur, outright renal failure is rare early after transplantation. If urine output remains depressed, furosemide and dopamine can be administered. If oliguria persists then CNIs should be stopped temporarily. Rarely, dialysis is needed.

Gastrointestinal System

A variety of gastrointestinal (GI) problems have been reported both early and late after heart transplantation in children [60]. Of patients with GI complications, 9% go on to require surgery [60]. Stress ulcers are a concern in the post-operative period and as such patients should be given a type-2 histamine receptor antagonist prophylactically. Patients on corticosteroids or azathioprine are at increased risk of pancreatitis. Abdominal pain reported by these children warrants investigational follow-up. Other possible GI complications include cholecystitis, recurrent infection, malignancy, appendicitis and small bowel obstruction. Perforation can ultimately ensue, particularly where steroids are being used.

Immunosuppression

Immunosuppression in pediatric heart transplant recipients has been largely guided by protocols in the adult population and clinical experience. Randomized control trials are lacking due to low numbers and ethical considerations. The PHTS data show a decline in episodes of acute cellular rejection but deaths from CAV/chronic rejection have changed little [57].

After transplantation, immunosuppression is achieved by an initial induction protocol that is followed by maintenance therapy. The evidence on induction therapy remains equivocal. There is reportedly no difference in survival 14 days post-transplant [4]. Nevertheless, its use has surged from 37% of patients in 2001 to 68% of patients in 2014 [4]. Most centers use either anti-thymocyte globulin (ATG) (from rabbits or horses), or interleukin 2 receptor (IL-2R) blockers. Approximately half of children who receive induction therapy get ATG induction therapy and a quarter are treated with an IL-2R blocker [4]. Induction therapy is useful for children with a low urine-output post-operatively to delay commencement of nephrotoxic calcineurin inhibitors.

Maintenance regimens are normally based on a calcineurin inhibitor (CNI) such as tacrolimus or cyclosporine. The antiproliferative drug mycophenolate mofetil (MMF) can be used in combination and has been shown to have superiority over azathioprine in adults [58]. There is evidence to suggest that steroid-avoidance regimens can achieve equally good outcomes with fewer side-effects in children who are not sensitized [59].

A fine balance is required to prevent the recipient's immune system from damaging the graft without enduring the untoward effects of immunosuppression such as infection and malignancy. At 1 year post-transplantation approximately 70% of children are on MMF, but this number falls to about 50% by 5 years. This is because, although MMF in combination with tacrolimus is highly effective, MMF's side-effect profile makes it difficult for children to remain compliant.

Infection

Taking precautions to prevent infection is an essential part of the post-operative management plan. Infection is a leading cause of mortality

early on after transplantation [4]. The usual sources of infection for the surgical patient—lines, drains and catheters—are replaced in the operating room and should be removed as soon as possible after transplantation. A prophylactic, short course of intravenous antibiotics is given in the immediate post-operative period. Patients who require prolonged intensive care or patients already colonized with MRSA require coverage with vancomycin. Prophylaxis for *Pneumocystis jirovecii* is initiated in all patients. Patients previously on MCS therapy are at increased risk of fungal infections (particularly *Candida* and *Aspergillus*). Although fluconazole can be administered prophylactically, caution is needed because of the interaction with CNIs. Fluconazole inhibits the cytochrome P450 system that is required for CNI metabolism. Therefore, at least a 50% dose-reduction is required for tacrolimus [61].

Acute Rejection

Rejection in the first week after transplantation is rare, especially with the use of induction therapy. The PHTS database has been an invaluable tool for monitoring cases of early rejection because the ISHLT data only includes episodes occurring after discharge. The incidence of treated rejection in the first year fell from 36% in 2008 to under 20% in 2014 [4].

Children are monitored closely in the days following transplantation for symptoms and signs of early rejection. Any abdominal pain, tachycardia, new arrhythmias and oliguria should be investigated further with an ECG and possibly EMB to exclude rejection. Patients tend to deteriorate quickly during episodes of early rejection and therefore any regression from the normal course of post-operative recovery should be followed up without delay. Treatment is with intravenous corticosteroids.

Long-Term Complications

Cardiac Allograft Vasculopathy

With improvements in survival, the development of cardiac allograft vasculopathy (CAV) and chronic rejection are of increasing concern. In children who survive to 3 years post-transplantation, CAV is a leading cause of death after graft failure [4] (see Fig. 15.6). Risk factors for the development of CAV include the age of the recipient, the age of the donor, and retransplantation [4]. At 9 years after transplantation, 16% of infants developed CAV, compared with 37% of 11–17 year olds [4]. The presence of viral genome, particularly adenovirus, in myocardium biopsy samples is strongly associated with the development of CAV in children [65]. A retrospective study [66] has demonstrated that recipients who

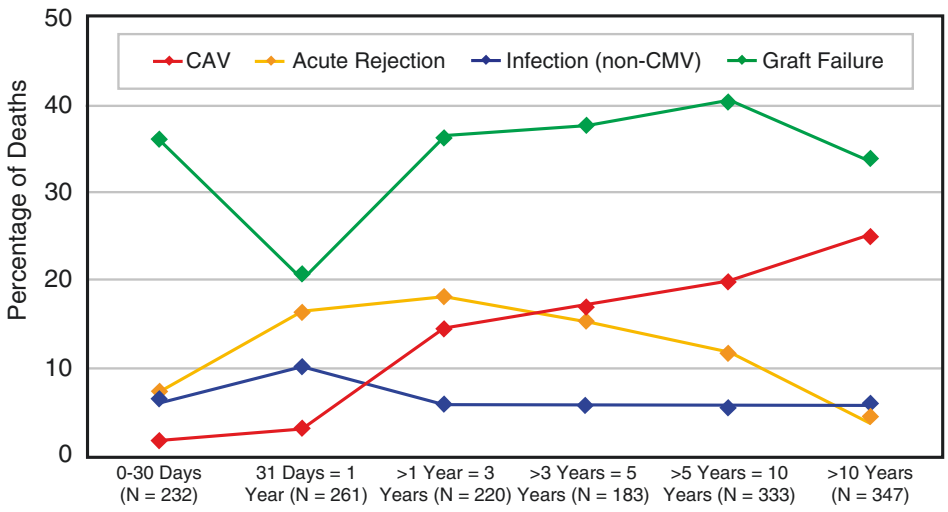

Fig. 15.6 A comparison of the leading causes of death by time since transplantation (Reused with permission from Dipchand et al. [72])

are CMV-positive pre-transplantation may be at increased risk for CAV.

Children with CAV often lack ischemic chest pain but may experience abdominal discomfort instead. It is common for syncope or sudden death to be the first clinical manifestations of CAV in children. As such, surveillance coronary angiograms are frequently part of the long-term management plan. In adults, intravascular ultrasound has shown to be more sensitive for detecting CAV but this has yet to be proven in children. Diastolic dysfunction develops early on due to microvascular disease. This eventually progresses to systolic dysfunction and carries a poor survival rate. No effective treatment options exist. Beta blockers may provide benefits owing to their anti-ischemic effects. As with adults, stenting does not improve outcomes highlighted by the 52% graft loss at 1-year post-procedure [67]. Retransplantation remains the only effective treatment once systolic failure ensues.

Infection and Malignancy

The lifelong immunosuppression endured by children puts them at risk of infection from a broad spectrum of pathogens. Most infections are successfully treated, however, infection remains the second most common cause of death in the first month after transplantation, and the most common reason for re-hospitalization in the first year [4]. Both opportunistic pathogens and ordinary pathogens afflict immunosuppressed children. Bacterial infections predominate in the first month while viral infections peak at 2 months [62].

Any signs of infection after transplantation should be treated immediately with broad spectrum antibiotics until the causative pathogen is identified. A full infection screen is done, paying attention to the chest radiograph for evidence of pneumonia. Although invasive, bronchial lavage should be considered more often in the immunocompromised child given the benefits associated with rapid and focused treatment. In recent years, *Streptococcus pneumoniae* has been increasingly identified as the cause of pneumonia in children on immunosuppression. The respiratory viruses—influenza, parainfluenza, RSV and adenovirus—are also of concern, particularly soon after transplantation and especially in infants.

Cytomegalovirus (CMV) infection occurs mostly in the lungs and gastrointestinal tract [63]. Although it is common for CMV prophylaxis to be used in recipients who receive hearts from CMV positive donors, its use has been shown to have no impact on the development of CAV or mortality [64]. Freedom from CMV infection in this group is 91% at 5 years post-transplantation [64]. Infection from CMV is detected with either PCR or pp65 antigen testing. Early detection usually results in successful treatment with ganciclovir or valganciclovir.

Children are more susceptible than adults to Ebstein-Barr virus (EBV) induced post-transplant lymphoproliferative disease (PTLD). This is because immunity to EBV is typically acquired in adulthood. EBV infection can be difficult to identify as, even in the immunosuppressed patient, it can be asymptomatic or simply cause mild, non-specific symptoms. Children with positive serology for EBV pre-transplant are still at risk however. In addition to the disease itself, PTLD is a concern because the treatment can cause rebound rejection and lead to graft failure. This in fact accounts for half of deaths in children diagnosed with PTLD.

Survival and Outcomes

Survival in pediatric heart transplantation has shown considerable improvements over the last decade. Long-term survival in children now surpasses that of adults. Median survival (a measure of the time at which half of recipients are still alive) is 20.6 years for infants, 17.2 years for children between 1 and 5 years old, 13.9 years for children between 6 and 10 years old and 12.4 years for children older than 10 [4] (see Fig. 15.7). The increase in life expectancy is due to a decline in early mortality. One-year survival is now 90%. The decrease in survival with increasing age is likely due to a lower incidence of CAV in younger patients and the immune

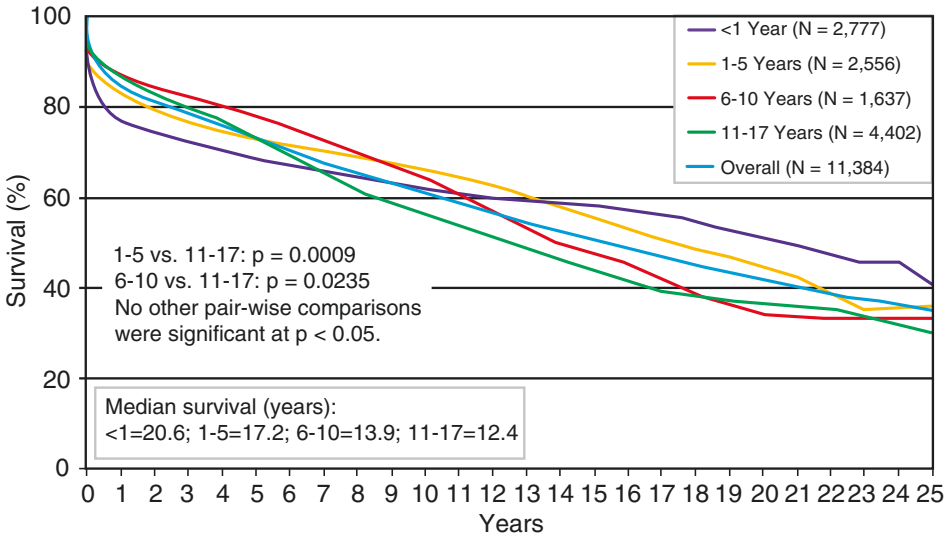

Fig. 15.7 Kaplan-Meier curve showing the survival of pediatric heart transplant recipients by age group at the time of surgery (Reused with permission from Dipchand et al. [4])

"privilege" of infants. A pre-transplant diagnosis of cardiomyopathy is associated with increased survival compared with CHD [4]. Data from the ISHTL show 10-year survival is 12% less for CHD patients than cardiomyopathy patients. The use of prednisone is associated with a decreased survival [4]. Although now commonly used, induction therapy does not confer a survival benefit [4]. Of note is the increase in graft loss after 1 year for black patients. Lower socioeconomic status is also a factor associated with decreased survival beyond 1 year [68].

Summary

The field of pediatric heart transplantation has progressed rapidly in the recent era. Five-year survival is over 80% because of improvements in preventing early mortality and better outcomes for infants with CHD. The conditional half-life for infants is over 20 years at the first year post-transplantation. Changes to the allocation algorithm and VADs for children under 20 kg are helping to improve wait list mortality. Tangible data illustrating that previously perceived risk factors (such as CPR) do not impede donor hearts from being used have also helped in this regard. Rates of rejection have been helped by newer immunosuppressive regimens although, unfortunately, this has had little impact on the incidence of CAV.

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Combined Heart and Other Organ Transplant

16

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Abbreviations

AMR	Antibody mediated rejection
CAV	Cardiac allograft vasculopathy
DSA	Donor specific antibody
OHT	Orthotopic heart transplantation

Clinical Pearls

- As with single organ transplantation, combined organ transplantation has shown improvements in survival with the development of better immunosuppressive regiments.
- Numbers for combined heart-lung (CHL) transplants have decreased in the recent era owing to more indications being made available for single lung transplantation.
- The most common indication for combined heart-lung transplantation is congenital heart disease with pulmonary hypertension (most commonly Eisenmenger's syndrome). Increasingly, single lung transplantation with surgical repair of the heart is done as an alternative therapy.
- Combined heart-kidney transplantation is considered for patients with end-stage heart failure who have suffered irreversable renal disease as a result of chronic underperfusion of the kidneys secondary to heart disease.
- Survival for combined heart-kidney transplant recipients is superior to that of single OHT patients especially in heart failure patients who became reliant on dialysis.
- Acute cellular rejection occurs more frequently in the lung than the heart in combined heart-lung transplant recipients. However, overall rates of cardiac allograft rejection and CAV are lower than in single OHT.
- Survival for combined heart-lung transplantation is worse in the short-term but comparable in the long-term to single OHT. For combined heart-liver transplants, mortality is approximately equal to single OHT. This is in part due to protection against AMR conferred by the transplanted liver that absorbs DSAs.

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Introduction

The development of novel immunosuppressives, as mentioned in Chap. 10, has been at the forefront of significant advances and improvements in the care of transplant patients. Inevitably, accompanying this improvement, the last 30 years have seen increased numbers of combined organ transplants. The most common combination involving cardiac transplantation is the heart-lung transplantation [1]; however, heart-kidney, heart-liver, and even heart-lung-liver or heart-lung-kidney combinations are increasing in occurrence. This chapter intends to cover the additional clinical aspects involved in these transplantations from a cardiologist's perspective; because heart-lung transplantation is by far the most frequent of these combinations, the majority of the chapter will focus on this particular combination as compared to the heart-kidney and heart-liver combinations.

Heart-Lung Transplantation

In a historical course similar to that of cardiac transplantation alone, combined heart-lung transplantation in humans was first attempted in the late 1960s but was not a viable procedure for favorable long-term outcome until the early 1980s, with the first successful heart-lung transplantation in 1981 by Reitz [2]. As of 2016, nearly 4000 adult heart-lung transplants have been performed worldwide [1].

Indications

According to ISHLT data [1], the most common listed indications for combined heart-lung transplantations were due to congenital heart disease with or without associated pulmonary hypertension (35.5%) or idiopathic/primary pulmonary artery hypertension (IPAH; 27.4%). Other, rarer reasons include acquired cardiovascular disease and cystic fibrosis. In the past, heart-lung transplantation was far more common for primary lung diseases such as emphysema, idiopathic pulmonary fibrosis, and suppurative lung diseases. However, increasing demand for donor hearts and increasing evidence of the non-inferiority of the double-lung transplant [3] has resulted in a decreased percentage of heart-lung transplants being performed for these indications.

Eisenmenger's Syndrome

Eisenmenger's syndrome is defined as the process in which a long-term left-to-right cardiac shunt resulting from a congenital heart defect causes pulmonary arterial hypertension, leading to eventual reversal of the shunt into a left-to-right shunt, causing cyanosis. The shunt may occur at the atrial, ventricular or aortopulmonary level depending on where the original defect is. The location of the shunt determines the resulting physiology as the child develops: in patients with nonrestrictive atrial defects such as an atrial septal defect, the maturation of the pulmonary circulation combined with the compliance of the ventricles results in normal pulmonary pressures, and is able to accommodate the left-to-right shunt. However, the development of Eisenmenger's syndrome and right-to-left shunt results in a pulmonary hypertension-like scenario, with right ventricular dilation and decreased right ventricular contractility [4]. In contrast, patients with post-tricuspid defects, such as a ventricular septal defect, there is continued systemic right ventricular pressure following the neonatal period, and as a result, even after Eisenmenger's response, right ventricular function remains preserved [5, 6] (Fig. 16.1).

Pulmonary Atresia/Hypoplasia

In those with progressive heart failure and surgically uncorrectable congenital heart disease, such as atresia or diffuse hypoplasia of the pulmonary arteries, dual heart-lung transplantation may also be indicated.

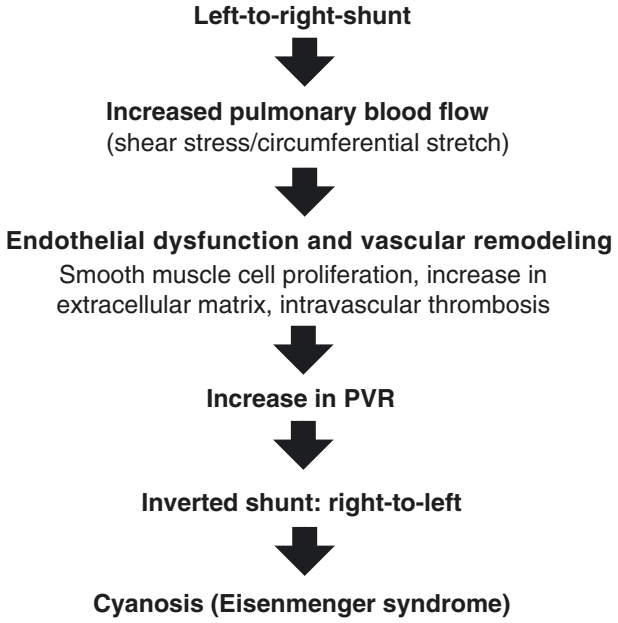

Fig. 16.1 Key stages in the development of Eisenmenger's syndrome (Reused with permission from Beghetti and Galie [7])

Advanced Cardiopulmonary Disease

Heart-lung transplantation may be a viable option in patients with either end-stage heart disease with concomitant lung disease, or more commonly, end-stage lung disease with concomitant heart disease too severe for single organ transplantation. There are no specific guidelines for conditions in which cardiac transplantation alone versus dual heart-lung transplant should be performed. From a cardiologist's perspective, the severity of the heart disease is first considered with respect to the possibility of cardiac transplant, and the decision to perform dual transplantation is based on consultation with pulmonologists, taking into account the severity of lung disease and prognosis with the existing lungs. However, the reverse scenario is more common, with cardiac disease secondary to primary lung disease; for example, severe right ventricular dysfunction due to pulmonary hypertension in a patient with parenchymal lung disease. The cardiac and pulmonary diseases may also be unrelated, such as case of emphysema and ischemic cardiomyopathy in a smoker.

Primary/Secondary Pulmonary Hypertension

Patients being considered for dual heart-lung transplant with pulmonary hypertension typically suffer from idiopathic pulmonary hypertension, secondary pulmonary hypertension or pulmonary hypertension following a previous attempt at repair for a congenital heart defect.

Heart-Lung Transplant or Bilateral Lung Transplant?

For cases of Eisenmenger's syndrome and congenital heart disease, especially those with multiple anatomical abnormalities, dual heart-lung transplantation is the commonly preferred choice, based on analyses of UNOS data demonstrating superior outcomes after heart-lung vs bilateral or single lung transplant in this cohort [8] and subsequent confirmatory studies [9, 10]. However, in cases where the congenital abnormality is amenable to surgical repair, isolated lung transplant has been demonstrated to achieve similar survival and complication outcomes to dual heart-lung transplant [11].

For pulmonary hypertension, the choice of whether to deploy dual-heart lung transplant or bilateral lung transplantation only, varies by center; a review of practice patterns across 35 centers worldwide demonstrates that North American centers tend to prefer double-lung transplants over dual heart-lung transplant, whereas the converse is true in Europe [12]; possible explanations have included the relative scarcity of donor hearts in North America. Furthermore, available evidence suggests that for primary or secondary hypertension without other severe complications, bilateral lung transplantation is non-inferior to dual heart-lung transplantation in terms of survival [13, 14]. However, a more controversial area remains regarding the choice of procedure for patients with severe right ventricular dysfunction in addition to pulmonary hypertension. While studies are limited, a recent multicenter analysis from the SRTR database demonstrated that of patients hospitalized

prior to transplantation due to right heart failure, there was a statistically significant survival benefit of dual heart-lung transplant over bilateral lung transplant. Further supporting the notion that heart-lung transplant may be more beneficial in this cohort is a 217-patient study demonstrating superior freedom from BOS-related death and no difference in long-term survival in the dual organ transplant group compared with bilateral lung transplant [15]. Thus, in for patients with severe right ventricular dysfunction in addition to pulmonary hypertension, dual heart-lung transplant is generally preferred to bilateral lung transplantation alone. At some centers, isolated heart transplant is considered for congenital heart disease patients with evidence of reasonable right heart function, i.e. if pulmonary vascular resistance is 5 Wood units or less and/or the transpulmonary pressure gradient is less than 12 mmHg [16, 17].

Recipient Selection, Evaluation and Management for Heart-Lung Transplantation

The general guidelines for listing for dual heart-lung transplantation are very similar to those for cardiac transplantation alone, as addressed in Chap. 3; factors such as a recipient age older than 60, multiple comorbidities, previous thoracic surgery, are considered unfavorably with regard to listing, although correlation with poorer outcome has not been definitively established in the dual-transplant population. Patients with disease processes requiring dual heart-lung transplantation often have a somewhat unpredictable clinical course, and in combination with a combined donor shortage, can result in long waits. Partially because of this, a significant proportion of patients listed are high risk due to progressive decline of cardiac and pulmonary function.

With regard to formal evaluation for transplant, the process is very similar to that of cardiac transplantation alone, as addressed in Chap. 3; transplantation is generally considered when patients have marked functional limitations in activities of daily living, combined with poor exercise tolerance as measured by cardiopulmonary exercise testing. General guidelines recommend transplantation based upon a predicted life expectancy of 2 years or less despite optimal medical therapy and in the absence of contraindications [3], although the exact timing is controversial.

For those with congenital heart disease and Eisenmenger's syndrome, additional clinical features that should prompt consideration for listing for dual heart/lung transplantation include worsening cyanosis, worsening of right ventricular function and worsening pulmonary hypertension unresponsive to treatment, and decreasing oxygen saturation (below 60% on exercise). These should be evaluated in conjunction with hemodynamics, each patient's unique cardiac anatomy and the overall health and functionality of the patient. Many congenital heart disease patients present with their own unique complications and pathophysiology and do not fit neatly into standard model of single-organ failure on which current recommendations are based. Additional risks are present, such as in those with a failing Fontan circulation who are sicker due to protein-losing enteropathy and progressive hepatic and renal dysfunction. Furthermore, the number of possible donors may be limited due to pre-formed antibodies secondary to frequent prior blood transfusions. Many of these patients have undergone previous surgeries and present technical challenges due to adhesions, altered anatomy, and the presence of vascular collaterals [9–11,16,17]. Deteriorating quality of life due to progressive decline in cardiopulmonary function and increased hospital readmissions can be markers for referral and listing [9, 10, 16] (Fig. 16.2).

For those with combined cardiac and pulmonary disease, additional factors such as consistently low oxygen saturation, increasing frequency of exacerbations, a forced expiratory volume of below 30% of predicted are known to be associated with poor survival [18], and thus should merit consideration for listing for dual heart-lung transplant.

A thorough pre-operative assessment can guide listing and aid in achieving optimal management. In addition to the usual pre-operative assessments mentioned in Chap. 3, detailed imaging with computed tomography should be performed to assess for aorto-pulmonary collaterals

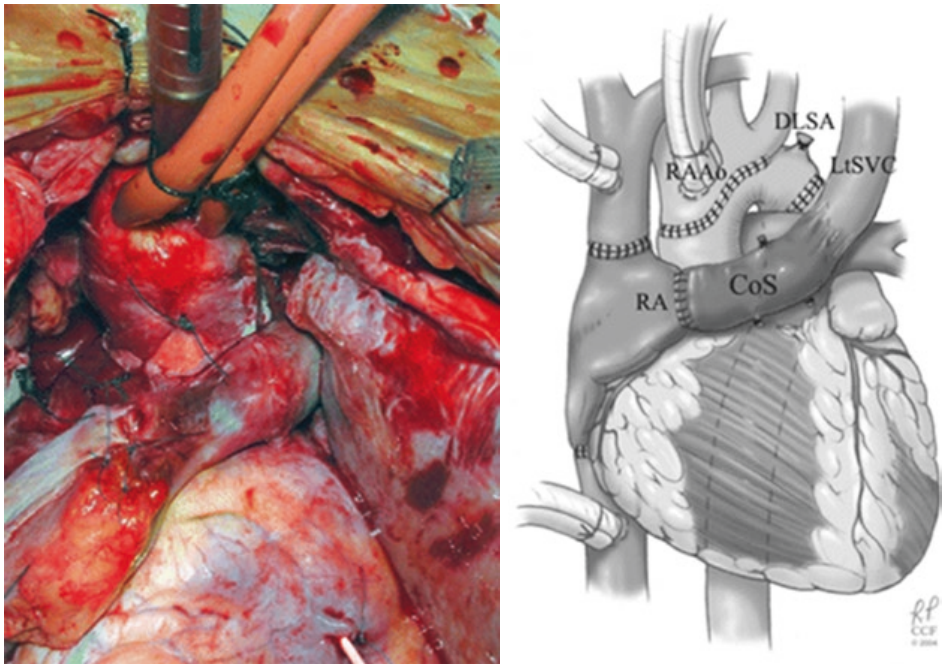

Fig. 16.2 Heart-lung transplant in a patient with complex congenital heart disease and Eisenmenger's syndrome (Reused with permission from Idreesand Pettersson [3])

in congenital heart disease patients, which have been demonstrated to result in increased bleeding and would need to be controlled early during cardiopulmonary bypass [10]. Patients with primary lung disease will require additional assessment of their lung function, including pulmonary function tests and CT of the chest.

As with cardiac transplantation, patients should be constantly monitored and reassessed as to whether they remain eligible for dual heart-lung transplant; a failure to delist when patients deteriorate while on the waiting list may result in worse outcomes [3]. Patients who deteriorate rapidly often require extracorporeal support, an accepted strategy as bridge-to-transplantation in both individual cardiac and lung transplantation fields. However, the role of ECMO as bridge-to-transplant in dual-organ candidates is less clear, with current data demonstrating higher mortality [3, 19].

Donor Evaluation in Heart-Lung Transplantation

Donor Evaluation

Like the recipient evaluation process, the assessment of the heart-lung combined donor follows a similar screening and assessment protocol to that of single cardiac donors (see Chap. 3). Similar to the heart, lung donor history (trauma, smoking, etc) is considered; donor age and ischemic time are considered with no firm cut-off, although in combination with a heart, increased values would preclude acceptance. Infection is assessed with bronchoscopy. Also considered are donor lung function and donor/recipient size matching.

Donor lung function is typically measured by the arterial partial pressure of oxygen (PaO_2). Conventionally, acceptable gas exchange is indicated by a PaO_2/FiO_2 of greater than 300 mmHg [20]. However, donors with an initial PaO_2/FiO_2 of <300 that subsequently improves to >300 with recruitment maneuvers have been shown to demonstrate equal survival to those with an initial PaO_2/FiO_2 >300, and UNOS multicenter data fails to demonstrate an association with decreased survival in patients with PaO_2 of below 200 [21].

With regard to size matching, donor/recipient lung recipient size matching needs to be separately considered from heart size matching. Total lung capacity (TLC), recipient pathology (obstructive vs. restrictive), and height are all considered, although there are no official guidelines in the setting of heart-lung transplantation. Patients with emphysema should be matched to a donor with a 67–100% of the recipient's TLC [20]; for pulmonary hypertension and cystic

fibrosis patients, there is consensus that the predicted total lung capacity (pTLC) of the donor can safely be up to 120% of the recipient actual TLC. Due to the limitations in TLC that occur in pulmonary fibrosis, the consensus recommendation for donors' pTLC is to be within 20% of the halfway point between the recipient's actual TLC and pTLC [20].

Procurement and Surgical Considerations

With regard to procurement of the donor heart/lung block, a median sternotomy incision is made for initial inspection of the heart/lung block. The block is then mobilized, taking care to achieve minimal handling of the pulmonary tissue. Management of the cardiac donor is addressed in Chap. 7, and similar protocols are applied to the heart-lung donor; the heart is flushed with cold cardioplegia solution, and the lungs are simultaneously flushed with cold modified UW/Collins solution after prostaglandins are administered into the pulmonary artery. The heart-lung block is then removed and placed into a sterile cold electrolyte solution for transport; the trachea should be occluded during storage and transport. While ex-vivo perfusion technologies have emerged as successful methods of reducing ischemic time for both heart and lung preservation alone, dual organ ex-vivo perfusion development remains at the pre-clinical stage [22].

The recipient operative procedure is performed by initiating cardiopulmonary bypass. The heart and lungs are removed, with care taken to preserve the phrenic nerves and to address the bronchial artery circulation so as to prevent post-operative bleeding complications; the donor heart and lungs are inserted. The tracheal anastomosis is then performed, followed by the right atrial anastomosis and the aortic anastomosis. Due to the limited vascularity of the area, care is taken to keep the donor trachea as short as possible [23]. Effective and careful hemostasis is a highly important factor in successful heart/lung transplantation, given the increased risk of post-operative bleeding in this cohort [3].

Post-operative Management: Special Considerations

Overall, the post-operative management guidelines outlined in Chap. 9 still hold true for dual heart-lung transplants, and as detailed in Chaps. 10 and 11, the immunosuppression and infection protocols used in heart transplant are also applicable to patients undergoing heart-lung transplantation. However, some additional specific factors regarding lung management must also be considered. From the cardiologist perspective, many of these aspects will be addressed by the pulmonology team, but it is prudent to be aware of potential complications.

Hemodynamic and Pulmonary Management

Post-operative hemodynamic instability should be addressed with inotropic agents (see Chap. 9) preferred over excessive fluid administration, due to the need to minimize pulmonary interstitial fluid accumulation in the newly transplanted lung. This allows filling pressures to remain low and maintain sufficient circulation.

As in heart transplantation, mechanical ventilation with a volume cycle ventilator is used immediately in the post-operative period to achieve adequate oxygenation, with a target of 90% or greater, with FIO_2 comparatively low as possible. In the early stages, positive end-expiratory pressure is also applied up to 4–5 cmH_2O, with higher levels warranted only in the setting of inadequate oxygenation (due to poor graft function). Suction of the airway should be performed regularly, along with percussion and vibration to mobilize secretions. While intubated, fiber-optic bronchoscopy may also be performed to examine the anastomosis and surrounding donor tissue for signs of ischemic injury. If graft function is satisfactory, it is desirable to wean off mechanical ventilation and extubate as soon as possible. Following this, patients should be encouraged to take regular deep breaths and coughs (to remove airway secretions that cannot be detected due to denervation), with regular spirometry assessment and vibropercussion.

Lung Primary Graft Dysfunction

Chapter 9 has already covered cardiac primary graft dysfunction; with lungs, the definition of primary graft dysfunction is a little different—PGD is a syndrome encompassing a spectrum of mild to severe lung graft injury that occurs within 72 h of transplantation [24]. Like with heart transplant, the syndrome is related to injury to the graft sustained by the removal from its natural blood supply, exposure to warm/cold ischemia, manipulation, and then subsequent reperfusion [24]. The defining clinical features of PGD are progressive hypoxemia at onset and diffuse radiographic infiltrates associated with capillary leak into the graft; there is alveolar and interstitial edema early in the process. Hyaline membranes often develop, similar to the histopathology seen in adult respiratory distress syndrome (ARDS) [24]. Like with cardiac PGD, this process may range in severity from very mild with no/barely visible radiographic infiltrates and relatively normal alveolar-to-arterial oxygen gradients to severe and life-threatening with thick, dense infiltrates and severe abnormalities of gas exchange. While data on PGD in heart-lung transplant cohorts is relatively limited, there are data to suggest that PGD is a leading cause of perioperative mortality in lung transplant recipients and decreased long-term survival, even in those who initially survive [25]. Treatment options are mainly supportive.

Heart-Lung Transplant: Specific Complications

For heart-lung transplants, the approach to mitigating and managing complications is similar to that for isolated heart transplant patients, detailed in Chaps. 9, 10 and 11. However, cardiologists should also be aware of the potential lung-specific complications in this cohort, as most complications following dual heart-lung transplant are lung-related.

Rejection

Acute cellular rejection (ACR) of the lung allograft is common after heart-lung transplantation; in fact, acute rejection of the lung allograft occurs more frequently than acute rejection of the cardiac allograft in these patients (60% vs 50% incidence at 5 years) [26], although the reason for this discordance is not known. Interestingly, both cardiac rejection rates and cardiac allograft vasculopathy rates in heart-lung patients are reduced compared to rates in isolated heart transplant patients [27], although the exact reason for this phenomenon is not known. In many programs, routine surveillance heart biopsies are reduced as a result of less observed rejection.

Lung ACR is most likely to occur during the first year post-transplant [28]. Exact incidences are difficult to determine, as many cases are clinically silent and only discovered by surveillance bronchoscopic biopsies, which are not regularly performed from center to center. Treatment for ACR is reported in 40–50% of patients in the first year post-transplant [1], and consists of augmentation of the immunosuppression with corticosteroids.

The clinical presentation of ACR is generally non-specific, and varies depending on the severity of the process, from completely asymptomatic to manifestations of fever, diffuse pulmonary infiltrates, and hypoxemia. In stable asymptomatic patients, regular home surveillance by spirometry is still needed, as "silent" rejection may be detected by a drop in spirometry.

ACR is typically diagnosed by bronchoscopic, transbronchial biopsies with histology showing perivascular and interstitial lymphocytic infiltrates. The severity of ACR is divided into grades of none, minimal, moderate, and severe based on the extent of the lymphocytic infiltrates using the International Society for Heart and Lung Transplant grading system [29]. In this system, a severity grade is assigned to both the perivascular/interstitial component (a-grade) and airway component (b-grade).

Importantly, lung ACR is strongly associated with subsequent chronic allograft rejection. There is considerable data to support the notion that frequent and/or severe episodes of ACR are associated with a higher risk of chronic lung allograft dysfunction (CLAD) [30, 31] (Fig. 16.3).

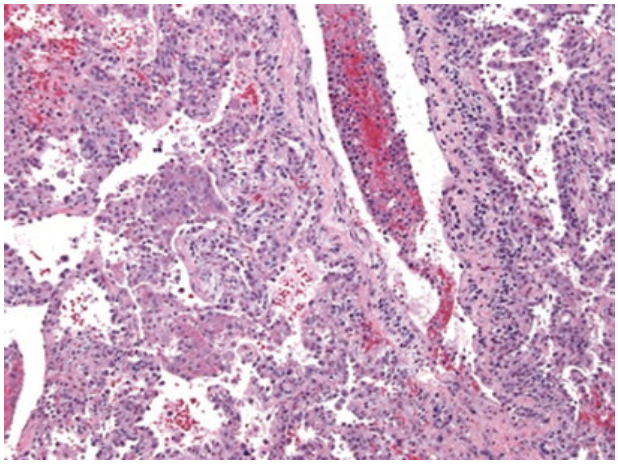

Fig. 16.3 Severe acute cellular rejection in the lung allograft; perivascular spaces and the alveolar septa are expanded by a mononuclear inflammatory infiltrate (Reused with permission from Stewart et al. [29])

Chronic Lung Allograft Dysfunction

Chronic lung allograft dysfunction (CLAD) is detected clinically by a decline in lung function: commonly approximated by measuring the forced expiratory volume in 1 s (FEV_1). The histopathologic findings for CLAD are distinct from the aforementioned a-grade or b-grade ACR. Historically, chronic rejection of the lung allograft has been synonymous with the term bronchiolitis obliterans syndrome (BOS) which refers to lesions found in the terminal (non-cartilaginous) airways. Because these lesions were often associated with lymphocytic infiltrates, it was thought that BOS was equivalent to chronic rejection. It is now known that other factors, independent of the immune response against the lung allograft, contribute to the pathogenesis of BOS. In addition, other pathological processes that lead to chronic rejection have been identified. In addition to BOS, other patterns of rejection with distinct histological findings have been described. These include restrictive allograft syndrome (RAS), characterized by a decline in FEV_1 of more than 20% and a decline in total lung capacity (TLC) of more than 10% (Fig. 16.4).

Bronchiolitis Obliterans Syndrome

Patients with the BOS phenotype of CLAD typically present with progressive airflow obstruction that may be associated with dyspnea and cough [33], and many ultimately expire due to respiratory failure or secondary infection. While the exact etiology is unknown, there is strong evidence to suggest that it is mediated by immunologic injury [34].

Diagnosis is most definitively made with a surgical biopsy, but in practice most patients are diagnosed clinically. Patients show progressive airflow obstruction that cannot be attributed to any specific cause [35]. In order for a diagnosis of BOS to be made, a persistent 20% drop in FEV_1 [33, 35] should be seen, along with exclusion of acute rejection, infection, or large airway stenosis by bronchoscopy with bronchoalveolar lavage and transbronchial biopsies [35].

Unfortunately, BOS is common after heart-lung transplantation, occurring in anywhere from 40% to 80% of patients by 5 years after transplant [36], and survival is reduced in patients with BOS compared with those who do not suffer from BOS [37]. The rate of progression of BOS is heterogeneous in its presentation; some patients may develop a sudden drop in lung function that may remain stable for years, while others may present with a very rapid and progressive loss of lung function leading to death within a few months. To date, there is no proven effective treatment for BOS. Many treatment strategies have been tried, including augmentation of immunosuppression, total lymphoid irradiation, and photopheresis [38].

Other Patterns of Rejection

As mentioned earlier, in addition to the classical findings of fibromyxoid luminal obliteration seen in most cases of BOS, other phenotypes for chronic rejection have been described. RAS, neutrophilic reversible allograft dysfunction (NRAD) and follicular bronchiolitis have so far been identified. The latter two are classified by some pathologists as subtypes of BOS. RAS is characterized by fibrosis of the upper lobes and pleural thickening. This can be visualized radiographically as a honeycomb appearance in the apices. The histologic findings of RAS are

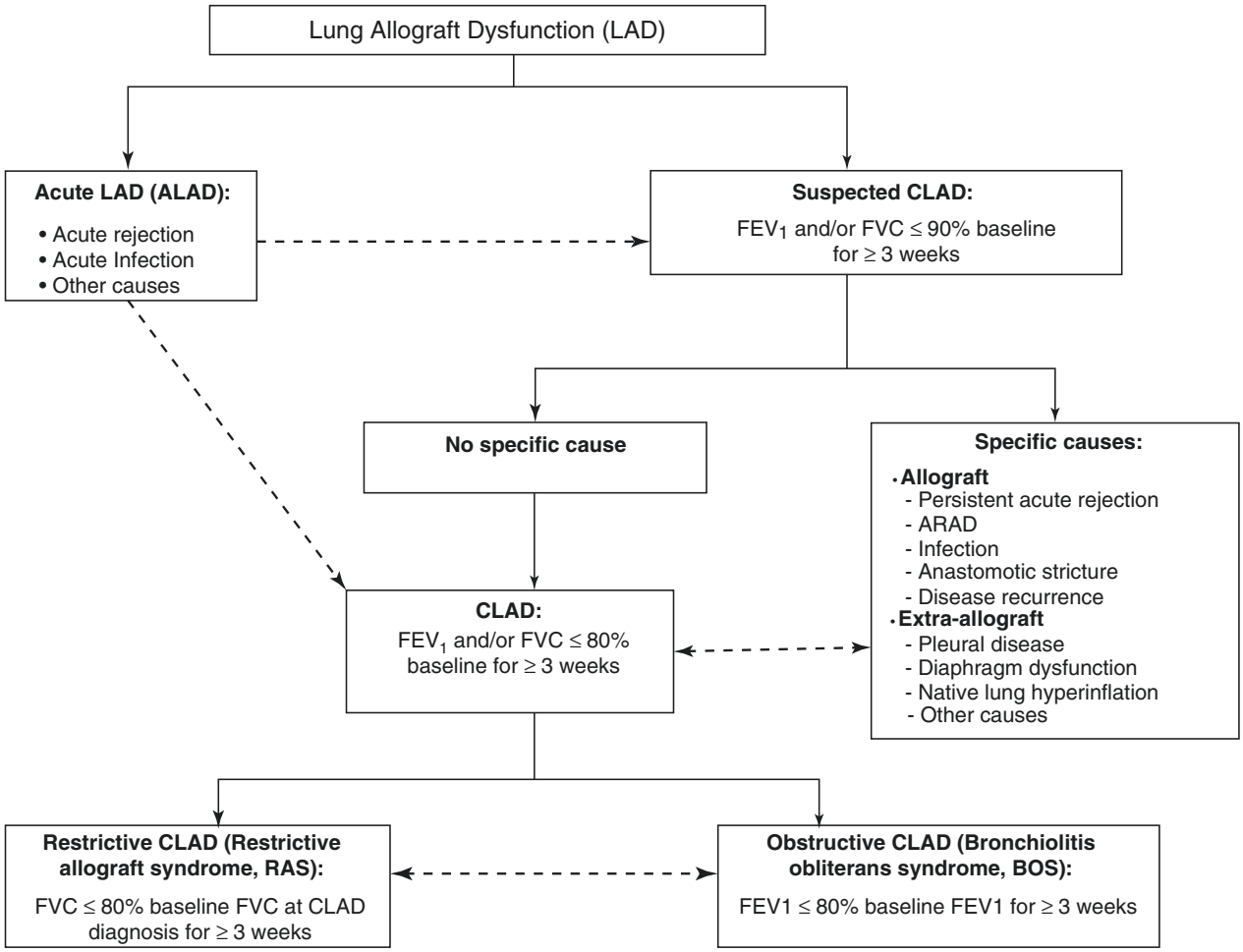

Fig. 16.4 This flow chart suggests an approach that can be used to evaluate a lung transplant recipient's decline in post-bronchodilator forced expiratory volume in 1 s (*FEV_1*) with or without a decline in forced vital capacity (*FVC*) of ≥10%. This may be acute lung allograft dysfunction (*ALAD*) and may normalize with treatment. When the lung function decline, however, persists for at least 3 weeks without the FEV_1 and/or FVC returning to >90% of the post-operative best values, it is suggested this is chronic, and chronic lung allograft dysfunction (*CLAD*) is suspected. Extended pulmonary function tests (*PFT*), including spirometry and lung volumes, high-resolution computed tomography (*HRCT*) of the thorax, and bronchoscopy with bronchoalveolar lavage (*BAL*) and transbronchial biopsy specimens may identify a cause or causes of suspected CLAD that may still be (completely) reversible upon specific treatment. If the FEV_1 and/or FVC declines further to ≤80% of the post-operative best values, despite treatment or without identifying a clear cause, a specific CLAD phenotype should be identified. (Suspected) CLAD could also be a consequence of ALAD if the lung function decline persists. Some patients never develop suspected CLAD but may already have CLAD when they are diagnosed. *BOS* bronchiolitis obliterans syndrome, *CXR* routine chest X-ray, *FEV_1* forced expiratory volume in 1 s, *SLT* single lung transplant, *ARAD* azithromycin-responsive allograft dysfunction, *RAS* restrictive allograft syndrome (Reused with permission from Verleden et al. [32])

inflammatory and fibrotic changes of the peripheral lung tissues, namely the alveoli, interlobular septum and pleura. NRAD is characterized by neutrophilia in the bronchoalveolar lavage, and by an improvement in FEV_1 with azithromycin. Follicular bronchiolitis is associated with prior *Aspergillus* infection. There is lymphoid hyperplasia around the airways and eventually this progresses to bronchiectasis.

Survival after Heart-Lung Transplantation

Since the early 1980s, when the dual heart-lung transplant was first performed, the outcomes have improved with each subsequent era [3]. A common theme is that although late survival has improved, the most significant improvements are noted during the early post-transplant period. For patients transplanted between 1982 and 2013, 1-year

survival was 52% and 10-yeart survival was 32% [39]. Early mortality is worse in combined heart-lung compared with single heart or single lung transplantation. Late mortality, however, is better than for single lung transplantation but still worse than single heart transplantation. In patients who survive the first year post-transplant, the conditional median survival is 10.3 years. Over the years, better patient selection, refinement of surgical techniques, immunosuppressive therapy preventing graft rejection, and improved understanding of risk factors for morbidity and mortality have all contributed to these improved outcomes [3].

While longer-term outcomes after dual heart-lung transplant are very similar to outcomes after lung transplantation, they are significantly worse than after heart transplantation; most complications after heart-lung transplant are lung-related. The most common causes of death in the initial 30-day period are due to post-transplant graft failure, technical complications, and infection; after 1 year, bronchiolitis obliterans syndrome (BOS) and chronic lung allograft dysfunction (CLAD) are the major causes of mortality [1].

Despite limited data, risk factor analyses of mortality demonstrate that patients reliant on mechanical ventilation or circulatory support prior to dual heart-lung transplant suffer worse outcomes that those not reliant [19]. Furthermore, an ISHLT data analyses reveals that older age of the donor and indications other than IPAH are predictors of mortality [1]. Further analysis of isolated lung transplant data from the ISHLT also demonstrates that donor diabetes, CMV mismatch, prior recipient transfusion history, center volume, donor-recipient height difference, higher bilirubin, low cardiac output, and higher creatinine are strongly associated with mortality [1, 3]. Given that most complications are lung-related in the heart-lung population, it would seem prudent to infer that these factors might also lead to increased mortality in a dual heart-lung transplant cohort.

Heart-Kidney Transplantation

History

Historically, the presence of severe renal disease co-existent with severe end-stage heart disease has been a contraindication to cardiac transplantation due to the increased risk for morbidity and mortality post-heart transplant in this cohort [40]. For the same reasons, patients with primary end-stage renal failure and coexisting severe heart disease have often been overlooked for transplantation. Furthermore, calcineurin inhibitors, a mainstay of immunosuppression, are known to exert nephrotoxic effects. As a result, there have been less than 1000 combined heart-kidney transplants performed in the history of transplantation, according to UNOS data [41]. However, the improvement in long-term outcomes over the past 25 years has led to this rare procedure being performed more frequently.

Selection

While there are no established guidelines on selecting heart-kidney transplant candidates, patients being considered for this procedure typically fall into three different categories: those with combined primary end-stage heart disease and intrinsic (primary) kidney disease; severe renal dysfunction secondary to severe heart failure; and end-stage intrinsic kidney disease with secondary heart disease.

Most common is the patient with co-existing combined end-stage primary heart and kidney disease. Many of these patients are on some form of dialysis. Common causes of the primary cardiac disease include idiopathic dilated cardiomyopathy and ischemic heart disease, while common causes of the renal disease include diabetes mellitus and chronic glomerulonephritis [42]. The majority of combined heart-kidney transplants, and hence the majority of data on this topic, have been performed on this cohort of patients [40]; it is considered more controversial to transplant patients with secondary renal or cardiac dysfunction.

Procedural Considerations

The heart-kidney transplant may be performed as a combined procedure, or as a staged operation, where the cardiac transplant is performed first, the patient is transferred to ICU to allow recovery

and ensure stabilization of cardiac function, and the patient is subsequently returned to the operating room for kidney transplantation. While there is no firm guideline, many centers use a staged procedure to avoid the following negative effects on the transplanted kidney: activation of the inflammatory cascade during CPB; the effect of vasoconstrictor drugs; and hemodynamic instability [43]. Many centers have used this procedure with no worse outcomes than either organ transplanted alone.

Diagnosis of Rejection

With regard to frequency of rejection after combined heart-kidney transplant, there is limited data; however, an early multicenter report demonstrates a lower incidence of acute cardiac and renal rejection than expected when compared to rates of rejection for the transplantation of each individual organ [42].

Rejection is often clinically diagnosed on the basis of increasing creatinine or dysuria. Following ultrasound, biopsies must be performed at intervals or when clinically directed; the gold standard of diagnosis remains according to histopathological ISHLT criteria [29], much like heart or lung acute cellular rejection.

Outcomes

Multiple studies have actually demonstrated superior outcomes in heart-kidney recipients compared to isolated heart transplant recipients in terms of long-term survival [40, 42, 44, 45], especially in end-stage heart failure patients dependent on dialysis. Other studies have shown no significant difference in survival [46, 47].

Heart-Liver Transplantation

The first combined heart-liver transplant occurred in 1984, described by Starzl et al., was performed on a 6-year-old girl who had liver failure secondary to familial hypercholesterolemia and heart failure as a result of coronary artery disease. There have been less than 200 heart-liver transplants performed in the history of transplantation in the United States, and hence this is a rare topic. Most of these were performed at high-volume centers. Potential candidates are those with end-stage heart and liver disease of varying etiology, end-stage heart and liver disease of related etiology [48], and end-stage heart disease where liver transplantation is needed in order to correct an underlying metabolic disorder. Familial amyloid polyneuropathy (FAP) and heart failure with associated cardiac cirrhosis are the most common indications for heart-liver transplant [49]. Other examples include biliary atresia and iron deposition disorders such as homozygous beta-thalassemia and genetic hemochromatosis. From the current existing data, carefully selected patients with coexisting heart and liver disease that undergo combined heart and liver transplantation experience acceptable patient and graft survival [48–50]. Compared with heart transplantation alone, there are fewer episodes of antibody mediated rejection (AMR). It is hypothesized that the liver confers protection by absorbing donor specific antibodies. The exact mechanism has not been demonstrated but could be through the phagocytic action of Kupffer cells. Survival is comparable to single orthotopic heart transplantation with 1- and 5-year survival at 83.5% and 73.2% respectively [51].

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The Total Artificial Heart

17

Francisco Arabia

Clinical Pearls

- The primary indication for the use of the total artificial heart (TAH) is in those patients who are heart transplant candidates with severe biventricular failure, have an imminent risk of death and for whom a suitable donor heart is not available.
- Contraindications to TAH include pre-existing cardiogenic shock with end organ dysfunction while on short-term support devices; these patients have an extremely poor prognosis.
- Surgical implantation of the TAH includes removal of the ventricles (except 1–2 mm of mitral and tricuspid valve tissue) with the native atria largely left intact; the TAH is then attached.
- PTFE-membranes, blue poly-isoprene bands and silicone membranes are applied to the device and surrounding structures to protect the TAH from future adhesions and avoid subsequent difficulty during explantation.
- Anticoagulation after TAH implantation is crucial and consists primarily of aspirin and warfarin.
- Common complications of the TAH include infections, thromboembolus causing neurological events (such as stroke), and bleeding with potential tamponade; patients should be monitored accordingly.

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Introduction: Brief History on the Total Artificial Heart and Principles

The development of the total artificial heart (TAH) for replacement of the failing human heart has attracted the spirit of humanity and the best minds in medical sciences, engineering, and ethics. Although the concept of developing a pump to propel blood appears simple, the development of the total artificial heart has rivaled the most important scientific projects of mankind.

In 1963, the U.S. Congress established the National Advisory Council to recommend the long-range research required for the development of a total artificial heart [1]. The first use of an artificial heart in a human took place in 1969 with the implantation of the Liotta TAH, which sustained the life of a patient for 64 h prior to a heart transplant. The next implantation of a TAH was delayed until 1981 when the Akutsu III was implanted also at the Texas Heart Institute [2]. The first long-term TAH implanted was the Jarvik-7 that was implanted in 1982 in Barney Clark; a dentist, who had been diagnosed with

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terminal heart failure and was not a heart transplant candidate. He survived 112 days but succumbed to strokes. Over 1600 patients have been implanted with 16 different total artificial hearts. Its main use has been as a bridge to transplant for those critically ill, and in desperate need of a donor heart.

Total Artificial Heart Models

The majority of the TAH's developed have failed to reach significant clinical use or approval. The technology faces significant medical and engineering challenges. The cost of development has always been expensive and always misses the best estimates. All TAHs, as with any type of MCS, have proven to have indications, benefits and shortcomings. The only TAH that has been successfully utilized in the world is the SynCardia TAH. The SynCardia TAH provides overwhelming evidence and data to support total heart replacement therapy.

Syncardia

The SynCardia™ TAH (SynCardia Systems, Inc., Tucson, AZ, USA) is an intracorporeal, pneumatically driven biventricular system that totally replaces the failing ventricles (see Fig. 17.1). In order for the SynCardia™ TAH (70 cc) to fit in a human, the recommendation is that the distance between the undersurface of the sternum and the anterior tenth thoracic vertebral body should be at least 10 cm (T-10 distance) in order to accommodate the device. This, in general, correlates with a body surface area (BSA) of >1.7 m^2. However, the SynCardia™ TAH has been successfully implanted in smaller patients and children with a T-10 below 10 cm. A smaller TAH with 50-cc ventricles is now under clinical investigation as a bridge-to-transplantation (BTT) in smaller patients. The 70 cc TAH remains efficacious in the management of INTERMACS profile 1 and 2 patients in the BTT population. To date, over 1600 SynCardia™ TAHs have been implanted throughout the world

Fig. 17.1 The SynCardia™ total artificial heart

and its utilizations continue to increase as its versatility is better understood. The SynCardia™ TAH has a portable driver (Freedom®; Syncardia Systems, Inc., Tucson, AZ, USA) that allows for patients to be discharged home.

Other Total Artificial Hearts

Abiocor TAH

The AbioCor® TAH (Abiomed, Inc., MA) has been utilized in patients with end-stage HF [3]. It is the only TAH that has been totally implantable (untethered), electric and to use the transcutaneous energy transmission system (see Fig. 17.2). This allowed for the absence of driveline piercing of the skin. However, only 14 of these devices have been implanted in humans with none surviving more than a year, with thromboembolic stroke the most common cause of death.

Carmat TAH

The Carmat® (Carmat SA, Velizy Villacoublay, France) is a TAH where most blood-contacting surfaces are biological (see Fig. 17.3). It consists of four bioprosthetic valves and two pulsatile

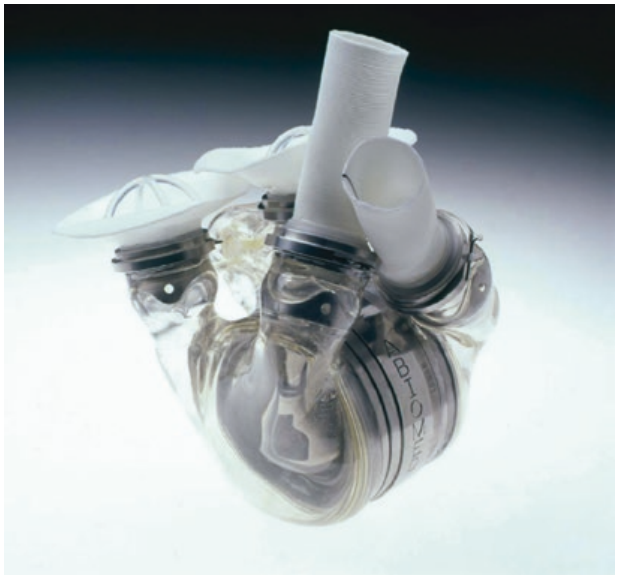

Fig. 17.2 The AbioCor® total artificial heart

Fig. 17.3 Carmat® total artificial heart (Reproduced with permission from Carmat SA)

bovine pericardial membranes. It is electrically driven. Its first use in humans occurred in late 2013 in France. Four patients have been implanted as of early 2016 with one long term survivor.

ReinHart TAH

The ReinHart® TAH has been designed at Aachen University in Germany. It is undergoing preliminary studies.

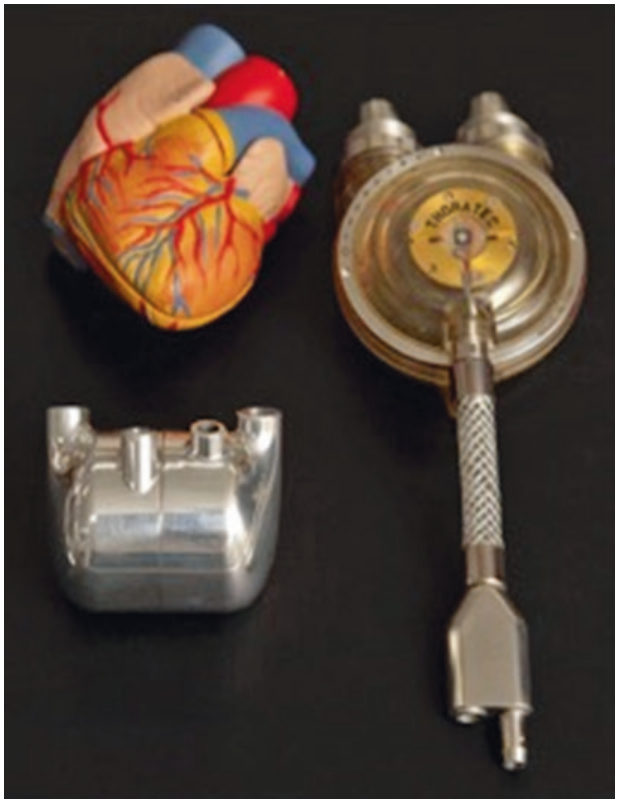

Fig. 17.4 BiVACOR® total artificial heart

BiVACOR TAH

The BiVACOR® (TX, USA) TAH utilizes one continuous moving impeller in order to propel blood in both ventricles (see Fig. 17.4). It is electrically driven and has one moving part. The impeller is magnetically levitated in the center of the TAH and propels blood to both sides of the circulation without the need for inflow or outflow valves. It can generate pulsatile flow and is currently undergoing animal trials.

Cleveland Clinic TAH

Also known as the SmartHeart® TAH (Cleveland Clinic, OH, USA), the Cleveland Clinic TAH is designed for long-term use in patients suffering from biventricular failure. It is in an early developmental phase and is undergoing animal trials.

Indications for Total Artificial Heart

Proper patient selection and timing of intervention are two of the most important factors in predicting a successful outcome for the patient who requires a TAH. The main indication for the use of TAH is in patients who are heart transplant candidates with severe biventricular failure in imminent risk of death and a suitable donor heart is not available. LVADs have proven very effective in either bridging patients to heart transplantation or as destination therapy in those patients who are not candidates [4, 5]. LVADs outcomes have continued to improve over the years and some patient subgroups experience near transplant survival outcomes. However, heart transplantation still has a better survival outcome over LVADs [6]. Furthermore, the use of isolated LVADs has unmasked a patient population that continues to experience right ventricular failure with an incidence approaching 40% [7]. There are several ventricular assist devices (VAD's) that have been utilized for temporary right ventricular (RV) support with the intent of providing support to the RV. However, the need for a right ventricular assist device (RVAD) identifies a patient population that has worse outcomes [8].

The TAH continues to be used as a BTT in patients with severe biventricular failure, i.e., INTERMACS profile 1 and primarily profile 2 [9, 10]. However, the last few years has seen an increase in its use and better understanding for the indications for its use. Many potential indications for the use of a TAH have been conceptualized for many years; however, it has been in recent times that the TAH has been utilized for these very ill patients. For this reason, few of these cases have reached the medical literature and others are too early to report.

The need for re-transplantation is essential to provide long term survival for a heart transplant recipient who is experiencing graft failure that is not responding to conventional therapy. In cases of severe and diffuse coronary artery vasculopathy not amenable to percutaneous interventions or coronary artery bypass grafting, retransplantation is the only definite therapy in a viable patient. If a donor has not become available and the patient is experiencing hemodynamic instability despite inotropic support, temporizing measures that will provide more time include the use of ECMO or biventricular support. The role of the TAH in this particular patient population provides several advantages as long as the TAH is implanted prior to total cardiovascular collapse and end-organ damage. The TAH allows for immunosuppression to be discontinued and potentially lowers the increased risk of infection and kidney damage. Furthermore, it allows the patient to be ambulatory and potentially the benefit of being discharged home [11]. The use of the TAH for this indication is associated with a survival rate of 47%. However, the use of the TAH for hemodynamic collapse in the onset of acute rejection has not been described. This will probably be associated with a high rate of complications and poor outcomes. The role of the TAH in the chronic graft failure scenario will probably continue to increase as the transplant population has a mean survival of approximately 10 years and the donor shortage continues [12, 13].

The use of the TAH in the pediatric population with advanced heart failure as the result of an idiopathic, viral or congenital structural abnormality provides significant advantages. In addition to correction of hemodynamic deterioration, it provides a surgical scenario that allows for the correction of some of the congenital abnormalities at the time of TAH implantation and prior to the time of transplantation. The 50 cc SynCardia™ TAH has been developed for this smaller body-size patient population [14–17]. If successful, it will further expand the use of this technology in children and small adults with a BSA as low as 1.0 m^2. Approximately 30 patients with congenital heart disease had been implanted with the Syncardia™ TAH by the end of 2013. The majority of these patients were implanted in the last few years and in multiple centers. Some of the congenital abnormalities in these patients include corrected transposition of the great vessels and single ventricle. Although reports are just starting to be reported, some of these patients are experiencing altered hemodynamics and a failing Fontan. It is the expectation that the next few years will provide more evidence-based medicine

regarding the management in this complex population with the TAH. The implantation of the SynCardia™ TAH or any newer TAH in patients with congenital heart disease will challenge surgeons to develop surgical modifications to the conventional implantation of the device as the cardiac abnormalities dictate modification and design.

The outcome of the patient with a primary cardiac malignancy is usually dismal. Although the majority of cardiac tumors are benign, a malignant tumor carries a fatal prognosis if unresectable. Diagnosis of these malignant tumors usually includes a biopsy at the time of presentation or occurs at the time of an optimistic but failed surgical resection. Imaging studies (echocardiography, computerized tomography, and MRI) are usually helpful but in some if not most instances failed to accurately delineate the extent of the disease [18]. Chemotherapy and radiation therapy have been utilized in unresectable cases. Heart transplantation has been utilized to treat selected patients with cardiac malignancies, however, several studies have shown poor outcomes. The use of ventricular assist devices has been reported and more recently the use of the HeartMate II LVAD used in the TAH configuration was described in a patient. A very small number of patients with cardiac tumors have received the Syncardia™ TAH. It is doubtful that there will be enough scientific information to make any prediction on outcomes. The use of the TAH in this population will generate controversy in the medical field. However, long-term use of the TAH followed by transplantation may one day play a role.

Acquired or ischemic ventricular septal defect (VSD) as a complication of myocardial infarction remains a condition with significant morbidity. Surgical correction is the most common therapy that carries a significant morbidity and mortality [19]. The use of MCS has been reported in the management of ischemic VSDs [20]. The successful use of the Syncardia™ TAH has also been reported [21]. A very small number of patients have been done for this indication to have a series of patients. The procedure probably will continue to have a significant morbidity and mortality as these patient populations have significant hemodynamic and physiologic impairment.

The patient populations experiencing infiltrative (i.e., amyloid) or hypertrophic cardiomyopathy are ideal candidates for the use of a TAH as this therapy eliminates the effect of the disease process in both affected ventricles. Although the use of left ventricular assist devices (LVAD) have been reported [22], the utilization of the TAH continues to increase in this population. Another population that benefit from the TAH technology are those patients who experience ventricular tachycardia (VT) storm or malignant arrhythmias despite multiple ablations. Although LVAD's have also been used in this setting, the TAH continues to find a role in this group of patients. However, medical reporting in these two populations will increase in the next few years.

LVAD's have been extremely successful in the management of congestive heart failure both in the BTT and destination therapy who are failing medical therapy. However, despite the best management, a number of BTT patients who have received LVADs continue to or relapse with right ventricular failure (RVF). The TAH has been successful in re-bridging these patients and eliminating the effects of RVF despite LVAD support [23]. However, this has not been tested in the destination (DT) population.

Implantation of Total Artificial Heart: Surgical Considerations

The conventional median sternotomy incision is performed and the pericardium is opened to expose the native heart. The drivelines for the prosthetic ventricles are then pulled outwards via a chest tube through pre-cut wounds under the left costal margin. Aortic and bicaval cannulations are performed, cardiopulmonary bypass is performed after appropriate heparinization, the heart is fibrillated and the aorta is cross-clamped. The patient is cooled to 32° F. The heart is then excised, starting with a ventriculectomy from right to left. Both native heart atria are left in

place, as well a small amount of ventricle along with 1–2 mm of mitral and tricuspid valve tissue attached to the annulus.

The left atrial quick connect is placed through the mitral valve annulus and sutured to the left atrial cuff and the remnant ventricular muscle. The right atrial quick connect is placed through the tricuspid valve annulus and sutured in a similar way. The arterial conduits are then anastomosed to their respective arteries (see Fig. 17.5). At this stage, the suture lines are checked for leaks and if applicable, Coseal (Baxter Healthcare, Los Angeles, CA) or Bioglue (CryoLife, Kennesaw, GA) can be used to further secure the suture lines. A sheet of ePTFE-membrane is secured to the posterior pericardium for the purpose of minimizing adhesions at the time of the explantation. Rewarming usually begins at this point.

Now the left prosthetic ventricle is attached, with care to ensure the correct orientation (preset beforehand). The inflow of the ventricle is connected to the left atrial quick connect and the aortic conduit while installing saline to remove as much air as possible from the prosthetic ventricle. The prosthetic right ventricle is connected in a similar fashion, first to the right atrial quick connect. Blood volume is then passed from the CPB machine to the patient by removing one of the tourniquets in the cava until blood fills and de-airs the right ventricle. The ventricle is then connected to the pulmonary artery conduit. A vent needle is placed in the ascending aorta, the patient is placed in the Trendelenburg position and the aortic cross-clamp is removed.

De-airing of the aorta occurs while TEE is used to visualize the aorta. The TAH is then set at 40 beats/min and gradually increased as the patient is weaned off CPB. Protamine is then used to reverse heparinization; once bleeding ceases, chest tubes are placed in the mediastinum for drainage purposes. Before chest closure, additional sheets of ePTFE are placed around the superior and inferior venae cavae to further prevent adhesions. Closure of the chest then occurs in the normal fashion, and subsequent TEE is essential to ensure no compression of the cavae or pulmonary veins.

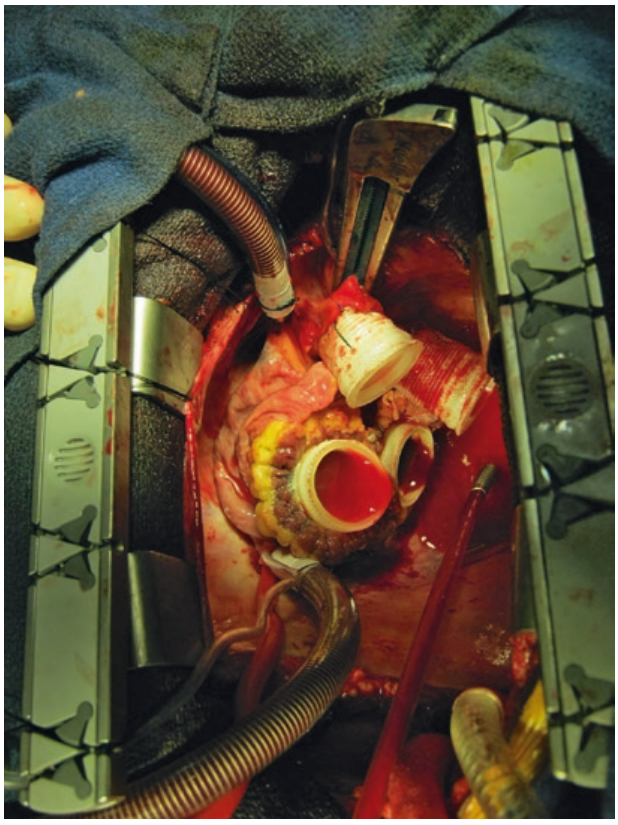

Fig. 17.5 Aortic and pulmonary conduits sutured in place during total artificial heart implantation

Technique for TAH Protection at the Time of Implantation

One of the main challenges of long-term mechanical circulatory support devices is its explantation at the time of heart transplantation. The human body generates a significant amount of scar tissue around the device as a foreign body reaction. This makes the operation significantly more difficult. Although there are no standards or agreement on the right way to protect the device once implanted, the following technique is recommended. The technique to facilitate mediastinal re-entry utilizes three components: (1) Blue polyisoprene bands (BBI; Bioseal, Placentia, CA), (2) Gore-tex (PTFE) sheets (20 × 15 cm × 0.1 mm, W. L. Gore & Associates, Flagstaff, AZ), and (3) Surgical grade silicone membrane 0.060 inches thick (Bentec Medical, Woodland, CA).

Blue bands are loosely placed circumferentially around the aorta and inferior vena cava (IVC). The entire length of each vascular structure

is covered in order to avoid adhesion formation, minimizing the necessity for dissecting the structure during the subsequent operation. Before the TAH is lowered into the mediastinal cavity, a 0.01 mm thick PTFE sheet is secured at the medial aspect of the mediastinum, by suturing the edges of the sheet with prolene sutures to areas lateral to the left pulmonary veins. During chest closure, one or two additional sheets of ePTFE are utilized to cover the entire device, as well as the right atrium and both venae cavae. The sheet over the right atrium can be tacked down with interrupted sutures to the pericardium near the venae cave to prevent migration (see Fig. 17.6). Finally, a segment of surgical silicone membrane 1 cm wide and as long as the sternum is the cut and placed above the sternal wires prior to sternal closure.

At transplant, a redo lateral oscillating blade saw is used to perform the sternotomy in a routine fashion at a level above the silicone membrane. The membrane serves as the first protective layer which can be easily removed, as no adhesions form around it. The BBs are identified around the encircled vessels. The clips on the BBs are removed and a small hole is cut into one end. An umbilical tape is threaded through that hole and subsequently placed around the vessel, as the BB is removed. As there are no adhesions around the encircled vessels (aorta, IVC, SVC), minimal dissection is required and CPB can be initiated expeditiously, if required. The PTFE membranes are then removed from around the device, the anterior surface of the heart or TAH. This facilitates exposure of the device as adhesions are minimized.

Clinical Course and Outcomes of Patients with Total Artificial Heart

Bridge to Transplantation

The majority of the world's experience has been with the SynCardia™ TAH. In one of the original series reported by Johnson et al. in 1992, actuarial survival was 62% at 30 days [24]. A landmark study came in 2004 when Copeland et al. reported a survival to transplantation of 79% versus 46% for patients who received the TAH versus a control group, respectively [25]. A more recent series in 2009 reported on 100 patients who received the SynCardia™ TAH. Of these patients, 91% had an INTERMACS profile of 1. Survival to transplantation was 68.3%, while the most common cause of death in this population was multiple organ

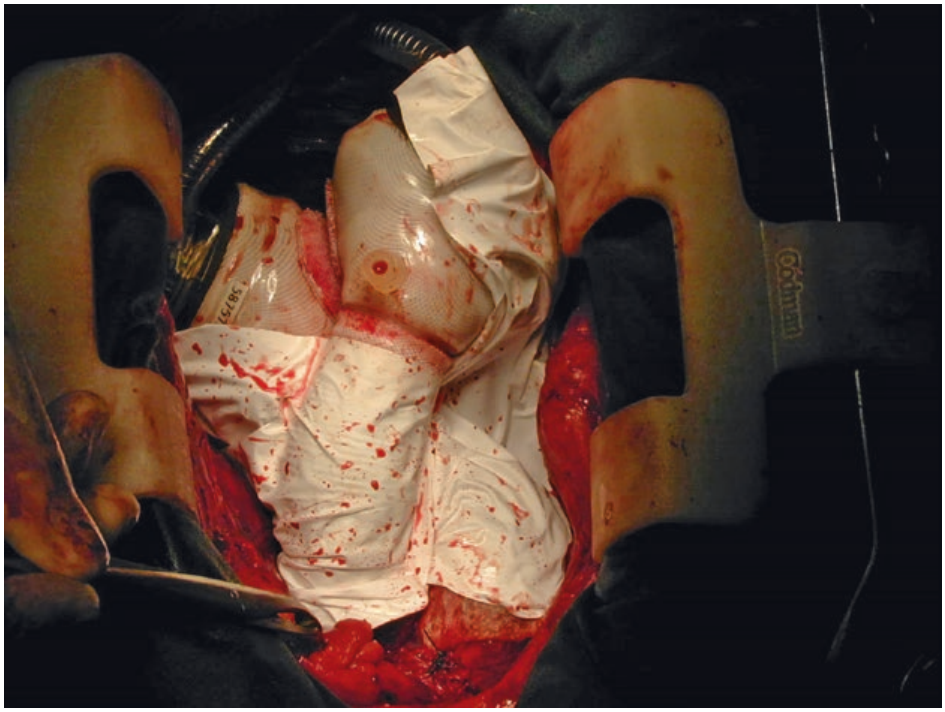

Fig. 17.6 Demonstration of a newly-implanted total artificial heart covered with an ePTFE membrane

failure. Strokes occurred in 7.9% of the patients [26]. Recent data analysis of 359 patients in the Intermacs Registry reveals that 85% of patients who receive the TAH in an experienced center are alive or have been transplanted at 6 months. Furthermore, about 80% are alive at 1 year [27]. Anticoagulation with the TAH has consisted primarily of aspirin and warfarin, use of other pharmacologic agents, such as dypiridamole and pentoxyfiline, have remained at the discretion of the implanting center.

Management

Post-operative management in the ICU is crucial for a successful patient outcome. In many cases when there is mediastinal bleeding that is concerning in the operative room, the sternum is left open and the chest protected with an adhesive cover. The patient is then monitored for bleeding in the ICU. Commonly, if there is no bleeding and the patient remains hemodynamically stable for about 24 h, the patient is returned to the operating room for mediastinal lavage and sternal closure. Mediastinal bleeding causing tamponade is possible over the first 2 weeks. A progressive decline on the TAH left and right outputs are indicative of tamponade (while the TAH itself is non-compressible, the native atria remain compressible and vulnerable to extrinsic compression). This has to be addressed expeditiously and the patient re-explored. Liver and renal dysfunction are common and of different levels of severity usually depending on how sick the patient was prior to implantation. The worst prognosis for a patient receiving a TAH is for the patient who has been on short-term support devices like ECMO for several days prior (>3 days). Patients, who continue to experience end-organ dysfunction while on short-term support devices, should not be considered for TAH.

Management of the patient outside the ICU revolves more commonly around rehabilitation, proper anticoagulation, blood pressure management and understanding the device. The patient and the care-giver, usually family members, are instructed and tested on proper device management like any other LVAD. Special instruction is given regarding the Freedom Driver (outpatient). Approximately 50% of the patients implanted can be discharged home. Patients are followed in clinic on a weekly basis for the first month and then the visits are spaced. Proper care of the drive lines is similar to other outpatient devices.

Common Complications

The most common complications that occur with the TAH are usually related to infections, neurological events and bleeding. The most common cause of death is related to multiple organ failure. This seems to be related to intervention on a patient that has severe disease with irreversible organ damage. Proper selection of patients and timing of the intervention are essential for a good survival outcome.

Special Considerations

For many years, the only SynCardia TAH has been the 70 cc (volume of each single ventricle). Recently a 50 cc TAH has been introduced and is undergoing testing as a bridge-to-transplant. The trial cohort is the smaller individual, usually a young adult or female who cannot accomodate the larger model. The trials are taking place in North America and in Europe. The 70 cc TAH is also undergoing a Destination Therapy trial for patients who are not candidates for transplantation and show evidence of irreversible biventricular failure. Information regarding feasibility and outcomes should be available in the years to come.

Future of Total Artificial Heart

The understanding of end-stage heart failure will continue to evolve as heart disease is better understood. Medical management will advance with newer and more sophisticated pharmacologic agents that address genetics, cardiomyocytes and the neurohormonal axis. Heart transplantation may have expanded to its limit.

The role of xenotransplantation remains challenging. With the advent of technological discoveries, medical advances and miniaturization, the road to biomechanics and organ replacement has expanded. TAHs and LVADs will continue to improve and their use will increase. Despite there being many TAHs that have been designed over the last 60 years, the SynCardia™ TAH remains the most implanted and widely used. Survival with this device as a BTT has reached 79%. However, future work in the TAH field over the next 5–10 years will pose challenges for this technology to become more effective and to gain societal acceptance. Some of these challenges include: lower or no anticoagulation; smaller, minimal power requirements; quiet functioning; and ease of implantation and monitoring. The devices will have to cause no alteration in normal human physiology and improve patient wellbeing and quality of life. They will have to have no parts outside the body. They will be a device that will be categorized as 'implant and forget'.

In conclusion, the concept of the TAH has been overshadowed by the success of the LVAD to treat primarily left ventricular failure. However, as we gain experience with LVADs, the need for the TAH concept gains more acceptance in order to treat the sickest patients with biventricular failure where LVAD support is not sufficient.

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The Future of Heart Transplantation

18

Jon Kobashigawa

Introduction

The field of heart transplant has made undeniable progress since the first human-to-human heart transplant was performed in 1967. Advances in translational medicine bring tremendous potential to the field of heart transplantation. As heart transplantation remains the preferred therapy for end-stage heart failure, this chapter provides an overview of the most promising innovations in heart transplantation, including advances in immunosuppression and inducing tolerance. Acknowledgment will also be given to recent advances in the prevention of heart failure, as well as the rise of mechanical circulatory support devices as destination therapy, which may reduce the demand for donor hearts in a time of short supply.

Acquired Tolerance: the Holy Grail of Transplant, and How It Might Be Achieved

As emphasized previously in Chap. 10, contemporary immunosuppression plays a crucial role in maintaining the success of heart transplantation in the modern era. Unfortunately, life-long immunosuppression does not only prevent rejection and reduce the risk of subsequent poor outcomes. Long-term treatment also results in toxicity, particularly nephrotoxicity, as well as increased risk of infections and malignancy.

While there have been advances in immunosuppression in the last two decades, improvements in long-term survival have plateaued [1]. Future improvement in post-cardiac transplant survival is more likely to be achieved by targeting the mechanisms responsible for long-term mortality. This includes cardiac allograft vasculopathy, which is essentially a form of chronic rejection and could be targeted effectively by theoretical induction of tolerance. Furthermore, complete tolerance would lessen the need for immunosuppression, and thus reduce malignancy-related complications. In order to achieve the holy grail of acquired tolerance, one must understand the mechanisms behind chronic rejection and utilize novel strategies to abrogate them; much work is ongoing in this arena.

Manipulation of T- and B-cell Mechanisms

While the traditional methods of immunosuppression and previous attempts at inducing tolerance with agents such as ATG have targeted the pathways leading to activation of T-cells [2], recent research focuses on the role of regulatory T cells

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(T-regs) [3]. In the thymus, naturally occurring CD25+CD4+ T-regs that develop under the control of transcription factor Foxp3 suppress immune responses to foreign antigens in the context of both animal and human models of solid organ transplantation [3]. Furthermore, existing pharmacologic agents demonstrated to reduce rejection also increase T-reg frequencies [4]. Thus, these alloantigen-induced T-reg cells are able to prevent acute as well as chronic graft rejection. Interestingly, while these T-regs can be induced by alloantigen pretreatment [5, 6], the presence of the allograft as the source of donor alloantigen is essential for maintaining the unresponsive state [7]. The ability to generate and maintain these specific alloantigen reactive T-regs could theoretically induce tolerance in future, preventing rejection while remaining immunosuppression-free.

While B-cells are recognized more as antibody-secreting cells in the pathogenesis of rejection, they also function as antibody-presenting cells that interact with T-cells [8], leading to antibody mediated rejection, and express complement receptors through which adaptive immunity is regulated [9]. Analogous to the regulatory T-cell pathways mentioned previously, only recently have the immune-regulatory roles of B cells come to light; indeed, there is some evidence that they are increased in tolerant human renal transplant recipients, as compared to stable recipients receiving immunosuppression [10, 11], and their presence in tertiary lymphoid tissue may even regulate immune responses [12]. Pre-clinical models demonstrate that B-regulatory cells (B-regs) synergistically increase the number of T-regs [13], and secrete the anti-inflammatory cytokine IL-10 [14]. In humans the B cell subset CD19+CD24hiCD38hi secretes the highest amount of IL-10 in response to CD40 stimulation, compared to other peripheral blood B cell subsets [14]. However, like T-regs, the role of B-regs in the possible induction of tolerance remains to be fully defined; how these findings can subsequently be exploited to maintain tolerance remains to be seen.

Strategies to Achieve Chimerism

Chimerism, defined as the existence of two allogeneic cell lines, which would enable specific tolerance to donor antigens while simultaneously retaining the ability to fight infection and prevent malignancy, remains the ultimate goal. In recent years, researchers have attempted to establish central tolerance via transplantation of donor bone marrow. One study involving six human kidney transplant patients appropriately conditioned with non-myeloablative therapy, including cyclophosphamide, ATG and thymic irradiation, bone marrow transplantation has been demonstrated to induce tolerance requiring no immunosuppression. However, all reports of this method have resulted in loss of mixed chimerism within months of transplantation [15], possibly due to inflammatory responses [16].

A newer approach by Leventhal et al. [17], using bioengineered mobilized cellular product enriched for hematopoietic stem cells and tolerogenic graft facilitating cells combined with non-myeloablative conditioning, was employed in a recent study involving 19 kidney allograft recipients with highly mismatched donors. Thus far, 12 of the 19 patients have been effectively weaned off immunosuppression, with intact grafts and maintenance of stable mixed chimerism.

In the future, this early success of induction of stable mixed chimerism across HLA barriers may be achievable in the regular clinical practice of heart transplantation. A new clinical trial entitled "Bone Marrow Transplant to Induce Tolerance in Heart Transplant Recipients" is currently taking place at the University of Louisville [18] and results are keenly anticipated. Further tolerance-induction research will depend on two different aspects: further investigation of the mechanism of tolerance, and further studies to increase safety and broaden the applicability of initial studies using enhanced stem cell transplantation.

New Directions in Immunosuppression

Novel Immunosuppressive Agents

Given that it is unlikely that induced tolerance will be achieved in the near future, the use of immunosuppression medicine and immune monitoring will still be required. Thus, minimizing immunosuppression and immunosuppression-associated

complications while maintaining efficacy remains the goal of post-transplant management.

During the past few decades, new drugs have been added into post-transplantation clinical practice. From the development of more powerful and specific immunosuppressants, especially beneficial for sensitized patients (see Chap. 6), to new treatments for cardiac allograft vasculopathy (see Chaps. 10 and 12), advances in the science of immunology seem to hold the key to expanding the success of heart transplantation in our treatment of end-stage cardiac disease.

T-cell mediated acute cellular rejection remains a common issue post-transplant. A sustained T-cell response following antigen recognition requires costimulatory signals to be delivered through accessory T-cell surface molecules. An example of such a costimulatory pathway is CD28-B7. Inhibition of CD28 has been demonstrated in animal models to therefore result in reduced T-cell proliferation and prolonged allograft survival. This highly specific mechanism of immunosuppression may also negate the undesired adverse effects seen in other immunosuppressants. Belatacept is a humanized fusion protein, a homolog of CD28, which binds to the B7 molecule and inhibits its interaction with the true CD28. Currently, phase 3 trials are taking place with belatacept in kidney transplantation; phase 2 trials have shown that when used in combination with MMF, basiliximab and steroids, it allows safe avoidance of CNIs with good outcomes [19, 20].

Eculizumab, a humanized monoclonal antibody directed against the terminal complement protein C5, is also being investigated in a pilot trial in heart transplant recipients. By inhibiting the cleavage of C5, it prevents the formation of the membrane attack complex [21]. In sensitized renal transplant recipients with high levels of donor-specific alloantibody, peri-operative eculizumab administration is associated with significantly decreased incidence of early AMR [22]; the hope is that this finding will translate to cardiac transplant recipients.

Other new drugs under evaluation include drugs for maintenance therapy (anti-protein kinase C [23], anti-Janus kinase-3 [24], B-lymphocyte stimulator [25] and novel CNIs).

Personalized Medicine for Immunosuppression

As mentioned in Chap. 10, maintaining an optimal immunosuppressant level is crucial to suppress rejection, while avoiding infection. Currently, therapeutic drug monitoring, clinical evaluations, endomyocardial biopsy, echocardiography, and the T-cell immune assay are used as the principal tools for rejection monitoring during drug weaning.

However, pharmacogenetic polymorphisms may have the potential to predict future adverse events from certain immunosuppressants and more specifically, individual dosages of different immunosuppressants. For example, certain single nucleotide polymorphisms (SNP), such as the ones found in the CYP3AP1 pseudogene, which is strongly associated with hepatic CYP3A5 activity, are more common in African Americans. Subsequent studies have suggested that CYP3AP1 genotype is a major factor in determining the dose requirement for tacrolimus [26]; a recent pharmacogenetic analysis of tacrolimus that included a large group of African American patients post-kidney transplant showed that African Americans had consistently lower median troughs despite 60% higher daily doses. Furthermore, the CYP3A5*3 variant was associated with a reduction in troughs [27].

Nevertheless, genetic variations do not completely account for trough variability; clinical factors and other comorbidities also play a role [27]. Further explication of these pharmacogenetic mechanisms might lead to targeted dosing based on genetic profiling. Hopefully with further explication of these pharmacogenetic mechanisms [28, 29], dosing equations that use genotype and relevant clinical variables can be developed, in place of dosing based on weight. These equations may also be able to provide transplant physicians more personalized targets of immunosuppression for patients (rather than the current suggested "range").

Genomics for Rejection Monitoring and Outcome Prediction

The primary focus of care in organ transplant recipients has always been to prevent rejection. While this is currently achieved in many ways,

including monitoring of serum immunosuppressant levels, clinical assessments, echocardiography, tissue endomyocardial biopsy remains the gold standard. Unfortunately, as highlighted in Chap. 12, biopsy is an invasive process with potential complications, and rates of pathologist discordance remain high. Genomic medicine, a discipline that uses an individual's genomic information to help guide clinical care, offers an alternative, non-invasive avenue to monitor for rejection in the transplant recipient. Through the analysis of specific DNA, RNA and protein targets, genomics offers a personalized approach to organ rejection surveillance. Most appealing is that most genomic testing can be done in the form of a laboratory test without requirement for invasive procedures or hospitalization.

Gene Expression Profiling

While covered in depth in Chap. 12, gene expression profiling using the Allomap test remains the only FDA-approved non-invasive test in the surveillance of rejection, and in clinical trials is non-inferior to the endomyocadial biopsy for rejection surveillance in stable, low-risk patients greater than 2 months post-transplantation While the negative predictive value is extremely high at 99% (i.e. for predicting quiescent patients that do not require biopsy), positive predictive value remains low at 7%. Further retrospective cohort studies have subsequently demonstrated associations between Allomap score variability and risk of subsequent mortality [30, 31].

Donor-Derived Cell-Free DNA

Donor-derived cell-free DNA (dd-cfDNA) is a new modality currently under investigation. Like Allomap, it is a non-invasive blood test; it exploits the fact that the donor genome is separate and unique compared to the recipient genome, and that components of donor DNA can be detected in the serum of the recipient [32]. The basic principles behind dd-cfDNA testing in transplantation rely on the fact that rejection causes damage to donor graft cells, leading to the release of DNA fragments from the donor organ cells into the periphery. These fragments of dd-cfDNA can be detected and quantified, and assessed over time to correlate to clinical organ function [33].

The concept of dd-cfDNA testing was originally pioneered in sex-mismatched donor-recipient pairs in solid organ transplantation, with male donors and female recipients; the SRY gene marker of the Y-chromosome was employed as a target in order to detect dd-cfDNA in the periphery of recipients [34, 35]. Following on from this, a more universal approach not limited to sex-mismatched recipients was pioneered in liver/kidney/pancreas transplant recipients; instead of sex-specific DNA markers, DNA fragments released from apoptotic donor leukocytes were instead used as a DNA target, assessing for donor-specific HLA DR genes [36]. At 1 year post-transplant, donor specific HLA-DR genes were identified in 32% of the recipients. However, no correlation was found between the presence of donor HLA-DR and the incidence of rejection episodes.

The analysis of donor-specific HLA-DR, while useful in reinforcing the concept that dd-cfDNA could be found in recipients, was too specific and would have required specific assays to be developed for each donor-recipient pair. Thus, a broader approach was subsequently pioneered by Snyder et al., in which DNA from heart transplant donors and recipients was sequenced in a genome-wide manner [33]. Through genotype analysis, recipient plasma cell-free DNA was scoured for donor-specific alleles of single nucleotide polymorphisms (SNP) not present in the recipient's genome. The fractional concentration of dd-cdDNA compared to total cell-free DNA in each sample was subsequently calculated. These plasma samples were collected longitudinally and compared to concomitant endomyocardial biopsy samples assessed by pathologists for grading of rejection over the course of the first year post-transplant.

Based on these analyses, it was established that a dd-cfDNA value of 1.7% could be used as a threshold to generate an 83% true positive rate and 16% false positive rate for rejection. Furthermore,

a dd-cfDNA concentration below 1% appeared to demonstrate a "normal" value for healthy cardiac transplant recipients. In patients who experienced significant rejection episodes, the concentration of dd-cfDNA rose prior to clinical and histopathological evidence of rejection–but once treated for acute rejection, dd-cfDNA levels decreased to the baseline values found prior to rejection. These results have been duplicated in a prospective 65-patient study by De Vlaminick et al. in heart transplant recipients [37] and a 63-patient study by Grskovic et al. [38]; in the latter study, it was also noted that if dd-cfDNA did not fall greater than twofold after rejection treatment that there was a higher incidence of persistent low-grade rejection, suggesting insufficient treatment.

Interestingly, dd-cfDNA has also been demonstrated to be useful in detecting certain types of infection in transplant recipients. In lung transplantation patients with cytomegalovirus (CMV) infection, the level of dd-cfDNA has been used to differentiate infection versus rejection [39]. In this study, levels of dd-cfDNA enabled differentiation between no rejection vs. moderate to severe rejection. Notably, patients with CMV infection demonstrated elevated dd-cfDNA levels, but not to the degree of patients with rejection. In future, this application may have potential with regard to assessing clinically deteriorating patients in whom the diagnosis of rejection vs. infection must be made quickly.

Overall, these data support the idea that dd-cfDNA may be a useful biomarker for organ health, and theoretically would be advantageous over Allomap due to its high positive predictive value, its ability to be used before 2 months post-transplant (unlike Allomap), and its potential ability to be more useful for cases of antibody-mediated rejection. Larger, multicenter studies to further validate the use of dd-cfDNA monitoring are required. However, this type of SNP genome parallel sequencing of both the donor and recipient is expensive, and one would need to potentially maintain donor DNA samples years after transplant (for as long as the recipient is alive). Promisingly, a quick and more economical method using a combination of assays that allows for the detection of dd-cfDNA in a short time was recently developed [40]; in this study by Beck et al., they only used SNPs already investigated for their minor allelic frequency and that had frequencies greater than 40%. Using the Hardy-Weinberg principle, a SNP with a minor allelic frequency of between 40% and 50% would be found homozygous in both the donor and recipient in about 25% of cases for each allele. Based on this, the probability of both the donor and recipient having a different allele was calculated to be approximately 12.5%. Thus, to identify at least 3 SNPs no fewer than 30–35 different SNPs with the minor allelic frequency mentioned above would have to be scoured; this would require considerably less resources than the 3000 SNPs that would need to be analyzed if the SNPs were unselected.

Assessment of MicroRNA

The use of microRNAs (miRNA) as biomarkers of rejection represent another exciting recent development in the field of genomic medicine as applied to transplantation. miRNAs are a class of short RNA sequences that act as post-transcriptional regulators, binding to messenger RNA (mRNA) causing either degradation or silencing of the translation of mRNA. While there are only 1000 miRNAs (with more being detected), there are approximately 30,000 mRNAs, and thus one individual miRNA may regulate the expression of many mRNAs and have a widespread effect on gene expression. With regard to the detection of rejection, the microRNAs implicated in the regulation of B-cell and T-cell differentiation and function, T-cell receptor signaling, toll-like receptor signaling, cytokine production, T-regulatory cell function, and antigen presentation are of most interest [41]. These miRNAs can be found in plasma in stable form and are shed during cell turnover–which makes them potentially very useful for the purposes of a peripheral blood test to detect rejection. While investigation of miRNAs for detection of rejection initially began with intragraft miRNAs, given the high rate of pathologist discordance and need for more definitive biopsy diagnosis, the eventual

goal of genomic applications in transplantation is to avoid invasive biopsy procedures. Thus, newer miRNA research has also examined the potential of peripheral miRNAs, taking into account the need for an accurate non-invasive method of rejection detection.

The concept that miRNAs are differentially expressed during acute rejection was pioneered by Sui et al., who correlated biopsy samples with acute rejection with the expression of 20 intragraft miRNAs. They demonstrated in renal transplant patients that these miRNAs were differentially expressed in a specific pattern with 8 up-regulated and 12 down-regulated [42]. Despite the small sample size of 9 (3 with rejection, 6 controls), this study lent credence to the concept of defining an organ-specific signature or pattern of miRNA expression as a marker of rejection. A further validation cohort study by Anglicheau et al. [43], with a greater number of renal transplant recipients (33–7 in test cohort of which 3 had rejection, 4 were healthy, 26 in validation cohort), showed that the miRNAs of miR-142-5p, miR-155 and miR-223 predicted biopsy-proven acute rejection with a sensitivity and specificity greater than 90%. Notably, miR-155 is encoded within an exon of the gene B-cell integration cluster (*bic*), and B-cell and T-cell receptor activation as well as toll-like receptor activation leads to increased *bic* expression, suggesting a role of these processes in acute rejection [44].

The first study to translate this concept to peripheral miRNA was published in 2014 by Van Huyen et al. This study demonstrated that plasma levels of circulating miRNA could be used as a biomarker for the detection of rejection [45]. In this study, 14 miRNAs of interest were assessed, involving 4 associated with endothelium activation, 3 cardiac myocyte remodeling, and 7 associated with inflammation; the selection of miRNAs assessed was based on those previously known to be involved with graft rejection, cardiovascular pathogenesis, endothelial injury/activation, vascular inflammation, immune signaling pathways and T-cell activation. Tissue and plasma samples were collected from 60 heart transplant recipients, 30 of whom had acute rejection and 30 of whom were matched controls (matched on recipient and donor age, cold ischemic time, time from transplant to first biopsy, immunosuppression). Every patient had concomitant tissue biopsy for histopathology evaluation along with intragraft and peripheral miRNA analysis. Of the 14 miRNAs assessed, 7 were highly differentially expressed in intragraft biopsies, and 4 were highly differentially expressed peripherally, with strong statistical significance. Specifically, serum levels of miR-31, miR-92a and miR-155 were significantly higher in the sera of patients with rejection compared to normal and the level of miR-10a was significantly lower. A further cohort of 53 patients (31 with rejection, 22 healthy) further validated the ability of these 4 miRNAs to discriminate rejecting from non-rejecting samples; crucially, a subsequent subgroup analysis of those with cellular rejection versus antibody-mediated rejection (AMR) showed that these 4 miRNAs continued to differentiate between normal and either form of rejection. Furthermore, the 4 circulating miRNAs were differentially expressed in cases of rejection regardless of whether the rejection was early (<1 year post transplant) or late (>1 year post transplant) rejection.

While most studies assessing intragraft or peripheral miRNA have focused on their ability to discriminate rejection, other work has also been performed correlating miRNAs with other negative sequelae post-transplant such as development of CAV. A 52-patient (30 with CAV, 22 without) study by Singh et al. [46] assessed levels of five different miRNAs known to be associated with endothelial activation/injury and correlated them with the presence of CAV at the time of angiography; two of the miRNAs, miR-126-5p and miR-92a-3p, were found after multivariate analysis to be able to discriminate patients with CAV compared to those without.

Certainly, these studies confirm that both intragraft and peripheral circulating miRNAs have potential as viable biomarkers of rejection. Both acute cellular and antibody mediated rejection, as well as acute and chronic forms of rejection have been detected with high accuracy using this modality. This avenue of genomic medicine offers exciting potential, as they may be able to

help reduce or eventually replace the invasive endomyocardial biopsy for the screening of graft rejection.

Assessment of Molecular Messenger RNA

Assessment of molecular RNA, much like assessment of microRNA, seeks to define a definitive molecular signature or pattern of expression for rejection, given the current high rates of intra-pathologist discordance. Furthermore, with the conventional histopathological criteria, there are many "borderline" or ambiguous cases. To solve this problem, Halloran et al. [47], using data from kidney transplant biopsies and from the Genome Canada Study created a new disease classification for both ACR and AMR with the use of mRNA microarrays. This work was predicated on the notion that ACR classification is frequently ambiguous and that kidney transplant AMR is frequently C4d negative and has been greatly underestimated by conventional criteria. The use of microarrays helped to define the mRNA transcripts induced by acute kidney injury which correlated with reduced function. For example, expression of the endothelium-associated mRNA transcripts was increased in injured and diseased kidneys, with several increased in AMR. Based on the expression values of select mRNA transcripts for each biopsy, an AMR score was developed. The AMR score correlated with the presence of AMR microcirculation lesions and the detection of DSA and was high in both C4d-positive and C4d-negative AMR. The AMR score also predicted future graft loss in Cox regression analysis better than the conventional diagnosis of AMR.

In the realm of heart transplantation, there is limited research thus far on mRNA for discrimination of rejection. Of note, a recent study by Tible et al. [48] demonstrated that the biomarkers of phosphorylated 70 S6-kinase and phosphorylated S6 ribosomal protein are elevated in heart biopsies with AMR. Expression of these markers has been correlated with microcirculation inflammation and donor-specific antibody (DSA). Importantly, a 300-biopsy international multicenter study led by Halloran et al. (the INTERHEART study) correlating intragraft mRNA to biopsies and clinical outcomes is also currently underway [49]. Based on preliminary results, expression of transcript sets reflecting T cell and macrophage infiltration, and gamma-interferon effects correlated strongly with each other and with transcripts indicating tissue/myocardium injury. This molecular phenotype significantly correlated with Quilty, microcirculation lesions and decreased LVEF, but not with the histologic diagnosis of rejection. Furthermore, in multivariate analysis, LVEF was associated with gamma-interferon inducible transcripts, time post-transplantation, ischemic injury and clinically indicated biopsies, but not the diagnosis of rejection. These results suggest that the current ISHLT system for diagnosing rejection does not reflect the molecular phenotype in endomyocardial biopsy and lacks clinical relevance, and that interpretation of Quilty lesions has to be revisited. It is therefore hoped that further results from this study will help in establishing a molecular classification for ACR and AMR in heart transplantation, to improve the current diagnostic system.

Regenerative Medicine

Stem Cell Therapy

Central to the donor heart shortage is the high demand for donor hearts in the face of an increasing prevalence of end-stage heart failure necessitating transplant. Thus, a therapy that could cause the diseased heart to regenerate and regain function would be a panacea in this field. Over the last two decades, intense investigations into the injured heart and potential for cardiac regeneration have taken place, intersecting the fields of developmental biology, stem cells and biomaterials. While cardiac tissue has long been thought of as not being able to regenerate, unlike certain types of neural tissue, there is some recent evidence to suggest at least slow, limited plasticity in the adult human heart exists [50, 51]. The ultimate aim is to regenerate or create new myocardium that is electrically and mechanically integrated into the heart, and thus functions as

uninjured myocardium would. The field of stem cell biology is of particular interest and is the area in which greatest strides have been made in recent years.

A crucial question in stem cell therapy is the relevance of various cell types that might lead to cardiovascular cell generation if transplanted. Indeed, the mechanism of cell therapy is still poorly understood. From initial studies, it appeared that bone marrow mononuclear cells (BMCs) might be a viable therapeutic option [52–54], as they appeared to be able to transdifferentiate into cardiomyocytes following implantation and accordingly improve heart function. However, further research has since elucidated a more indirect mechanism involving downstream paracrine effect via angiogenesis and left ventricular remodeling [55]. Skeletal muscle stem cells, or myoblasts, have also been trialed, with some benefit, but there have been safety concerns with regard to arrhythmic events caused by the non-integrated skeletal muscle cells [56]. Further stem cell sources include cardiac progenitor cells (CPCs) [57], embryonic stem cells [58] or induced pluripotent stem cells [59, 60]; of these CPCs may be the most promising. In pre-clinical animal models, the injection of CPCs into infarcted cardiac tissue has been demonstrated to improve tissue viability and ventricular function [61, 62]. Recently, cardiosphere-derived cells growing from percutaneous endomyocardial biopsy right ventricular samples, which mix the heart-derived stem cell property together with mesenchymal stem cells, have also shown promising therapeutic benefits in animal models [61–63]. It has been postulated that these CPCs serve as "role models" as they stimulate endogenous regeneration and improve tissue resistance to ischemic stress [63]. Unfortunately, long-term cell engraftment rates after transplantation of stem cells remains low [64], and it may be that the benefits observed from these therapies are due to downstream paracrine effects exerted rather than direct regeneration of tissue from the transplanted cells.

There have been two phase I studies of cardiac derived stem cells in humans. The CADUCEUS (cardiosphere-derived autologous stem cells to reverse ventricular dysfunction) trial found that intracoronary infusion of autologous CDCs after myocardial infarction was able to safely decrease the size of infarct area [65]. The SCIPIO trial (cardiac stem cell infusion in patients with ischemic cardiomyopathy) also demonstrated this [66], as well as improved LVEF in ischemic cardiomyopathy patients treated with CDCs compared to controls. Certainly, these phase I results warrant further phase II investigation which is currently being planned. Overall, while the field of regenerative medicine is both intriguing and promising, the mechanisms of improvement are currently beyond our complete understanding.

Organ Engineering

The field of tissue engineering applies bioengineering principles with the aim of building biological substitutes for failing or absent tissues and organs. The bioartificial tissue would then be used as a "patch" on the diseased organ, while a bioartificial organ would be transplanted to replace the failing organ (or to take the place of an absent one). Traditionally, the engineering of a viable heart has been considered infeasible, given the complex nature of myocardium as a contractile tissue with specific structural and physiological specifications. However, much progress has been made in recent years.

Regarding cardiac tissue patches for the diseased heart, numerous new approaches have been explored. In rat models, neonatal rat cardiomyoctyes were cultured on Poly (N-isopropylacrylamide)-grafted polystyrene dishes and detached as a square cell sheet at 20 °C temperature. These sheets were stacked together through induction of a hydrophobic/hydrophilic surface switch to make thicker contractile sheets, eventually achieving a one-centimeter-thick engineered tissue layer. Following transplantation of these cell sheets onto infarcted rat hearts, cardiac performance was significantly improved and successful engraftment occurred [67]. With regard to human trials, a small Japanese clinical trial using autologous skeletal myoblasts in cell sheets demonstrated successful treatment of one patient

with dilated cardiomyopathy [68]. With advances in stem cell technology, more research is now focused on human cardiac tissue engineering rather than animal models [69]; it is now thought that that simultaneous tri-culturing of cardiomyocytes, endothelial cells and mesenchymal cells such as fibroblasts is required for survival and integration of engineered heart tissue with the host myocardium [70]. However, despite recent improvements, there remain inherent limitations to engineering mere sheets of tissue; engineering tissues with a functional thickness continues to be challenging in the absence of a complex vascular network to meet the high metabolic demand of the working heart.

Perhaps the most exciting concept is one of whole organ engineering; early studies by Taylor et al. [71, 72] have pioneered a method by which the whole deceased donor rat, pig or human heart is decellularized by detergent perfusion while still retaining a cellular vascular network throughout the extracellular matrix. This scaffold may be relined with functional autologous endothelial cells in the vessels, as well as autologous cardiac progenitor cells for the muscle spaces. Within as few as 8 days from stem cell transplantation, the engineered heart can contract again; indeed small animal models have shown engineered whole hearts to be contractile (to 2% of adult pump function) and drug-responsive [73]. While there is a long way to go, it may ultimately be whole organ engineering that provides the definitive answer to the donor heart shortage.

The Future of Transplantation: Where Transplantation May not Be Needed at All?

An ideal method of solving the donor heart shortage would be a solution where far fewer patients require transplant. As such, advances in the knowledge of mechanisms of heart failure and treatment as well as advances in mechanical circulatory support (as detailed in Chaps. 1, 2 and 17) are inextricably linked to the future of heart transplantation. Such advances in medications involve the novel agents of ivabradine and sacubitril/valsartan, which appear to greatly improve prognosis in the NYHA class II-IV cohort [74, 75]; with regard to advances in mechanical circulatory support, data from the INTERMACS registry demonstrates that continuous-flow LVADs are increasingly being used as destination therapy, with nearly half of implants now intended as such [76]. Continuing improvements in LVAD technology may eventually result in LVADs becoming a viable alternative to heart transplantation. Finally, while the total artificial heart is now commonly used and may be a long-term solution of the future, it does not yet offer comparable quality of life and survival to heart transplantation.

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