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Review Article

Surgical considerations for cardiac allograft rejection☆,☆☆,☆☆☆

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ABSTRACT

This article reviews the surgical considerations of cardiac allograft rejection after heart transplantation and describes current treatment modalities for the failing graft. Cardiac allograft rejection can be a moribund diagnosis, especially when it is acute and high grade. It is broadly categorized into hyperacute, acute cellular, and antibody-mediated rejection. Treatment includes a multitude of medical and immunomodulation therapies for graft recovery. Severe rejection requires mechanical circulatory support for hemodynamic stability to maintain end-organ function. Retransplantation for graft loss is the ultimate therapy; however, it portends poor outcomes.

Contents

1. Background

Cardiac allograft rejection is one of the most common causes of death of heart transplant recipients [1]. Close to a quarter of recipients experience graft rejection within the first year following transplantation, resulting in 10% of recipient fatalities [2]. Rejection is broadly categorized into hyperacute rejection, acute cellular rejection, and antibody-mediated rejection. In the absence of accurate noninvasive markers for allograft rejection, heart transplant recipients are routinely screened with endomyocardial biopsies which are obtained with a transcatheter bioptome. Three to five samples are usually taken from the right ventricular septum. Biopsy schedules vary across centers. At our institution, endomyocardial biopsies are obtained weekly for the first month, monthly up to 6 months, every other month for 6–

Abbreviations: ACR, acute cellular rejection; *AMR*, antibody-mediated rejection; *BiVAD*, biventricular assist device; *CNI*, calcineurin inhibitor; *DSA*, donor-specific antibody; *IABP*, intra-aortic balloon pump; *LVAD*, left ventricular assist device; *MCSD*, mechanical circulatory support device; *MMF*, mycophenolate mofetil; *PSI*, proliferation signal inhibitor; *RVAD*, right ventricular assist device; *TAH*, total artificial heart; *VAD*, ventricular assist device; *VA ECMO*, venoarterial extracorporeal membrane oxygenation.

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Table 1
Standardized cardiac biopsy grading for acute cellular rejection

Grade	Severity	Histologic findings
Grade 0	No rejection	Normal architecture
Grade 1R	Mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2R	Moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3R	Severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis

Modified from Stewart and colleagues [5].

12 months after transplantation, every 3 months for years 1–2 after transplantation, and every 4 months for years 2–3 after transplantation.

Hyperacute rejection occurs in the presence of preformed antibodies to the graft; it presents shortly after reperfusion of the graft and portends an inevitable and lethal immune reaction on the new organ. Primary graft dysfunction — a distinct disease process — is defined as ventricular dysfunction within the first 24 h after transplantation that is not associated with a discernible cause. The incidence of primary graft dysfunction is close to 8% (ranging from 2% to 28%) and is associated with a 30% thirty-day mortality rate [3]. Discerning between hyperacute rejection and primary graft dysfunction remains challenging. Hence, one may speculate that in some instances — in the absence of a biopsy — hyperacute rejection goes unrecognized and mischaracterized as primary graft dysfunction.

Acute cellular rejection is a T-cell-mediated response defined by widespread lymphocyte infiltration and myocardial injury [4,5]. The histopathologic grading system for acute cellular rejection set by the International Society for Heart and Lung Transplantation [5] is summarized in Table 1.

Antibody-mediated rejection is product of recipient antibodies specific to donor human leukocyte antigens, which trigger complement deposition in the graft endothelium and activation of inflammatory pathways leading to microvascular injury. The diagnosis of antibody-mediated rejection is vague and remains technically challenging; however, it usually occurs between 1 and 2 months after transplantation and is accompanied by a rise in donor-specific antibodies. The histopathologic grading system for antibody mediated rejection set by the International Society for Heart and Lung Transplantation [6] is summarized in Table 2.

Table 2
Formulation for pathologic diagnosis of cardiac antibody-mediated rejection

Grade	Definition	Substrates
AMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
AMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
AMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+).
AMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
AMR 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.

Modified from Berry and colleagues [6]. Abbreviations: AMR, antibody-mediated rejection; H, histologic; I, immunopathologic.

2. Incidence

The incidence of acute rejection 1 year after transplantation is 25% with substantial variability among age groups, with younger recipients being at the highest risk [7]. Hyperacute rejection is relatively uncommon since the advent of prospective cross-matching and panel reactive antibody screening. Acute cellular rejection is the most common form of cardiac allograft rejection and usually occurs within the first 6 months after transplantation; however, it may occur at any time after engraftment. The reported incidence of acute cellular rejection ranges between 5% and 6% in the first year after transplantation [8,9]. The incidence of antibody-mediated rejection is not clear given the evolving diagnostic criteria and absence of routine screening at most transplantation centers [10].

3. Evolution of heart transplantation

Several factors are changing in heart transplantation that will likely have an impact on the incidence and management of cardiac allograft rejection. Bridging patients to transplantation with a ventricular assist device is a fundamental component of heart failure and waitlist management (see Section 5.2). Ventricular assist device utilization is associated with new human leukocyte antigen allosensitization [11,12]. Patients with ventricular assist device-associated sensitization are at higher risk of developing acute cellular rejection (hazard ratio of 2.99, P=.049) and antibody-mediated rejection (HR 3.41, P=.018) [13].

The disproportionate growth rate of the waitlist in comparison with the donor pool is constantly pushing transplant centers to consider high-risk or marginal organ donors. Recent alternatives to expand the donor pool are utilization of hepatitis C viremic donors [14], ex vivo heart perfusion systems [15], and donation after circulatory death [16]. It is unclear how these alternatives will impact the rate of cardiac allograft rejection. Close surveillance of these recipients is mandatory to ensure providing equivalent patient outcomes.

4. Procedural considerations

The operative technique of heart transplantation portends several anatomic and physiologic changes of clinical relevance. The cardiac plexus is divided during cardiectomy, and the graft is initially devoid of direct neuronal stimulation. Denervation prohibits recipients from experiencing ischemic angina and leads to the loss of reflex tachycardia to increase cardiac output during exercise [17]. One must rely on clinical signs or electrocardiographic changes to identify myocardial ischemia in the transplant recipient. Sympathetic cardiac reinnervation usually occurs 18 months after transplantation and parasympathetic reinnervation up to 24 months after transplantation [17].

Surgical implantation involves five major anastomoses: superior vena cava, inferior vena cava, left atrial cuff, ascending aorta, and pulmonary artery. The anastomotic line of the left atrial cuff lies close to the left circumflex coronary artery as it traverses the lateral border of the heart and the coronary sinus. Injury to either of these structures requires immediate surgical repair, usually with a bypass graft or a pericardial patch. The right phrenic nerve lies near the venae cavae and care must be taken to preserve its integrity. The sinoatrial node lies at the junction of the right atrium and the superior vena cava. A high degree of suspicion is required to identify surgical injury in the early postoperative period.

5. Treatment options

5.1. Medical therapy

Asymptomatic grade 1 rejection does not warrant treatment and may be followed with repeat endomyocardial biopsies given that only 18% of patients progress to moderate or severe rejection [18]. More

Table 3
Treatment options for cardiac allograft rejection

Grade	Asymptomatic	Reduced ejection fraction	Heart failure or shock
Hyperacute rejection	-	Immediate plasmapheresis and IV immune globulins	Mechanical circulatory support or retransplantation
ACR grade ≥2	Target higher CNI levels Oral steroid bolus and taper MMF to PSI	Oral steroid bolus and taper or IV pulse steroids	Treat based on clinical presentation, do not await biopsy findings IV pulse steroids
AMR grade ≥2 with no DSA	Target higher CNI levels MMF to PSI	IV pulse steroids Consider IV immune globulins	Cytolytic therapy Plasmapheresis
AMR grade ≥2 with increased DSA	Oral steroid bolus and taper MMF to PSI	IV pulse steroids IV immune globulin Consider ATG, rituximab, bortezomib	IV immune globulin Inotropic therapy IV heparin Mechanical circulatory support

Modified from Kim and colleagues [25]. Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; CNI, calcineurin inhibitor; DSA, donor-specific antibodies; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor; IV, intravenous.

serious histological findings or presence of signs and symptoms requires hospitalization and antirejection therapy. Table 3 summarizes the intensity of antirejection medical treatment based on histologic and clinical findings. Corticosteroids are the foundation of medical therapy, and escalation consists of utilizing calcineurin inhibitors, cell cycle agents, proliferation signal inhibitors, and monoclonal antibodies. Consideration of mechanical circulatory support should happen early in recipients with hemodynamic instability as an adjunct of maximal medical therapy to prevent end-organ dysfunction from hypoperfusion.

5.2. Mechanical circulatory support

Circulatory support is warranted in the setting of hemodynamic instability or circulatory collapse regardless of rejection severity. Table 4 summarizes the characteristics of current modalities for temporary mechanical circulatory support. Therapy may vary based on degree of shock, institutional availability of support modalities, and surgeon preference.

5.2.1. Extracorporeal membrane oxygenation

Venoarterial extracorporeal membrane oxygenation may provide immediate circulatory support at high flow rates and, depending on cannulation strategy, may provide ventricular offloading. It differs from cardiopulmonary bypass in the absence of a blood reservoir — which exposes blood to an air interface and is considered to contribute its characteristic systemic inflammatory response — and utilization of oxygenators designed for longer runs. In recent years, extracorporeal membrane oxygenation has gained widespread adoption given ease of use and versatility. In an observational case series, Takeda and colleagues reported improved outcomes in recipients suffering from primary graft dysfunction when compared to ventricular assist devices [19]. We expect that this rescue modality will continue to gain popularity in the postoperative care of transplant recipients as the newly implemented heart allocation criteria grant higher urgency to patients on extracorporeal membrane oxygenation (see Fig. 1) and may expedite retransplantation.

5.2.2. Ventricular assist devices

Most devices utilized for circulatory support rely on continuous flow and are usually clustered into temporary support devices (such as those summarized in Table 4) or durable support devices (such as the HeartMate and HeartWare devices). Temporary percutaneous devices are relatively easier to deploy and are gaining widespread adoption. Durable devices are utilized less frequently as a salvage for recipients experiencing early graft dysfunction as their implantation is permanent and they require preoperative patient evaluation by a multidisciplinary heart team. However, one must acknowledge the increased utilization of durable ventricular assist devices in candidates prior to transplantation. Fig. 2 illustrates the increasing proportion of heart transplant candidates who are bridged with a left ventricular assist device. These data from the Organ Procurement and Transplantation Network demonstrate that one of every two heart recipients is bridged with a ventricular assist device. The 1- and 2-year survival rate of patients with continuous-flow ventricular assist devices is 81% and 70%, respectively [20]. While these are excellent outcomes, ventricular assist devices are not completely devoid of morbidity. Sixty percent of patients require rehospitalization, and 50% suffer a major event (i.e., device malfunction, infection, bleeding, stroke, or death) within 6 months of implantation [20]. It is not clear whether these outcomes translate to recipients who undergo ventricular assist device implantation for graft rejection.

Table 4
Temporary mechanical circulatory support devices available

	IABP	VA ECMO	Centrimag	Impella 2.5	Impella 5.0	Tandem Heart	Impella RP	Protek Duo
Support	Afterload reduction ± improved coronary blood flow	Left, right, or biventricular	Left or right ventricle	Left ventricle	Left ventricle	Left ventricle	Right ventricle	Right ventricle
Flow	-	Up to 10 L/min	Up to 10 L/min	2.5 L/min	5 L/min	5 L/min	4 L/min	4 L/min
Insertion	Percutaneous	Open/percutaneous	Open/percutaneous	Percutaneous	Open/percutaneous	Open/percutaneous	Percutaneous	Percutaneous
Oxygenation	None	Yes	Optional, may add oxygenator	None	None	None	None	Yes
Durability (off-label)	Days	Days–weeks	Weeks	Days	Days	Weeks	Days	Weeks

Abbreviations: IABP, intra-aortic balloon pump; VA ECMO, venoarterial extracorporeal membrane oxygenation.

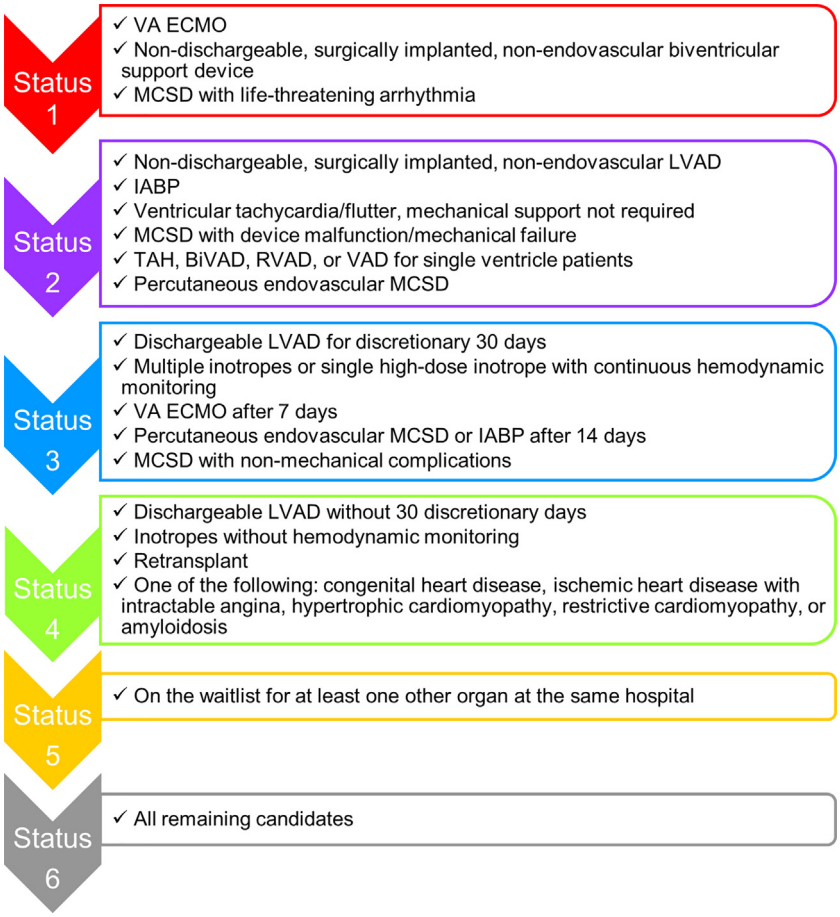

Fig. 1. Adult heart allocation criteria for medical urgency. Modified from https://optn.transplant.hrsa.gov/. Abbreviations: BiVAD, biventricular assist device; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MCSD, mechanical circulatory support device; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device; VA ECMO, venoarterial extracorporeal membrane oxygenation.

5.2.3. Total artificial heart

The total artificial heart is indicated to treat end-stage biventricular failure. This device has not gained widespread popularity from suboptimal outcomes, robust alternatives, and relatively high cost. Until recently, this device relied on positive-displacement pumps which lack the durability and reliability of rotary pumps [21]. The total artificial heart is benchmarked against durable ventricular assist devices which have consistently provided superior outcomes and increased durability [22]. The 1- and 2-year survival of patients with a total artificial heart is 52%

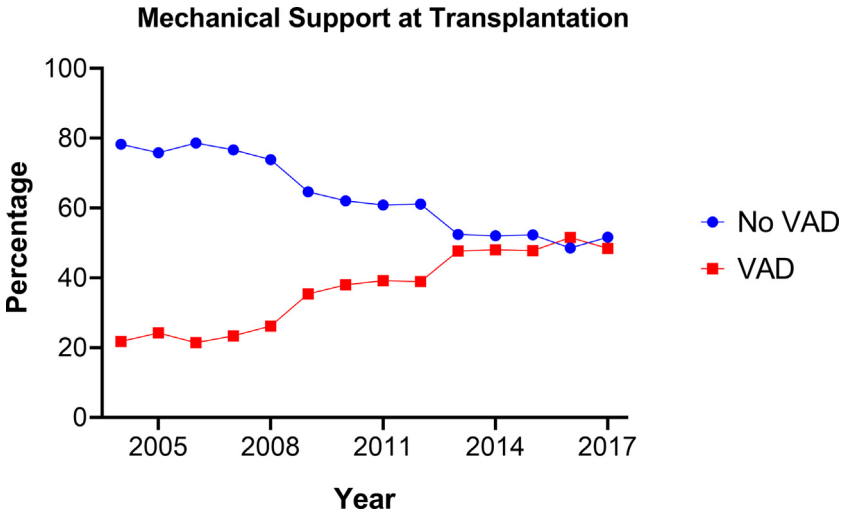

Fig. 2. Proportion of mechanical support at the time of transplantation over time. From the Organ Procurement and Transplantation Network database as of March 9, 2018. Abbreviation: VAD, ventricular assist device.

and 37%, respectively [20]. There are no substantial reports that examine whether these outcomes would translate to recipients who suffer from graft rejection. In addition, implantation of a total artificial heart requires cardiectomy, and any instance of pump failure results in abrupt hemodynamic collapse and circulatory arrest.

5.3. Retransplantation

Acute retransplantation confers a high risk of early perioperative death. Iribarne and colleagues reviewed patients who underwent retransplantation within 90 days in the United States and reported diminished survival in these recipients [23]. The 1-year survival rate of recipients who underwent acute retransplantation was 57% in comparison with 87% for primary transplant recipients.

The outcomes of patients that undergo repeat transplantation for graft rejection are poor. The Eurotransplant collaborative reported that 3% of all heart transplants performed in Europe are repeat transplants [24]. The 1-year survival of recipients retransplanted for graft rejection is 52% and only 40% for those that experience primary graft dysfunction. These outcomes are dismal in comparison with the average 1-year survival rate (78%) of other heart transplant recipients in Europe.

Retransplantation for graft rejection is rarely performed. Smits and colleagues described a shift in practice from the 1990s when half of retransplantations were done for graft rejection [24]. Conversely, over the past decade, only four retransplantations were done for graft rejection across all European centers. This shift occurred in recognition of suboptimal outcomes and scarcity of organs available for transplantation.

6. Conclusion

Cardiac allograft rejection can be a moribund diagnosis, especially when it is acute and high grade. Treatment includes a multitude of medical and immunomodulation therapies for graft recovery. Severe rejection requires mechanical circulatory support for hemodynamic stability to maintain end-organ function. Retransplantation for graft loss is the ultimate therapy; however, it portends poor outcomes.

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