# Chapter 10
# Right Heart Failure After Cardiac Transplantation

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## Case

A 40-year-old woman with history of Hodgkin's lymphoma, status post mediastinal radiation at ages 8 and 11, complicated by development of coronary artery disease and valvular heart disease, initially presented to the surgical intensive care unit (SICU) after aortic valve replacement, mitral valve replacement and tricuspid valve annuloplasty. She developed cardiac arrest and was cannulated for veno arterial extracorporeal membrane oxygenation (VA ECMO). She was urgently listed as a United Network for Organ Sharing (UNOS) status 1 candidate for orthotopic heart transplantation (OHT). She underwent OHT with a cold ischemic time of 200 min and warm ischemic time of 60 min. While in the

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operating room following heart transplantation, her hemodynamic data were as follows: right atrial pressure (RAP) 20 mmHg, right ventricular (RV) pressure 50/20 mmHg, and pulmonary artery (PA) pressure 50/36 mmHg, cardiac output 4 L/min, and cardiac index of 1.9 L/min/$m^2$. Her pulse was 100 bpm, blood pressure was 89/50 (MAP 63) mmHg, $O_2$ saturation 89% on a combination of epinephrine 6 mcg/min, milrinone 0.5 mcg/kg/min, norepinephrine 8 mcg/min, and inhaled epoprosterenol 30 ng/kg/min.

## 10.1 What Is the Differential Diagnosis?

The initial hemodynamic data suggests acute post-operative RV failure. The differential diagnoses in right heart failure (RHF) in a transplanted heart include: primary graft dysfunction (PGD), hyperacute rejection (HAR), post-operative pulmonary embolism and surgical complication.

PGD has been reported in 2.3–28.2% of patients undergoing OHT [1–5]. This range reflects the various definitions of PGD prior to the consensus definition established by the International Society of Heart and Lung Transplantation (ISHLT) in 2014 [6]. Of patients with PGD, isolated RV graft dysfunction and combined biventricular dysfunction occur in about 45% and 47% of patients respectively [7].

The diagnosis of PGD must be made within 24 h of OHT. The ISHLT hemodynamic definition of PGD-RV, shown in Table 10.1, refers to a right atrial pressure greater than 15 mmHg or a pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and cardiac index (CI) less than 2.0 L/min/$m^2$. A transpulmonary gradient (TPG) less than 15 mmHg with pulmonary artery systolic pressure (PASP) less than 50 mmHg is also suggestive. The need for a right ventricular assist device (RVAD) clearly suggests RV failure [6].

The RV is vulnerable to injury during the transplantation. Severe RHF can result from mechanical trauma, air embolism of the right coronary artery, severe tricuspid regurgitation and cardiac tamponade leading to increased RV filling

Table 10.1 Criteria for primary graft dysfunction—right ventricle

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|---|
| 1. RAP >15 mmHg<br>PCWP <15 mmHg<br>CI <2.0 L/min/m$^2$ |
| 2. TPG <15 mmHg ± PASP <50 mmHg |
| 3. Need for RVAD |

*RAP* right atrial pressure, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *TPG* transpulmonary pressure gradient, *PASP* pulmonary artery systolic pressure, *RVAD* right ventricular assist device
Adapted from Kobashigawa et al. [6]

pressures and RV dysfunction [8–10]. Immediately after OHT, there can be reperfusion and ischemic injury to the procured heart leading to right ventricular dysfunction [8, 11, 12]. Efforts are made to reduce ischemic time as much as possible, but may be limited in several situations.

Hyperacute rejection (HAR) is a rare and devastating complication that can occur post OHT with a mortality rate of about 70% [13, 14]. Its occurrence has been dramatically reduced by ensuring ABO compatibility among donors and recipients, though this complication can occur in the setting of preformed anti-HLA antibodies to the donor heart. HAR typically causes biventricular dysfunction.

Severe deconditioning postoperatively can predispose to pulmonary emboli. The incidences of venous thromboembolism (VTE) and pulmonary emboli have been reported as frequent complications [15, 16]. Acute pulmonary emboli can cause elevated pulmonary artery pressures leading to RHF. Chapter 6 highlights three cases of RHF due to pulmonary embolism.

## 10.2 What Is the Initial Approach in Elucidating the Etiology?

The initial assessment of post-transplant cardiac function is completed while the patient remains on cardiopulmonary bypass in the operating room. Per ISHLT guidelines, peri-

operative monitoring should include continuous ECG-monitoring, post-operative 12-lead ECG, invasive arterial pressure monitoring, direct measurement of RAP or central venous pressure (CVP), intermittent measurement of cardiac output, continuous measurement of arterial oxygen saturation, transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE), and continuous measurement of urinary output [17].

If there is allograft dysfunction of unclear etiology, a TTE or TEE may need to be repeated. In the event that there is hemodynamic compromise without a clear cause, particularly if filling pressures are equalized and elevated, the patient should return to the operating room to exclude cardiac tamponade by direct surgical exploration. If the patient requires mechanical support, a myocardial biopsy should be considered during the operation to evaluate for significant rejection [17].

Screening panel reactive antibodies are performed in all patients being considered for OHT [17]. Postoperatively, an immediate retrospective donor recipient crossmatch is run to screen for anti-HLA antibodies that can cause antibody mediated rejection (AMR). Donor-specific antibodies should be sent when there is a high suspicion for AMR, in which case an endomyocardial biopsy may need to be performed sooner than the periodic post-transplant schedule established by transplant centers.

## 10.3 What Is the Hemodynamic Assessment in a Transplanted Heart?

On invasive hemodynamic monitoring, attention should be given to the ratio of the right-sided compared with the left-sided pressures as well as pulmonary pressures in order to monitor for significant right-sided heart cardiac dysfunction. Chapter 9 also discusses the hemodynamic assessment in right ventricular cardiogenic shock. A normal RAP/PCWP ratio is about 0.5; an elevated ratio along with absolute elevations in RAP is suggestive of significant RV dysfunction [18, 19].

Pre-existing pulmonary hypertension can predispose to PGD. The exposure of an RV accustomed to normal pulmonary vascular resistance (PVR) in the donor to elevated pulmonary pressures in the recipient can result in circulatory collapse, which was first demonstrated in the 1950s in an animal model [20].

Preoperative PVR ≥ 3.0 Wood units or TPG ≥ 15 mmHg should warrant a vasodilator challenge [21–24]. PVR is calculated by taking the difference between the mean PA pressure and the PCWP and dividing that by the cardiac output (Eq. (10.1)). Preoperative PVR elevation is associated with increased mortality even when reversible [23, 25, 26]. PVR is useful to monitor the need and effectiveness of pulmonary vasodilators postoperatively. TPG is the difference between the mean pulmonary arterial pressure and PCWP (Eq. (10.2)). Additionally the pulmonary artery pulsatility index (PAPi), which is calculated by dividing the difference between the systolic pulmonary artery pressure and diastolic pulmonary artery pressure by the mean RAP (Eq. (10.3)), is predictive of RHF when using a cut off <1.0 [27]. While these values have not been studied in RHF with heart transplant specifically, it is reasonable to consider these parameters when evaluating the status of the right ventricle.

$$TPG = PA_{mean} - PCWP \tag{10.1}$$

$$PVR = \frac{PA_{mean} - PCWP}{CO} = \frac{TPG}{CO} \tag{10.2}$$

$$PAPi = \frac{\left(PA_{systolic} - PA_{diastolic}\right)}{RAP} \tag{10.3}$$

**Case Discussion**

Intraoperative TEE revealed preserved LV ejection fraction (EF) but severely hypokinetic RV. There was no evidence of cardiac tamponade or perforation. The clinical picture at this point was consistent with right ventricular dysfunction post-OHT.

## 10.4 What Are the Predictors of RHF Post OHT?

The RADIAL score is a validated scoring system that was developed to identify those at risk for PGD [5]. The score is based upon six multivariate risk factors: RAP ≥10 mmHg, recipient age ≥60 years, diabetes mellitus, inotrope dependence, donor age ≥30 years, ischemic time ≥ 240 min. Each criterion is assigned a point with increasing scores being at higher risk of PGD. Although this model was created for PGD, it also applies to isolated RV dysfunction [7].

Alhough the RADIAL score is helpful, it is important to note that it was derived and validated in a population of transplant recipients with a low prevalence of ventricular assist devices (VADs). A more contemporary cohort of patients, including those with continuous flow left ventricular assist devices (CF-LVADs) undergoing heart transplantation, was evaluated to determine risk factors [28]. In this study, patients with bridge to transplantation (BTT) CF-LVADs were at increased risk of PGD. Furthermore, increased time on device support, renal dysfunction, RV dysfunction, and pre-transplant amiodarone were associated with increased risk of PGD. The RADIAL score was evaluated in this study and did not appear to stratify risk in this contemporary cohort of patients.

## 10.5 Discuss the Pathophysiology of Acute RHF After Heart Transplantation

Early donor heart dysfunction is common as the heart has been denervated by the procurement and is dependent upon circulating catecholamines for chronotropy and inotropy. Initial donor heart dysfunction is common and occurs in up to about 50% of donor grafts [6]. The etiology is often multifactorial given the anatomy, location and physiologic stress experienced by the RV [29]. The RV of the heart graft is

susceptible to periprocedural myocardial strain, ischemia, cardioplegia and surgical trauma.

The donor heart goes through a series of events during procurement and implantation which could trigger RHF. These mechanisms of RHF are summarized in Fig. 10.1. The four main physiologic insults are brainstem death of the donor, hypothermic ischemia during transportation, warm ischemia during surgery, and reperfusion injury upon release of the cross-clamp [6].

The process of brainstem death creates a harsh environment that sensitizes the heart to ischemia-reperfusion injury. During brainstem death, a reduction in vasomotor tone leads to vasodilation. In order to counteract vasodilation, an immediate release of myocardial norepinephrine leads to mitochondrial and cytosolic calcium overload to help improve contractility [30]. This mitochondrial calcium can also trigger autophagy, apoptosis or necrosis. The calcium overload in the contractile proteins leads to contracture and is associated

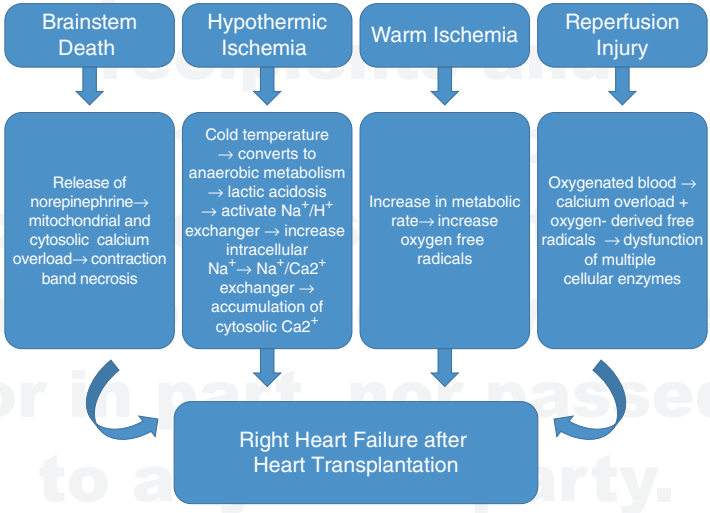


Figure 10.1 Summary of the pathophysiology of right heart failure in the transplanted heart

with the histologic appearance of "contraction band necrosis" [30–33]. During brain herniation, ischemia of the pituitary gland often occurs, leading to the derangement of the endocrine system further causing decreased contractility [34, 35]. In addition, there is a predilection for metabolic derangements to occur due to medications used to treat increased intracranial pressure and impaired myocardial oxygen delivery along with increased myocardial oxygen demand from catecholamine administration [30].

Following cross-clamp, the heart is perfused with a cold cardioplegic solution for transportation. There are several different hypothermic preservation systems available that slow but do not completely stop cellular metabolism [6, 36–38]. The goal is to reduce the formation of mitochondrial metabolism byproducts such as oxygen free radicals. The risk for ischemic injury is higher in older donor organs [39]. This risk may be related to unrecognized coronary artery disease, hypertrophy, or age-related decline in cardioprotective mechanisms [40, 41]. Due to the cold temperatures, around 4 °C, the metabolism is converted from aerobic to anaerobic. The loss of an aerobic environment inhibits the $Na^+/K^+$ ATP pump leading to cellular swelling. The anaerobic environment leads to lactic acidosis which activates the $Na^+/H^+$ exchanger increasing intracellular $Na^+$. The increase in intracellular $Na^+$ drives the $Na^+/Ca^{2+}$ exchanger which results in accumulation of cytosolic $Ca^{2+}$ [42–45].

When the donor heart is brought into the OR, it is removed from the hypothermic storage system. The donor organ is exposed to higher temperatures and this leads to an increase of the metabolic rate. The increase in metabolic rate increases the production of oxygen free radicals. Multiple studies have demonstrated deleterious effects of warm ischemic time on early survival in patients [3, 46].

Ischemia-reperfusion injury occurs when there is myocyte damage as a result of the restoration of oxygenated blood to the grafted heart. The introduction of oxygenated blood causes further calcium overload and oxygen-derived free radicals that lead to dysfunction of multiple cellular enzymes [47]. The release of calcium and oxygen free radicals activates

the formation of mitochondrial permeability transition pores (MPTP), which are non-specific channels that allow pro-apoptotic factors to be released into cell cytoplasm [48]. These factors lead to a mitochondrial swelling that can cause membrane rupture resulting in necrotic cell death and myocardial damage.

Recipient factors can also contribute to right ventricular failure. Underlying elevated PVR in the recipient along with the potential donor heart too small for a large recipient can overwhelm the RV of the donor heart causing right ventricular failure. Increased recipient PVR can trigger RHF in a donor heart that is in an ischemic state after procurement. Consequently, there is reduction of left-sided preload, which then results in a reduction of coronary perfusion and further decompensation [49].

Activation of the systemic inflammatory response syndrome (SIRS) results in lower systemic vascular resistance from vasodilation in some recipients [50]. Predisposing factors to SIRS activation include prolonged inotropic support, prolonged cross-clamp time, mechanical support prior to transplant, and recipients with high transfusion requirements [51, 52]. The exact pathophysiology is unclear though it is thought to be related to unopposed activation of vascular smooth muscle adenosine triphosphate sensitive potassium channels. Endogenous nitric oxide and vasopressin deficiency have also been considered as causes [52].

***Case Discussion***

Our patient had an elevated RADIAL score going into transplant based upon the total ischemic time, her inotrope dependence, and elevated RAP ≥10 mmHg. Additionally, she was transplanted from mechanical support and had multiple transfusions from her prior surgery. Furthermore, given her history of mediastinal radiation, there was concern that she may have had underlying lung disease.

## 10.6 How Should Post-operative Acute RHF Be Treated?

The initial management of acute RHF involves four main management strategies: preload optimization, hemodynamic stabilization, maintenance of sinus rhythm and AV synchrony, and ventilatory support. This approach is summarized in Fig. 10.2 [53]. Initially, medical therapy of RHF should be undertaken with inotropic agents to augment RV function and α-adrenergic agonists to support the blood pressure. Systemic vasodilators with pulmonary vasodilating properties can be used in the absence of systemic hypotension to reduce

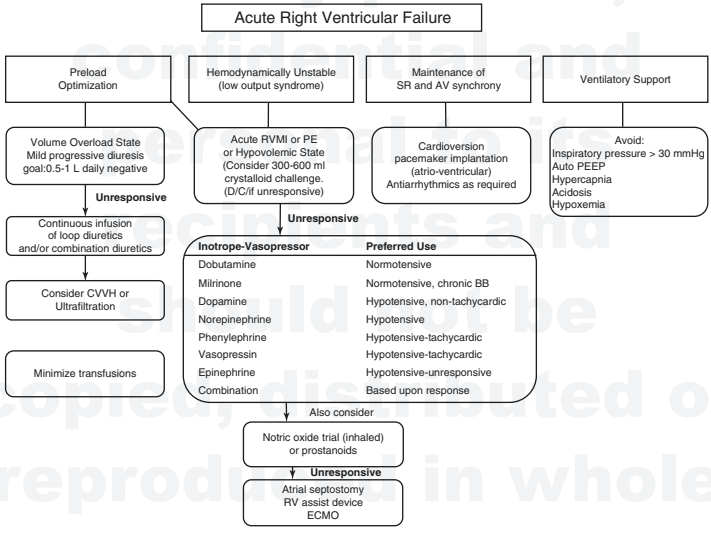


FIGURE 10.2 Management of right ventricular dysfunction after OHT. *CVVH* continuous venovenous hemofiltration, *RVMI* right ventricular myocardial infarction, *PE* pulmonary embolism, *D/c* discontinue, *BB* beta blocker, *RV* right ventricle, *ECMO* extracorporeal membrane oxygenation, *SR* sinus rhythm, *AV* atrioventricular, *PEEP* positive end-expiratory pressure; Used with permission from Wolters Kluwer Health, Inc. [53]

pulmonary afterload; these include nitroglycerin and sodium nitroprusside. Furthermore, selective pulmonary vasodilators including prostaglandins, inhaled nitric oxide, and sildenafil can be used in the management of RHF [54–62].

After heart transplantation, the preload should be optimized by monitoring invasive CVP. It is critically important to maintain CVP values below 15 mmHg in order to avoid venous congestion of abdominal organs and end-organ dysfunction. This goal can be achieved through initial diuresis to counteract positive fluid balance early in the postoperative course. Ultrafiltration or continuous venovenous hemofiltration may be necessary if there is diuretic refractoriness. If patients are not in sinus rhythm, cardioversion (chemical or electrical) can be considered as well as pacing in order to maintain AV synchrony. Finally, the ventilator settings should be optimized to reduce the workload on the heart including the limitation of inspiratory pressure, avoiding auto PEEP, control of hypercapnia, avoidance of acidemia, and hypoxia.

Prior to the advent of short-term mechanical support, severe PGD was fatal except when salvage re-transplantation was available. At present, both short-term and durable mechanical support should be considered if a patient is unresponsive to medical therapy. The device choice depends on how long the device may need to be in place and whether the patient will be extubated and be ambulated while on mechanical support. Temporary RVADs including RP-impella (Abiomed, Danvers, MA, USA) can be used for a short period of time only. ECMO outcomes have been evaluated in transplant patients with improved survival and ability to wean [1, 63]. More durable temporary RVAD support can be used with Centrimag (Levtronix, Waltham, MA), which allows patients to be extubated and rehabilitated. In the event that there is no recovery of the grafted heart, a redo-OHT can be considered. The key to mechanical support is early intervention when it is required. A delay in the use of mechanical support can to lead to higher mortality [64]. Chapter 9 reviews the indications and role for both percutaneous and surgical mechanical support for RHF. Any patient

who receives mechanical support should have a heart biopsy as discussed earlier [6].

**Case Conclusion**

Due to refractory RHF despite epinephrine 6 mcg/min, milrinone 0.5 mcg/kg/min, norepinephrine 8 mcg/min, and epoprosterenol 30 ng/kg/min, this patient was centrally cannulated for VA ECMO. RP impella and tandem heart were considered, but given her hypoxia, VA ECMO was selected. She was medically optimized with continuous infusion intravenous furosemide for aggressive diuresis in combination with ECMO to lower her CVP. In this context, inotropes were gradually weaned off, and subsequently, ECMO was decannulated.

**Clinical Pearls**

- The differential diagnoses for RHF in a transplanted heart include: primary graft dysfunction, hyperacute rejection (HAR), post-operative pulmonary embolism and surgical complication.
- The perioperative assessment of the transplanted heart should include continuous telemetry monitoring, invasive arterial and pulmonary artery catheter pressure monitoring, and urinary output monitoring.
- The pathophysiology of RHF typically involves recipient (elevated PVR, previous mechanical support, blood transfusions), donor (size mismatch, brain stem death) and surgical factors (reperfusion injury, prolonged cold or ischemic time).
- The initial management of acute RHF involves four main management strategies: preload optimization, hemodynamic stabilization, maintenance of sinus rhythm and AV synchrony, and ventilatory support.
- The key to mechanical support is early intervention when it is required.

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