Right Ventricular Dysfunction Post-Heart Transplantation

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Abstract

Right ventricular dysfunction is prevalent following orthotopic heart transplantation. The sequential insults of donor brain death, cardioplegia, ischemia, reperfusion injury and cardiopulmonary bypass interact together with raised recipient pulmonary vascular resistance to produce this common complication. Early recognition is important because the principles of management, which hinge on avoiding volume overload, inappropriate inotropic support, and the maintenance of adequate blood pressure to maintain coronary perfusion, differ substantially from other forms of acute heart failure. With improved management, and in particular, the availability of selective pulmonary vasodilators and advances in mechanical circulatory support, the prognosis has improved considerably within the last two decades.

Keywords

Right ventricle • Right ventricular failure • Primary graft failure • Heart failure • Catecholamine cardiotoxicity • Brain death • Orthotopic Heart Transplantation • Pulmonary hypertension

Introduction

Since the earliest heart transplantation series, right ventricular (RV) dysfunction has been a recognized component of primary graft failure (PGF) and an important contributor to early mortality [1]. In 1992, Costard-Jäckle reported a 6.6% incidence of RV failure (RVF) in the Stanford adult experience in the cyclosporine era, and found a 50% early mortality in patients with RVF [2]. Cosío Carmena reported a 22% incidence of PGF, with RV dysfunction predom-

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inating in 45% and contributing to a further 47% of cases. Patients with PGF experienced a 90-day mortality of 53% in this series [3]. Similarly, pediatric heart transplant series report a 4.2% [4] to 27.2% [5] early mortality, with PGF comprising 2.1% [4] to 20% [6]. Where explicitly stated, early mortality attributed to pulmonary hypertension or right ventricular failure ranged from 2.3% [7] to 8.3% of transplants [8].

Tracking the incidence of RV dysfunction after transplantion has been hampered by the absence of a consensus definition of PGF until recently [9]. As a result, within clinical registries, this important outcome is subsumed under the categories of "primary graft failure," "pulmonary hypertension," and "ventricular failure," which prevents consistent identification of patients retrospectively. This limits accurate estimation of the incidence of RVF, outcomes, predictive factors, and how the impact of these factors has changed over time. Nonetheless, understanding of the predisposing factors and the physiology of this complication has improved in the last three decades. This, together with the availability of more selective pulmonary vasodilators and advances in mechanical circulatory support, has better equipped clinicians to pre-empt and manage this complication.

This clinical scenario is uniquely prevalent following heart transplant because of the requirement for an "untrained" donor right ventricle to meet the afterload imposed by increased recipient pulmonary vascular resistance (PVR). Further, the donor heart bares the sequential insults of donor brain death, cardioplegia and ischemia-reperfusion injury, processes that impair the contractility of both ventricles, though seem to affect right ventricular contractility disproportionately. The graft is further impaired by the adverse effects of cardiopulmonary bypass on myocardial contractility, PVR and systemic vascular resistance (SVR), as well as the loss of chronotropic reserve that follows denervation.

This chapter reviews the physiological underpinnings, clinical recognition and principles of management of post-transplant right ventricular failure.

Physiology of Acute RV Failure in the Post-Transplant Setting

A Working Clinical Definition of Systolic RV Failure

Attempts to formulate a definition of RVF in terms of absolute hemodynamic values have been confounded by the poor reliability of these measures in defining patients with disproportionate systolic RV function. Further, the echocardiographic assessment of RV size and function is limited. In practice, a combination of clinical and echocardiographic findings is utilized, together with clinical judgment, to recognize this complication (Table 15.1).

Table 15.1 Features supporting a diagnosis of systolic right heart failure

Low Cardiac Output State with relatively preserved LV systolic function plus:
Elevated right ventricular filling pressures
• Elevated CVP or CVP: pulmonary artery wedge pressure ratio
• Dilated IVC with absent respiratory variation
• Paradoxical worsening of hemodynamics with increased preload
Diminished Right Ventricular Contractility
• Reduced Fractional Area Change
• Reduced TAPSE
Right ventricular dilatation
• Increased RV 4-chamber diastolic area
Abnormal septal geometry
Increasing tricuspid regurgitation
Diminished LV volume
• M-mode, Biplane EDV, 3D EDV
Relatively Preserved LV systolic function
• Biplane or 3D EF >45%

LV left ventricle, *RV* right ventricle, *CVP* central venous pressure, *IVC* inferior vena cava, *TAPSE* tricuspid annular plane systolic excursion, *EDV* end diastolic volume, *EF* ejection fraction

RVF is typically recognized by the occurrence of a low cardiac output state in the presence of *elevated RV filling pressures* and typically *diminished preload response*, or even paradoxical hemodynamic deterioration in the face of volume challenge. This is accompanied by *RV dilatation*, *RV systolic dysfunction*, often increased *tricuspid regurgitation* secondary to annular dilatation and septal displacement and *variably elevated RV systolic pressure* on echocardiography. The latter may not be markedly elevated even in the face of substantially increased PVR where RV systolic function is reduced and the RV is unable to generate a high pressure.

Limits of RV Adaptation to Volume and Pressure Loading

Clinical experience with patients with a morphological RV in the sub-aortic position, as well as those with pulmonary arterial hypertension establishes that a chronically pressure-loaded RV can sustain systemic systolic pressures for an extended period of time, albeit with an elevated risk of attrition due to RV failure and tricuspid regurgitation [10]. Experimentally this adaptation can be reproduced by slowly progressive pulmonary arterial constriction in animals [11]. On the other hand, experience with adult patients who have been exposed acutely to substantial RV afterload, commonly after pulmonary embolism, demonstrates that the acutely pressure loaded RV cannot generate systemic systolic pressures outside the neonatal period, a fact that is recapitulated in numerous animal models [12–14].

The initial response to acutely increased RV afterload is increased stroke volume associated with increased RV systolic pressure, which is effected in part by an increase in end-diastolic volume via the Frank-Starling mechanism, also known as *heterometric regulation*. However, after several minutes an increase in intrinsic RV contractility is also seen, representing an example of *homeometric regulation* (Anrep effect) [14–17].

When the limits of these adaptive mechanisms are exceeded, acute RVF ensues, being marked by progressive RV dilatation with increased filling pressures and diminished RV cardiac output, which is in turn associated with reduced LV filling, reduced LV cardiac output and hypotension [18–20]. Figure 15.1 illustrates these effects in representative experiment from a leporine PA banding model, in which the RV has begun to fail [14]. When RV afterload is abruptly increased, the onset of RVF can be rapid. With intermediate pressure load, an initial compensatory response is seen, though one that cannot be sustained over several hours of continued loading [21]. When such ventricles are unloaded again, residual impairment of systolic function may be seen [22].

The mechanisms underlying this failure are incompletely understood, though *relative ischemia* has long been recognized as a contributing factor. In an important early paper, Brooks confirmed the previous identified failure of RV adaptation to acute pressure loading in a canine RV pressure load model. They also described an increase in right coronary flow, which was likely due to coronary vasodilatation given that the perfusion pressure was reduced by elevated RV pressure and later systemic hypotension. With more substantial increments in RV afterload however, RCA flow declined, at a point coinciding with the onset of overt RV failure. Further, extrinsic perfusion of the RCA with supra-physiological flow rates permitted partial recovery of RV function and delayed the onset of RV failure [13]. Other groups have also documented diminished or exhausted coronary vasodilator reserve prior to the onset of RV failure [19, 23].

Using radioactive tracers (the microsphere method), Gold found evidence of relative subendocardial ischemia despite increased myocar-

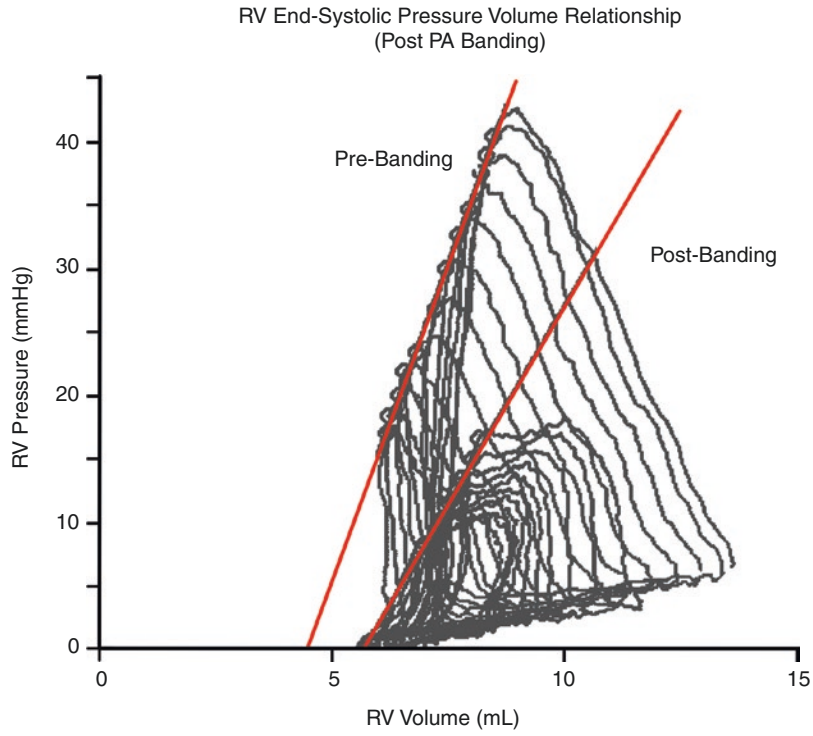

Fig. 15.1 Alteration of the end-systolic pressure volume relationship (ESPVR) in an ovine PA banding experiment is depicted. The reduced ESPVR slope, or RV Ees, is a relatively load-independent indicator of diminished RV contractility after PA banding. PA: Pulmonary Artery. *RV* Right Ventricle. With permission from Hon JK, Steendijk P, Khan H, Wong K, Yacoub M. Acute effects of pulmonary artery banding in sheep on right ventricle pressure-volume relations: relevance to the arterial switch operation. Acta Physiol Scand. 2001;172(2):97–106 © John Wiley and Sons [14]

dial blood flow, in a canine pressure-loading model. He further noted that restoration of systemic blood pressure to control levels, by aortic constriction, reversed both the RV systolic dysfunction together with subendocardial ischemia, a finding that was attributed to improved coronary perfusion pressure [20]. Others have documented similar improvement of RV function following exposure to increased left ventricular afterload in models of both acute [24] and chronic RV [25] failure due to pressure overload, as well as in models of intrinsic dysfunction [26]. As with the left ventricle, this perfusion-supply mismatch is exacerbated by conditions which increase RV systolic wall tension [27].

Calpain is an intracellular protease activated by calcium influx. Greyson observed that treatment with a calpain inhibitor was able to attenuate RV pressure-load induced RVF in pigs. The effect did not appear to be mediated by degradation of common calpain targets such as spectrin, desmin, troponin-I or SERCA2 [28]. A later report from his group suggested that the adhesion protein talin may be target of calpain's action in this setting [29].

Taken together the above studies demonstrated that (1) the naive non-neonatal RV cannot generate systemic systolic pressures in response to an acute pressure load and experiences acute systolic failure if it meets substantial afterload, (2) RV dysfunction induced by excessive pressure load may persist after the stimulus is removed, (3) the incidence of such dysfunction may be related to the peak systolic wall tension, and is mediated by relative ischemia, particularly of the

subendocardium, (4) calpain-mediated degradation of proteins such as talin may be an important mediator of this failure. The latter two points suggest that optimization of RV loading conditions such as to minimize wall tension, measures to optimize coronary perfusion pressure and perhaps inhibition of calpain may prove to be viable therapeutic modalities in the future.

Sequelae of Brain Death and its Impact on Graft Function

Hemodynamic perturbations have long been recognized following acute intracranial hypertension and brain death itself. The resulting injury contributes to primary myocardial dysfunction of the donor heart following transplantation, and as will be seen below, disproportionately affects the RV independently of the other hemodynamic insults that yet are in store for it.

Cardiovascular Responses to Brain Death in the Donor

Experiments by Novitsky in the chacma baboon described the stereotyped response to induction of brain death by acute intracranial hypertension [30], extending the description of Cushing over 80 years earlier [31]. These findings were corroborated by others in canine [32, 33], porcine [34, 35], feline [36] and murine [37, 38] models.

Typically in these experiments, acute intracranial hypertension was followed by concomitant vagal discharge and sympathetic discharge producing systemic hypertension in association with sinus bradycardia, often with conduction abnormalities (Cushing response). After this brief phase, vagal tone diminishes and a dramatic *hyperdynamic state* ensues, which is driven by both neural [39] and humoral [17, 30, 32, 33, 40] release of catecholamines. This phase is associated with sinus tachycardia, frequent atrial and ventricular ectopy and variable ST segment changes, and attenuates within the first 15 min following brain death. By 30–60 min, the sympathetic discharge abates, and a low cardiac output state associated with hypotension ensues. This early constellation of events has been described as an "*autonomic storm*" [30, 37]. A similar sequence is seen clinically following the onset of brain death in a potential organ donor.

When examined, animal hearts which have been subjected to this process display characteristic histological features including *myocardial contraction band necrosis*, which is considered to be the pathological hallmark, together with myocytolysis, coagulative necrosis, variable subendocardial hemorrhage, a monocytic infiltrate and contraction bands in the media of the epicardial coronaries. Electron microscopic features include electron dense material in the mitochondria, which exhibit disrupted cristae [41]. Similar features have been observed in potential human organ donors who had suffered brain death [42], those of patients who had died of acute intracranial hemorrhage [43], and following exposure to large doses of catecholamines [44, 45].

Shivalkar described the differential impacts of abrupt and gradual escalation of intracranial pressure in dogs, by comparison to a non-brain death group. The elevation in blood catecholamine hormone concentrations, intensity of the acute hyperdynamic response and extent of histological ischemic injury were each greatest in the abrupt brain death group, intermediate in the gradual escalation group, and absent in the non-brain death group [33]. In contrast, Bruinsma, however, did not find any association between the extent of histological injury and hemodynamic profile following brain death in a feline model [36].

Following the initial hyperdynamic response, the subsequent hypotension and low cardiac output state appears to be driven by a reduction in contractility and SVR. In order to differentiate the contribution of intrinsic myocardial dysfunction from that of the grossly deranged loading conditions in these experiments, Bittner reported the influence of brain death on the preload-recruitable stroke work (PRSW) relationship, a relatively load insensitive measure of contractility, in a canine model. He demonstrated a substantial reduction in the slope of the PRSW

relationship, which was present by 2 h, and sustained to at least 4 h following brain-death, indicating a decrease in contractility during this time. Interestingly RV function was, in relative terms, affected to a greater degree than that of the LV (34% vs. 22% reduction in PRSW gradient compared to baseline values) [46–48]. Panadali reported similar findings in pigs [49]. Examination of RV end-systolic elastance (RV Ees) in human donors has shown diminished RV function by comparison to patients undergoing coronary revascularization, and further, that RV Ees was lower in non-survivors than in survivors, 1 year after transplantation [50].

Szabó found that dogs subjected to PA constriction after brain death exhibited RV dilatation, and right-shifted stroke-work: RVEDP and regional pressure: length relationships, by comparison to control dogs. These animals were able to maintain RV stroke work, but the above results imply that RV performance was maintained by heterometric regulation, and that the ventricles of these dogs could not exploit homeometric regulation to adapt to the increased afterload [17].

Despite these various insults borne by the donor heart, with optimal hemodynamic management and 12–48 h of observation, a significant proportion may recover sufficiently to permit transplantation [51, 52].

Mechanisms and Modifiers of Post Brain-death Injury

The association of catecholamine hormone concentrations with the intensity of the hyperdynamic phase and severity of histological injury, together with the histological similarities between these hearts and those exposed to large concentrations of exogenous catecholamines led naturally to the hypothesis that the latter were causative. In support, Pilati demonstrated that massive sympathetic discharge induced in rabbits by injection of veratrine into the cisterna magna was associated with a reduction in Ees but that this was reversible with treatment with propranolol or phentolamine [53]. The failure of adrenalectomy to forestall histologically apparent injuries following brain death found in Novitzky's experiments, together with the prevention of the same following bilateral cardiac sympathectomy, suggested that neurological mechanisms may predominate [54, 55]. This was confirmed by Galiñanes' murine experiments, wherein replacement of the entire blood volume of brain-dead rats with that from control rats did not offer protection from the hemodynamic compromise induced by brain death, and conversely, transfusion of blood from acutely brain-dead rats into control rats did not induce hemodynamic compromise [38].

D'Amico [56], White [57], Owen [58] and Pandalai [49] have reported a reduction in stimulated adenylate cyclase activity in association with post brain-death dysfunction, implying an uncoupling of downstream adrenergic signaling. However, others found no variation in expression or affinity of adrenergic receptors after experimental brain death. [58, 59]. A further report from Pandali's group found that in addition to preventing systolic dysfunction post brain-death, β blockade preserves β-adrenoceptor signaling [60]. Owen suggested that this uncoupling is mediated by upregulation of an inhibitory G protein, Gi-α [58]. Contradicting these studies, Bittner et al reported an up regulation of β-adrenoceptors on canine myocardium post brain-death, which was associated with increased stimulated adenylate cyclase activity [61].

Calcium overload is assumed to play a central role in the pathophysiology of catecholamine-mediated toxicity, being associated with direct disruption to mitochondrial membranes and function, as well as potentiation of oxidative stress [45, 62]. Novitky and colleagues explored the impact of calcium channel blockade and reported that pretreatment of baboons with verapamil before brain-death modified the hemodynamic response and prevented the typically associated histological changes [63].

As with pressure-load induced myocardial dysfunction, oxygen supply-demand mismatch is thought to be a significant contributor to catecholamine-mediated toxicity, though the data are inconsistent [45, 62]. Early studies reported ST segment changes and increased myocardial lactate production during the acute hyperdynamic reaction [64]. However the former is inconsistent,

and the latter does not extend beyond the first 1–2 h post brain death [35], whilst myocardial dysfunction, as described above, does. Though some studies had postulated vascular spasm in response to catecholamines as a potential mechanism of injury [37], others found evidence of reactive vasodilatation which rose in tandem with measures of myocardial workload [65]. Further, measurement of myocardial high energy phosphates by biochemical assay [61] or magnetic-resonance spectroscopy (MRS) [66] showed no derangement following brain death implying that this auto regulatory response kept up with demand, and that ischemia was not the etiology of myocardial dysfunction in these studies. In contrast, Pinelli's experiments on pigs however did show diminished intracellular ATP, by MRS, following brain-death [35]. Szabó documented in dogs that hypotension due to low SVR and diminished coronary perfusion pressure accompanied the myocardial dysfunction that follows brain death, and that this dysfunction could be reversed in a cross-circulation model where myocardial loading conditions could be separated from coronary perfusion, and the latter restored to control levels. Further the relationship between maximal elastance (Emax) and the coronary perfusion pressure was identical in both the brain-dead and control animals, supporting the notion that it is hypotension related to reduced SVR, and not direct myocardial toxicity that mediates post brain-death dysfunction [67].

Brain death is accompanied by substantial dysregulation of inflammatory cytokines in many organs, with elevated IL-6, IL-6R, IL-1β and TGF-β levels in a porcine model [68]. In a study of human donors, Birks et al demonstrated elevated myocyte IL-6 and TNF-α mRNA, myocyte TNF-α protein expression and serum TNF-α concentration in unused donor hearts, by comparison to that in transplanted hearts [69]. Interestingly, the same group also observed that expression of TNF-α in a pre-transplant RV biopsy predicted the development of post-transplant RV failure [70].

Combined, the above data suggest that, (1) catecholamine mediated toxicity is likely to contribute to post-brain death RV dysfunction, (2) the latter is marked by a decrease in contractility and inability to exploit the homeometric response to increased afterload, (3) this may be mediated by uncoupling of β-adrenergic receptors from adenylate cyclase and by calcium overload, (4) whilst evidence of failed coronary autoregulation is inconsistent, a substantial component of myocardial dysfunction in this setting may be driven by diminished afterload and its impact on coronary perfusion pressure, and that (5) dysregulated inflammatory mediators at the time of transplant may contribute to RV dysfunction.

Impact of Ischemia, Graft Preservation, Bypass and Reperfusion

The detrimental impact of graft ischemia, ischemia-reperfusion injury and cardiopulmonary bypass on donor heart function has long been recognized and much planning in the peri-transplant period goes toward mitigating the effects of these variables.

Van Trigt and colleagues explored the impact of cold ischemia on graft function. They described a 43% reduction in the slope of the RV preload recruitable stroke work (PRSW) relationship following orthotopic heart transplant (OHT) from a non-brain dead canine donor, after a mean of 85 min of cold ischemic storage, whilst there was no impairment in LV contractility, implying a failure of RV myocardial protection during preservation. This is of a similar magnitude to the 37% reduction in PRSW gradient seen in the RV of animals who had undergone brain death pre-explantation [46], as described previously. The same group later described that the RV PRSW slope of grafts from brain dead donors was further diminished (by an additional 28%) after transplantation following 4 h of cold preservation, by comparison to those organs transplanted without preservation [71].

Further, Mankad described a time-dependent deterioration of biventricular diastolic function and LV systolic function following preservation of porcine hearts [72]. In contrast, hearts from porcine donors who did not undergo brain death

or extended cold ischemia had a preserved PRSW relationship, and further could increase contractility as evidenced by an increased PRSW slope, when transplanted to recipients with elevated PVR (almost twice the PVR faced by control and brain-dead animals). This increase in contractility presumably reflects a preserved capacity to exploit the Anrep mechanism in hearts that have not been insulted by brain death and preservation, and suggests that the impacts of brain death, cold ischemia and increased afterload on donor RV dysfunction are additive.

Though ischemic time remains a risk factor for PGF [3, 73, 74] and early mortality [75–80] in the present era, there are few clinical studies relating this to RVF specifically and in single center studies the association was negative [81]. In a small cohort, Ahlgren described a reduction in RV circumferential and longitudinal systolic function, which correlated with both warm and cold ischemic times [82]. Similarly Mastouri found diminished RV longitundinal contractility to be associated with total ischemic time in another small cohort [83].

Ventricular Interdependence in the Setting of Systolic RV Failure

Responding appropriately to this clinical syndrome mandates an appreciation of the manifestations and mechanisms of ventricular interdependence. Where RV systolic failure predominates, the response of left ventricular cardiac output to administration of volume and to variation in pulmonary and systemic resistance differs substantially from that seen in the more familiar clinical syndrome of acute decompensated left heart failure, and therapeutic maneuvers that are commonly employed in the latter situation may exacerbate the hemodynamics of a patient with the former.

Ventricular interdependence has been recognized in a number of clinical contexts, and such interactions stem from the co-location of both ventricles within a noncompliant pericardial space (a factor however, which does not generally apply post-transplant), a shared ventricular septum [84], together with the fact that the stroke volume of one ventricle determines the preload of the other: a corollary of their being connected in series and pumping at the same rate. Further, it has long been clear to cardiac histologists that the ventricles are mechanically interdependent not only on account of the shared septum, but due to shared superficial myocardial fibers [85]. This is further supported by recent findings using diffusion tensor imaging [86].

The presence of a shared septum links the diastolic filling of one ventricle to that of the other, particularly in the presence of a pericardium, representing a form of *diastolic interaction*. By implication, volume loading of the RV such as occurs during acute RV systolic dysfunction, causes diastolic septal displacement toward the left ventricle, which impairs filling, so lowering LV stroke volume [87–91]. Berisha demonstrated that excessive preload in the setting of acute RV myocardial infarction was associated with decreased RV stroke-work, presumably reflecting responses beyond the peak of their Starling curves [92]. Some of the LV unloading that occurs in this situation is due to reduced RV cardiac output as well as direct diastolic interaction. Such interactions have been recognized to occur in the context of pure right sided volume loading lesions [93, 94] as well as in acute pulmonary embolism [95] and chronic pulmonary hypertension [96] wherein the RV adapts in part by dilatation in order to exploit heterometric regulation. Similarly, Belenkie demonstrated reduced LV stroke work following volume loading in acute pulmonary hypertension due to experimental pulmonary embolism; in this model phlebotomy was associated with significantly improved LV preload and stroke work [97].

The occurrence of *systolic ventricular interaction* stems in large part from the fact that the left ventricle contributes to the pressure-volume work done by the RV [98]; the contribution ranges from about one quarter of its total stroke-work at rest [99] to over a third under conditions of increased RV afterload [100]. The converse is not true under normal conditions [101], but may be relevant under conditions of left heart systolic failure [102] as has recently been exploited by Schranz in the treatment of dilated cardiomyopathy [103].

Given that the LV contribution to RV stroke-work persisted in the presence of an artificial, non-contractile, RV free wall in Hoffman's experiments it follows that a combination of septal contraction and force transmission mediates this contribution [100].

An important form of systolic ventricular interaction from a transplant perspective is the impact of RV dilatation and systolic dysfunction on LV systolic function, which was most clearly demonstrated by Brookes in an in-vivo porcine model. Here, RCA occlusion was associated with a reduction in RV dilatation, septal flattening and reduced LV contractility as defined by the diminished slope of the LV PRSW:EDV relationship. In this model, pericardiectomy was associated with diminished septal shift which coincided with recovered LV contractility [104]. In Hoffman's experiments, the presence of a more capacious and redundant non-contractile RV free wall diminished the LV contribution to RV stroke-work, which may represent a further mechanism by which a dilated non-functional RV can further impair total cardiac output [100]. Takagaki found that, in the setting of marked RV dilatation and dysfunction, predominantly due to Ebstein's anomaly, RV excision and establishment of a Glenn circulation was associated with a dramatic improvement in LV volumes and contractility [105]. Davis [106] and Amà [107] demonstrated a reduction in LV contractility by load independent measures following moderate experimental RV hypertension in animal models.

An intriguing set of interactions, with respect to the possibilities for treatment, is the increase in RV contractility seen with increased LV afterload in the setting of RV systolic failure. Evidence for this phenomenon includes the experiments of Gold described previously, as well as the leporine models of Pinsky [108] and Apitz [24] wherein acute afterload-induced RV dysfunction was reversible by aortic constriction. The latter study also found that noradrenaline had a similar effect to aortic banding. The same authors intriguingly demonstrated, in a chronic leporine PA banding model, that mild aortic constriction could increase the RV ESPVR slope, whilst also improving multiple histological and cytokine markers of adverse remodeling in the RV [25]. Previous authors had attributed such effects to increased coronary flow, which may well be a contributory factor [13], but Belenkie and colleges demonstrated a similar response to aortic banding in a canine RV pressure overload model, whilst maintaining RCA perfusion at baseline levels via artificial perfusion. It is therefore possible that some of this effect is mediated by a combination of increased LV contractility via the Anrep effect, combined with left-to-right systolic interaction via the mechanisms suggested above. A more mechanically favorable septal position may also play a role [26].

Viewed as a whole, this body of experimental and, as-yet, limited clinical evidence, yields strong support for the concept that RV systolic dysfunction negatively influences LV systolic function, especially in the setting of RV volume overload, and the interesting possibility that the contribution of LV contraction to RV stroke-work might be exploited clinically by moderately increasing LV afterload in the setting of acute RV failure.

Risk Factors for Post-Transplant RV Failure

Impact of Recipient Pulmonary Hypertension

Recipient pulmonary hypertension has been the most consistently reported risk factor for RV dysfunction following heart transplantation [109] and has been recognized as such since the earliest transplants [110]. Increasing recognition of this association, ability to stratify risk, and the availability of more targeted therapies seem to have substantially altered the prognostic implications of this risk factor in the current era.

Early in the adult heart transplant experience, Greipp reported the results of the Stanford program's first 26 transplantation procedures, noting that three of these recipients died from RVF and pulmonary hypertension. Further, he observed that these patients had a substantially increased mean pulmonary vascular resistance (PVR) by comparison to other patients [1, 110].

Griepp's findings were further substantiated by multiple reports in the 1980s and early 1990s which reaffirmed an association between recipient pulmonary hypertension and PGF due to RV dysfunction [111–114], though some did not [115]. Many of these reports analyzed the impact of PVR as a categorical, rather than continuous, variable, which has led various authors to propose cutoff values of PVR (>4–6 Wood units), or transpulmonary gradient (TPG; >12–15 mmHg), beyond which pulmonary hypertension was felt to be a relative contraindication to transplantation [116–118]. Data from reports such as Kirklin's [119] however, seemed to suggest the absence of such a clear threshold. PVR as a risk factor was first analyzed in the ISHLT registry dataset in 2000, which confirmed a linear relationship between PVR and the odds ratio for 1-year mortality (Fig. 15.2) [109].

It has long been controversial as to which measure of pulmonary vascular impedance best describes the risk associated with transplantation. Early reports by Addonizio in a mixed adult and pediatric population advocated for use of pulmonary vascular resistance index (PVRI) given its correction for body size. These authors found that a PVRI greater than 6 Wood units.m^2 (WU.m^2) better predicted the incidence of RVF and death in their cohort, than a PVR greater than 6 WU.m^2 [111]. Kirklin reported similar findings [119]. Others found the TPG to be a more robust predictor of relevant outcomes in their cohorts at varying cutoffs [113, 121].

When PVR, PVRI and TPG were subjected to receiver-operating characteristic (ROC) analysis in an adult population by Chen, each of the measures was found to have similar areas under the ROC curve, and hence discriminating ability [114]. In fact, all are imperfect measures of pulmonary impedance and provide complementary information. The pulmonary vasculature is distensible and endothelium dependent dilatation of resistance vessels occurs in the presence of shear stress at higher flow rates, meaning that resistance is not independent of flow, and this is particularly so in disease states. Use of the PVR as a static measure of pulmonary impedance ignores this fact and it may be misleading in conditions

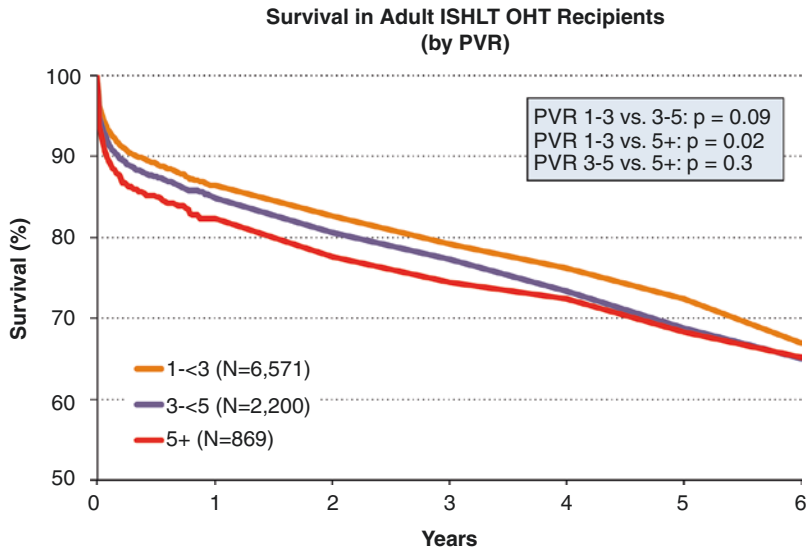

Fig. 15.2 The impact of pulmonary vascular resistance on mortality in ISHLT adult orthotopic heart transplant recipients between 1996 and 2002 is depicted. The greatest impact on mortality hazard is apparent early in the postoperative course. OHT: orthotopic heart transplantation. *PVR* pulmonary vascular resistance. With permission from Taylor DO, Edwards LB, Boucek MM, Trulock EP, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult heart transplant report—2004. J Heart Lung Transplant. 2004 Jul;23(7):796–803 © Elsevier [120]

of low flow [122]. Similarly, TPG is not truly independent of LA pressure, even under conditions of constant flow [123]. In keeping with this, Murali noted that the combination of a TPG >15 mmHg and a PVR >5 Wood units acted synergistically to influence early mortality [121]. These were similar to the findings of Gorlitzer a decade later (Fig. 15.3) [124].

An important modulator of the risk imparted by pulmonary hypertension, however it is defined, appears to be the capacity of the pulmonary vascular bed to reduce impedance in response to increased blood flow, or exogenous vasodilators, a phenomenon known as reactivity. A number of early authors found that the presence of vascular reactivity reduced the early hazard that is otherwise associated with fixed, or irreversible, elevation of PVR [111, 125–128]. Others found that the presence of vascular reactivity did not significantly alter early mortality hazard or that the mortality in such reactive recipients was still substantially greater than in patients without pulmonary hypertension [114, 129, 130]. The issue is further clouded by the lack of a common definition for what agents should be used to test for reactivity, which of the above hemodynamic parameters reactivity should be measured and how much of a response constitutes reactivity. The definition of the latter varies greatly between studies and differs from that proposed in pulmonary arterial hypertension guidelines [131, 132]. Complicating things further is the observation that though PVR is "fixed," in the face of an acute vasodilator challenge, it cannot be inferred that it is *irreversibly elevated*. Even in patients with non-reactive pulmonary hypertension, a substantial component of the pulmonary hypertension is passive, due to pulmonary venous hypertension. In this setting pulmonary pressure and resistance has been found to drop rapidly after support with a ventricular assist device [133–135] or indeed, transplantation [136–138].

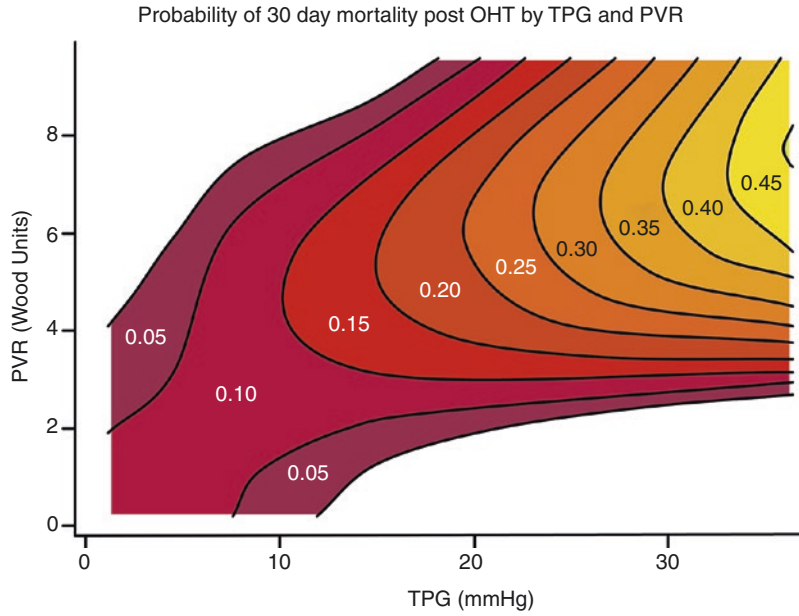

Fig. 15.3 The risk of 30-day mortality is depicted as a function of pulmonary vascular resistance in Wood Units and the transpulmonary gradient in mmHg is depicted, reflecting the experience of 718 adult heart recipients at the General Hospital, Vienna, between 1984 and 2001. Image has been redrawn [124] *OHT* orthotopic heart transplantation, *PVR* pulmonary vascular resistance, *TPG* transpulmonary gradient. With permission from Gorlitzer M, Ankersmit J, Fiegl N, Meinhart J, Lanzenberger M, Unal K, et al. Is the transpulmonary pressure gradient a predictor for mortality after orthotopic cardiac transplantation? Transpl Int Off J Eur Soc Organ Transplant. 2005 Apr;18(4):390–5 © John Wiley and Sons [124]

Interaction with Other Risk Factors for Primary Graft Failure

Multiple other risk factors have been described for primary graft failure and early mortality following heart transplantation and it is reasonable to assume that these may interact with the risk of RV failure, particularly given that some studies explicitly include RVF in their definition of PGF. Such risk factors are listed in (Table 15.2) [139–141].

Donor-recipient size match is a point of interest. Authors of early reports had speculated that larger donors may be useful to compensate for the elevated pulmonary resistance [111, 112]. Adult ISHLT data do not suggest a benefit to oversizing donors in this setting (Fig. 15.4) [142], and some pediatric reports find an increased risk of delayed sternal closure, pulmonary complications, graft failure and mortality [143]. Conversely, while analysis of the United Network for Organ Sharing (UNOS) registry data has not found associated poorer outcomes with size mismatch, in general, undersizing (ratio <0.8) is associated with greater mortality in the subset of patients with a PVR >4 WU [144]. This is consistent with an increase in early graft dysfunction that has been found in other studies [145, 146].

Table 15.2 Risk factors for primary graft dysfunction [139–141]

Increasing donor age
Recipient-donor size mismatch
Prolonged total and warm ischemic times
Increased recipient pulmonary vascular resistance
Previous recipient cardiac surgery
Recipient congenital heart disease diagnosis
Impaired recipient renal function
Recipient waiting list status at time of transplantation
Inpatient status at time of transplantation
Inotropes at time of transplantation
Ventilation at time of transplantation
Mechanical circulatory support at time of transplantation
Hemodialysis at time of transplantation

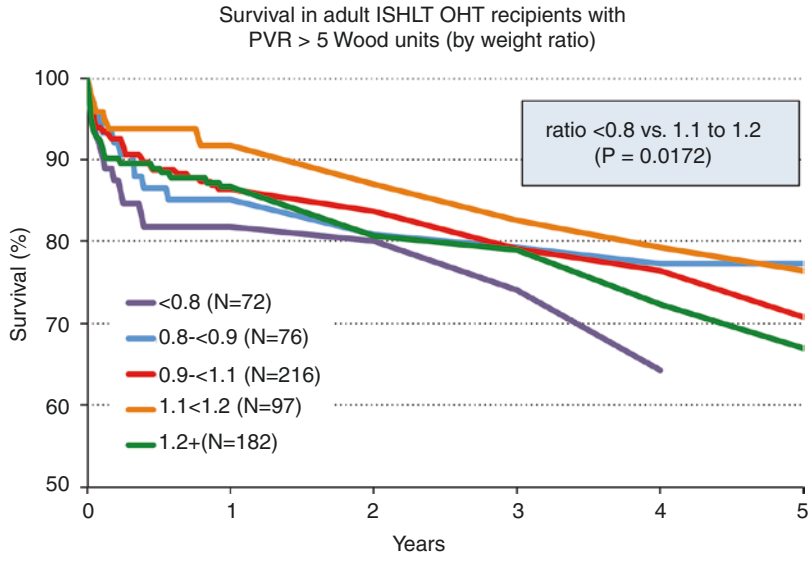

Fig. 15.4 The actuarial survival of adult heart transplant recipients with a pre-transplant pulmonary vascular resistance (PVR) >5 Wood Units, stratified by donor-recipient weight ratio, is shown. Oversizing of donors (ratio >1.2) was not associated with a mortality advantage, but undersizing (ratio <0.8) was associated with the lowest survival, being significantly reduced by comparison to the group with a ratio between 1.1 and 1.2. *OHT* orthotopic heart transplantation, *PVR* pulmonary vascular resistance. With permission from Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report—2011. J Heart Lung Transplant. 2011 Oct;30(10):1078–94 © Elsevier [142]

A Changing Landscape

Over time, a substantial reduction in early mortality has been seen following transplantation in general, and this has also been the case for recipients with pulmonary hypertension [109, 142]. An interesting contrast emerges when the hazard associated with pulmonary hypertension in adult recipients in the ISHLT registry up to 2000 is contrasted with a more recent analysis between 2003 and 2008 (Fig. 15.5) [142]. In the latter period, PVR remains an independent risk factor for 1-year mortality, but the hazard ratio for any given PVR has dramatically reduced. One may speculate that this is due to improved recognition of this clinical problem, early, and in some cases, preemptive vasodilator therapy and increasing experience with mechanical circulatory support.

Management

Optimal management of acute RV dysfunction in the post-transplant setting necessitates pre-empting its occurrence in higher risk scenarios, early recognition and institution of appropriate therapeutic interventions. Appropriate management of acute systolic RV failure differs significantly from that employed in predominant LV systolic dysfunction. Priorities in management include optimization of preload, reduction of PVR, and avoiding inappropriate inotropic support and reduction in LV afterload.

Preemptive Management

A number of approaches have been described to mitigate risk, particularly in patients with pulmonary hypertension.

First, given the interaction with other PGF risk factors as described above, potentially modifiable risk factors such as donor:recipient size match, and minimization of ischemic time must be considered in peri-operative decision making.

An important tool in the setting of adult systolic heart failure with fixed, elevated PVR has been the use of *ventricular assist devices* as a "*bridge to candidacy*." Such use has been

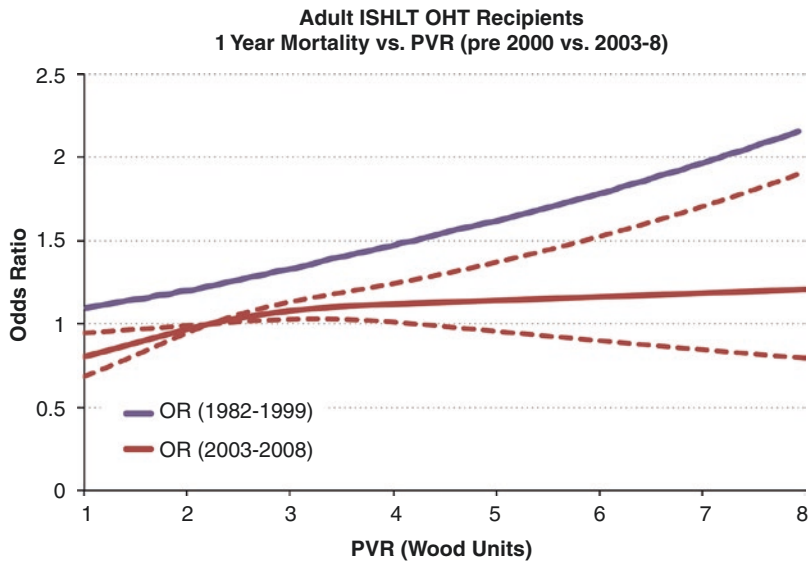

Fig. 15.5 The impact of pulmonary vascular resistance, in multivariable analysis, on 1-year mortality is compared between two eras: 1984–2000 [109] and 2000–2005. A clear difference between the two eras, with respect to mortality hazard imposed by a given degree of pulmonary hypertension, is seen. *OHT* orthotopic heart transplantation, *PVR* pulmonary vascular resistance. With permission from Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report—2011. J Heart Lung Transplant. 2011 Oct;30(10):1078–94 © Elsevier [142]

associated with pulmonary vascular remodeling and reversal of the previously "fixed" elevated PVR, with such patients experiencing a similar risk of post-transplant mortality to recipients without pulmonary hypertension at baseline [134, 135]. In pediatric centers VAD has not generally been employed for this indication alone in the absence of medically unmanageable decompensated heart failure, primarily because of the increased morbidity and mortality associated with current VAD options in children [147] and improving outcomes of patients with pulmonary hypertension as noted above.

There are also preliminary data suggesting that pulmonary vascular remodeling can occur with the use of pulmonary vasodilators such as bosentan and sildenafil [148–150], but more data are required given the potential risks of pulmonary vasodilators in the setting of left heart disease.

In light of the previously discussed data, we do not oversize donors in the setting of confirmed or suspected elevated PVR but avoid under-sizing (weight ratio >0.9).

Heterotopic transplantation was proposed as a way to retain the recipient's already conditioned RV in recipients with pulmonary hypertension [151]. However, it was associated with increased mortality due to pulmonary complications related to mass effect, and the retention of a failing LV which contributes to death by arrhythmia and systemic thromboembolism [129]. More recent registry analyses however [152], suggest that these complications may be lower in well-selected candidates, though it is not clear what place, if any, this therapeutic option has in the current era and it remains a low volume activity accounting for 0.2% of all transplant in the ISHLT registry in 2012 [153].

Domino transplantation, involving the retrieval of a donor heart from a patient with pulmonary hypertension who is undergoing heart-lung transplantation for a heart transplant recipient has been employed successfully [154]. However, broader application is limited by small numbers of end stage PAH patients undergoing transplantation, and the no longer routine preference for heart-lung transplantation as opposed to lung transplantation only in these recipients.

Heart-lung transplantation remains an option for candidates with associated respiratory failure, non-cardiac PAH (WHO Group II) and perhaps for some patients with markedly elevated, fixed, PVR. This strategy, however, is limited by the poorer graft survival in lung transplantation [155, 156].

Optimizing Volume Status

The acutely failing RV is sensitive to excessive volume and optimization of volume status is an important goal of therapy. Generally in the peri-operative period volume overload, rather than hypovolemia, is the rule and such ventricles may be operating at or beyond the peak of their Starling curve, with pejorative effects on overall cardiac output that are exacerbated by the complex inter-ventricular interactions described above [157].

Clues to this physiological state are hypotension or evidence of a low cardiac output state and central venous pressure, which is elevated, often to more than 15 cmH_2O, with non-response or even adverse hemodynamic response to volume challenge. Pulse pressure variability (and its echocardiographic correlates) is often maintained in this setting and is a misleading marker of volume status in this clinical context [158, 159]. Frequently echocardiography will show progressive RV dilatation and increasing tricuspid regurgitation.

While the published data are sparse, our clinical experience suggests that aggressive measures to effect control of volume are warranted in this scenario [159]. In the face of diuretic resistance or rapidly worsening clinical parameters, we have found that phlebotomy of 2–5 mL/kg can result in substantial hemodynamic improvement.

Minimizing RV Afterload

Minimizing RV afterload remains an important goal in the peri-operative setting. It is to be reemphasized that patients with RV failure may have hemodynamically significant elevation of PVR

without a marked elevation of measured or estimated RVSP.

As with all cardiac ICU patients, optimization of ventilation with a view to minimizing both derecruitment and atelectasis, and overinflation, is important. Additionally, hypoxia, hypercarbia and acidosis should be minimized. In unstable patients the adverse response to noxious stimuli may be abrogated by analgesia, sedation and, where necessary, paralysis.

Selective pulmonary vasodilators are employed to decrease PVR whilst maintaining or increasing the SVR. In this regard nitric oxide has seen common use [160–162] and, given its direct respiratory route of administration, effects pulmonary vasodilatation with minimal systemic effects and less tendency to potentiate V:Q mismatch and worsen hypoxemia than parenteral agents. Other vasodilators including inhaled iloprost, prostaglandin E1, prostacyclin, sildenafil and sodium nitroprusside have been reported though their effects are less specific to the pulmonary circulation [160, 163–165]. It is likely that pre-emptive initiation of selective pulmonary vasodilators, particularly nitric oxide, in high risk patients whilst weaning from cardiopulmonary bypass may diminish the risk of associated RV failure [166, 167], and this is our current practice.

Optimizing Inotropic Support

Agents used in this setting historically have included isoproterenol and dobutamine, each of which couples chronotropic and inotropic effects with systemic and pulmonary vasodilatation, thus optimizing ventriculovascular coupling. However vasodilation may limit use in hypotensive states and epinephrine may be preferred in this setting [168].

Phosphodiesterase inhibitors, including milrinone and enoximone have been found to have similar inodilator properties, with the theoretical advantage that they operate downstream of the adrenergic receptor and adenylate cyclase, which are often dysregulated in the transplant setting. They are felt to have a synergistic effect when combined with catecholaminergic drugs [169].

Levosimendan acts via a calcium sensitizing mechanism, with physiological effects that are comparable to the above inodilator agents. It was reportedly useful in the management of preoperative RV dysfunction and PGF post transplant [170, 171], though late follow-up of such patients was less encouraging [172].

The response to inotropic support, particularly with catecholaminergic agents, is subdued in the context of PGF and this may be disproportionately the case for RV dysfunction. Inappropriate inotropic therapy may exacerbate both systemic and pulmonary vasoconstriction, which may in turn compromise cardiac output to a greater degree than any incremental improvement in contractility.

Maintenance of Systemic Blood Pressure

Though the published clinical data in support are again limited, maintenance of systemic blood pressure is felt to be an important therapeutic goal, given the previously described favorable effects on RV performance via improved coronary perfusion, mechanically advantageous septal position and exploitation of beneficial systolic ventricular interaction. There is little data to guide how this is best achieved, although norepinephrine, vasopressin and intra-aortic balloon pump (IABP) usage have all been reported [173]. Tolerance of vasopressors in this setting is contingent on adequate LV systolic function, which may not always be the case with primary graft failure.

Mechanical Circulatory Support

Mechanical support options for post transplant graft dysfunction include IABP, various centrifugal LVAD, RVAD or BiVAD options, and central or peripheral ECMO. Despite a favorable early report of IABP in 5 patients with post transplant RVF [173], it has been displaced by other modalities in adult practice, and experience is negligible in pediatric centers. Early reports of pulsatile

and centrifugal LVAD usage for PGF were marked by extremely low survival [174–177] and other centers have commented on a similarly disappointing experience with RVAD for predominant RV dysfunction [178, 179].

In contrast, ECMO presents a cheaper, less surgically traumatic option with improved reported survival. Marasco reported a 66% survival following mechanical circulatory support of varying modalities for refractory primary graft failure (their definition included patients with RVF) [179]. In a subsequent article she reported a 39 patient series of ECMO cannulation for PGF (again including RVF); 74% survived to hospital discharge [180]. Similarly, d'Alessandro reported a 50% survival to discharge in a large early graft failure series, and Listijono reported an 82% 30-day survival in the adult population [178, 181]. Some pediatric centers have also presented similar results [143, 182], though others reported less favorable outcomes [183]. Given the adult experience and the far more extensive experience with postoperative ECMO than RVAD, it seems likely that ECMO is the current support modality of choice for RV dysfunction post transplant in children also.

Prognosis and Long-term Outcome

Perioperative Mortality and Morbidity

As noted in the introductory section, the morbidity and mortality attributable to post-transplant RV dysfunction is difficult to track due to marked variation in definition and non-inclusion of this variable in registry datasets.

It seems likely, however, that whilst the occurrence of RV dysfunction continues [3], the attributable mortality in many reports has decreased over time, even in patients who would previously have been considered high risk [184]. Some component of this is due to early and even pre-emptive use of pulmonary vasodilators [3]. and improvements in mechanical circulatory support have also played a large role [178, 180]. These improvements may in fact constitute a large part of the dramatic reduction in early mortality documented in registry datasets since their inception [185].

Longer-term Pulmonary Vascular and RV Remodeling

Serial evaluation of PVR over time has found evidence of continued vascular remodeling post heart transplantation. Indeed, a majority of patients with elevated PVR due to left atrial hypertension will experience normalization of PVR by 2 weeks post transplantation [129, 136, 186, 187], despite histologically apparent muscularization of pulmonary arterioles at the time transplant in many such patients [188, 189].

When compared to the non-transplanted normal population, evidence of adverse RV remodeling with RV dilatation [136], reduced longitudinal systolic function [83] and tricuspid regurgitation are seen over the medium term [136]. The impact of these findings is unclear, as, both in high risk subsets such as patients with pulmonary hypertension, and in patients with overt RVF, the difference in mortality appears generally to occur early, with no difference in late hazard [3, 178, 180].

Conclusions

In the present era, with increasing complexity of transplantation and increasing use of marginal donors, post-transplant RV dysfunction remains prevalent: its occurrence is not always predictable and certainly not avoidable. Recent standardization of nomenclature should, in time, contribute to clarifying these temporal trends in incidence and outcome.

It remains an important source of morbidity and mortality, though with improving recognition and preoperative management, including the availability of selective pulmonary vasodilators and improvements in mechanical circulatory support, improvements in early outcome are being seen.

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