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Management of Right Ventricular Failure in the Era of Ventricular Assist Device Therapy

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Abstract The increasing incidence of patients with advanced heart failure, limited donor availability, and continued advancements in the field of mechanical circulatory support have made implantation of left ventricular assist device therapy (LVAD) an attractive option for patients with end-stage heart failure. Perioperative right ventricular failure (RVF) occurs frequently in patients undergoing LVAD implantation and is associated with significant morbidity and mortality. This review will discuss the pathophysiology of RVF, recent efforts to risk-stratify patients preoperatively, and current preoperative, perioperative, and postoperative management strategies.

Keywords Congestive heart failure · Right ventricular failure · Left ventricular assist device · Right ventricular assist device · Biventricular assist device · Destination therapy · Bridge-to-transplantation

Introduction

Congestive heart failure remains one of the leading causes of hospitalization of adults in the United States. The indirect and direct costs associated with this illness are approaching $40 million and are on the rise. Advances in pharmacologic and device therapy have resulted in reductions in morbidity and mortality, thereby contributing to increasing numbers of patients with advanced heart failure. For many decades, cardiac transplantation has offered the greatest morbidity and mortality benefit for patients with end-stage heart failure. However, the number of patients with advanced heart failure in the United States far exceeds the number of available donors. In addition, continued advancements in the field of mechanical circulatory support will likely rival the survival benefit associated with cardiac transplantation, and without the incumbent risks of immunosuppression.

Currently, left ventricular assist devices (LVADs) are used as a bridge to cardiac transplantation (BTT) and as destination therapy (DT) in patients with end-stage heart failure [1, 2••, 3••], and as a bridge to recovery in patients in whom cardiac recovery is anticipated. Right ventricular function is an important variable affecting the clinical outcome of patients undergoing implantation of an LVAD. A substantial number of patients being considered for an LVAD have some degree of right ventricular dysfunction preoperatively, and many develop significant right ventricular failure (RVF) in the perioperative period, the latter of which may result in significant adverse outcomes [4–8, 9•, 10•]. Right ventricular assist devices (RVAD) are available for short-term support of patients with RVF. However, options for long-term mechanical circulatory support of the right ventricle are lacking. Therefore, identification of patients at high risk for the development of RVF is paramount. Such risk assessment is even more critical in the DT population, in whom cardiac transplantation, a treatment option for refractory RVF, is not the ultimate goal. Numerous preoperative variables predictive of RVF in patients with implanted LVADs have been identified, and several risk models have been developed in effort to risk-stratify patients [4, 5, 8, 9•, 10•, 11–13]. Unfortunately, the lack of consistently identified predictors of RVF across these studies has made identification of patients who would benefit from biventricular support difficult. Future efforts to resolve such

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inconsistencies is vital, especially in light of recent data suggesting that planned use of biventricular mechanical support (BiVAD) may result in improved clinical outcomes when compared to delayed use of RVADs [14, 15•].

In this review, and in the context of LVAD implantation, the pathophysiology of RVF, recent efforts to risk-stratify patients preoperatively, and preoperative and perioperative management strategies will be discussed.

Right Ventricular Failure

RVF may be defined as the inability of the right ventricle to maintain adequate loading of the left ventricle in the setting of adequate right ventricular preload, or to do so at the expense of significantly elevated central venous pressures. RVF is a common sequela of advanced left heart failure, and may develop acutely in myocarditis or indolently in patients with chronic left heart failure. In the early stages of RVF, right ventricular end-diastolic and right atrial pressures increase, ultimately resulting in hepatic congestion and coagulopathies. In the latter stages, the right ventricle no longer is able to maintain adequate filling of the left ventricle and a decline in cardiac output ensues. RVF is typically defined as the need for right ventricular support, either pharmacologic or mechanical, for more than 14 days, and has been reported in 20% to 30% of patients receiving LVADs [16]. Multiple factors contribute to the pathophysiology of RVF after LVAD implantation and include preoperative right ventricular dysfunction and pulmonary hypertension, ischemia, perioperative fluctuations in pulmonary vascular resistance, excessive right ventricular preload, and altered interventricular balance.

Preexisting right ventricular dysfunction increases the susceptibility of the right ventricle to further decline after LVAD implantation. Such preoperative dysfunction may be the result of chronically elevated afterload or secondary to myopathy of the right ventricle itself. The right ventricle typically is less susceptible to ischemic damage when compared to the left ventricle. There likely are multiple reasons for this relative myocardial protection, but notables include less myocardial mass and a more favorable oxygen supply-and-demand ratio. Despite these protective mechanisms, obstructive disease of the right coronary artery and/or its downstream right ventricular marginal branches may contribute to right ventricular dysfunction.

According to Laplace's law, wall tension and myocardial oxygen demand are increased by variables that increase right ventricular volume (preload) and pressure (afterload). Conversely, increases in wall thickness will decrease wall tension. After initiation of LVAD support, the resultant unloading of the left ventricle may cause the interventricular septum to shift leftward. Such morphologic changes may alter the septal contribution to right ventricular systole and result in impaired right ventricular performance [17]. In addition, excessive LVAD flows may result in excessive right ventricular preload. During cardiopulmonary bypass, complement activation and blood transfusions increase pulmonary vascular resistance and result in increased right ventricular afterload [18]. Acutely, the right ventricle is unable to hypertrophy concentrically, wall tension and myocardial oxygen demand increase, and impairment in right ventricular systolic function occurs. The right ventricle subsequently begins to dilate and right ventricular output is initially maintained at the expense of elevated right atrial and right ventricular end-diastolic pressures. Right ventricular dilatation may result in tricuspid annular dilatation and distortion of the subvalvular apparatus, both of which may result in poor coaptation of the tricuspid valve leaflets and resultant tricuspid regurgitation. Significant tricuspid regurgitation may result in further volume overload of the right ventricle. When the typical compensatory mechanisms no longer are adequate, the right ventricle is unable to sufficiently load the left ventricle and cardiac output and end-organ perfusion may be compromised. Ultimately, pharmacologic intervention and/or mechanical circulatory support may become necessary to sustain end-organ perfusion.

Although the beneficial effects of continuous-flow LVADs have been well documented, the effects of these devices on right ventricular function only recently have been evaluated in detail. Historically, there has been concern that the continuous unloading of the left ventricle may result in more leftward shift of the septum and resultant decline in right ventricular performance. Conversely, others have felt that the incomplete unloading of the left ventricle afforded by continuous-flow LVADs maintains septal position and improved right ventricular function. Lee et al. [19•] evaluated echocardiograms and right heart catheterizations from 40 patients undergoing HeartMate II (HMII; Thoratec Corporation, Pleasanton, CA) support as a BTT in an effort to assess the hemodynamic effects of a continuous-flow device on right ventricular function. RVF, defined as either the need for inotropic support and/or nitric oxide for 14 days or more or implantation of an RVAD, occurred in only two patients (5%). The authors postulated that although there may be alterations in interventricular balance in the setting of continuous-flow LVADs, such effects on right ventricular function are offset by decreases in right ventricular afterload and an increase in right ventricular preload [19•]. Patel et al. [20] compared the incidence of RVF in pulsatile versus continuous-flow support after implantation of the HeartMate I (XVE; Thoratec Corporation, Pleasanton, CA) and the HMII devices in 87 patients. RVF, as defined previously occurred in 15 (35%) XVE patients and 14

(41%) HMII patients, and survival was similar at 3, 6, and 12 months.

Preoperative Management

In the preoperative period, efforts to optimize patients for LVAD implantation should focus on several areas, including nutrition, coagulation, hemodynamics, and end-organ function. In patients undergoing elective LVAD implantation as BTT or DT, there often is ample time to develop appropriate treatment strategies to improve these variables and, consequently, postoperative outcomes. However, in patients undergoing urgent and/or emergent LVAD implantation, there often is little time to address many of the preoperative variables predictive of RVF, which are discussed later in this review (Table 1) [5, 8, 9•, 10•, 21•].

Optimization of left and right heart hemodynamics is critical before LVAD implantation. Various pharmacologic and device strategies have been used in attempts to normalize or significantly improve right ventricular preload, afterload, and inotropy before surgery. In our institution, pulmonary artery catheters are placed preoperatively, and intravenous diuretics, vasodilators, and inotropes often are used for several days to optimize these hemodynamic variables. We also have used intra-aortic balloon pumps and percutaneous implantation of the TandemHeart System (Cardiac Assist, Inc., Pittsburgh, PA) to improve pharmacologically refractory hemodynamics.

In patients with significant right ventricular dysfunction before implantation, hepatic congestion and malnutrition often coexist and result in significant coagulopathies. Such alterations in coagulation, and the associated elevation in central venous pressures, may result in significant perioperative bleeding necessitating transfusion of blood products. The increases in right ventricular preload and pulmonary vascular resistance associated with blood transfusion may further impair right ventricular performance perioperatively. In our institution, vitamin K often is administered preoperatively, and thromboelastography is used to further quantify and qualify abnormalities in coagulation. Nutritional supplementation also should be considered in patients with significant malnutrition as evidenced by a low albumin,

Table 1 Preoperative predictors of right ventricular failure in patients undergoing LVAD implantation

Group	Patients, *n*	BTT/DT, %	LVAD(s)	RVF Definition	Predictors
Ochia et al. [5]	245/23	97/2	HeartMate IP 1000[a]; HeartMate VE[a]; Novacor N100[b]	RVAD	Preoperative mechanical support; female sex; nonischemic cardiomyopathy
Dang et al. [8]	108/42	NR	HeartMate[a]	RVAD; inotropes for ≥14 days; vasodilators for ≥ 14 days	Intraoperative central venous pressure
Matthews et al. [10•]	197/68	94/6	HeartMate IP 1000[a]; HeartMate VE, XVE, and II[a]; Thoratec IVAD[a]; Novacor[b]; MicroMed[c]	RVAD; inotropes for ≥14 days; nitric oxide for ≥2 days; discharge on inotropes	Preoperative vasopressor; aspartate aminotransferase ≥80 IU/L; bilirubin ≥2.0 mg/dL; creatinine ≥2.3 mg/dL
Drakos et al. [21•]	175/77	58/42	HeartMate IP 1000[a]; HeartMate VE, XVE, and II[a]; Novacor[b]	RVAD; inotropes for ≥14 days; nitric oxide for ≥2 days; discharge on inotropes	Intra-aortic balloon pump; pulmonary vascular resistance; destination therapy
Fitzpatrick et al. [9•]	266/99	NR	Thoratec PVAD[a]; TCI IP[d]; TCI VE[d]; HeartMate XVE[a]; HeartMate II[a]; Bio-Medicus Perfusion System[e]; Abiomed BVS 5000[f]	RVAD	Cardiac index ≤2.2 L/min/m^2; right ventricular stroke work index ≤0.25; severe right ventricular dysfunction; creatinine ≥1.9 mg/dL; previous sternotomy; systolic blood pressure ≤96 mm Hg

[a] Manufactured by Thoratec Corporation, Pleasanton, CA

[b] Manufactured by WorldHeart Corporation, Oakland, CA

[c] Manufactured by MicroMed Cardiovascular, Inc., Houston, TX

[d] Manufactured by Thermo Cardiosystems, Inc. (Thoratec Corporation), Woburn, MA

[e] Manufactured by Medtronic, Inc., Minneapolis, MN

[f] Manufactured by ABIOMED, Inc., Danvers, MA

BTT bridge to cardiac transplantation, *DT* destination therapy, *LVAD* left ventricular assist device, *NR* not reported, *RVAD* right ventricular assist device, *RVF* right ventricular failure

pre-albumin, and/or an increased international normalized ratio.

Intraoperative Management

The main objectives in the operating room at the time of LVAD implantation are to maintain adequate end-organ perfusion and oxygen delivery. Intraoperatively, these goals are achieved by two main mechanisms. First, adequate systemic perfusion must be maintained via a combination of native left ventricular output across the aortic valve and LVAD output through the outflow cannula. Second, there must be adequate systemic venous return to the pulmonary vascular bed and, ultimately, the left ventricle. Initiation of LVAD support should begin with low flows to avoid the deleterious effects of leftward septal shift and right ventricular volume overload previously discussed. Transesophageal echocardiography should be used to assess septal position, right ventricular function, and left ventricular loading. Continuous hemodynamic monitoring via pulmonary artery catheter and radial arterial line also should be utilized. Pulmonary vasodilators including nitroprusside, nitric oxide, and iloprost may be used to combat the fluctuations in pulmonary vascular resistance associated with cardiopulmonary bypass and blood transfusion. Milrinone, dobutamine, and epinephrine may be used to provide right ventricular inotropic support. Pulmonary vasodilators and low LVAD flows should be the initial strategy because both result in decreased right ventricular wall tension and myocardial oxygen demand; inotropes often are necessary in the short term, but should be used sparingly because they have opposite effects.

In the absence of significantly elevated pulmonary vascular resistance and/or right ventricular dysfunction, adequate systemic perfusion and venous return are achieved by maintaining appropriate intravascular volume and adjusting LVAD flows to maintain adequate perfusion. However, when either or both of these aforementioned impediments exist, adequate loading of the left ventricle and maintenance of systemic perfusion occur at the expense of severely elevated central venous pressures. If right ventricular function continues to deteriorate, adequate loading of the ventricle is not possible, systemic perfusion declines, and circulatory collapse may ensue. If pharmacologic therapy and low LVAD flows do not reverse the tide, mechanical circulatory support for the right ventricle should be considered.

There are several mechanical options to support the right ventricle. These include pulmonary artery balloon pumps and RVADs. Pulmonary artery balloon pumps have been shown to decrease pulmonary artery systolic pressures and have been used for short-term support of the right ventricle after routine cardiac procedures ultimately with successful weaning [22, 23]. Intraoperatively, axial and centrifugal continuous-flow RVADs, as well as pulsatile devices, have been used to provide mechanical circulatory support for the failing right ventricle [24–26]. The intraoperative decision to implant such devices is largely driven by unfavorable hemodynamics despite optimization of volume status and pharmacologic therapy.

Postoperative Management

Pulsatile LVADs and, more recently, continuous-flow LVADs have reduced pulmonary hypertension in patients with advanced heart failure [27]. Presumably, this reduction in pulmonary pressures results from unloading of the left ventricle. Such hemodynamic improvements often are not immediate and may take place over days, weeks, or months. Conversely, in the perioperative period, pulmonary pressures actually may increase as previously discussed. During this time, management of the patient with an LVAD largely centers on management of the right ventricle (specifically right ventricular preload, afterload, and inotropy). Both transesophageal and transthoracic echocardiography may be used periodically to assess right ventricular function, septal position, and left ventricular loading. In addition, assessment of these variables aids in assessing response to changes in LVAD flows.

Adequate, but not excessive, preload of the right ventricle is important to maintain adequate left ventricular filling without excessive right ventricular volume overload. In the immediate postoperative period, LVAD flows should be kept low enough to avoid right ventricular volume overload but high enough to maintain adequate end-organ perfusion. In addition to optimizing preload, right ventricular performance may be modulated by using inhaled/intravenous vasodilators and/or inotropes. Milrinone, dobutamine, and epinephrine all have been used when weaning patients from cardiopulmonary bypass, and often are continued for days after LVAD implantation to augment right ventricular contractility. Inhaled nitric oxide and prostacyclins have been successfully added to lower pulmonary vascular resistance in the immediate postoperative period with minimal effect on systemic pressures [28–30]. In addition, nitroglycerin, nitroprusside, nesiritide, and sildenafil all have been used to decrease pulmonary vascular resistance. Sildenafil has been shown to decrease pulmonary vascular resistance and improve right ventricular function in patients with persistent pulmonary hypertension after LVAD implantation [31].

In the postoperative period, monitoring hemodynamic and LVAD flow trends is essential in maintaining adequate right ventricular function. The combination of increased central venous pressure and decreased LVAD flow often is a harbinger of RVF. In addition, elevated central venous

pressures may alter glomerular filtration and result in impaired diuresis, the latter of which may result in additional elevation of central venous pressures and volume overload contributing to further impairment of right ventricular function. Early recognition of such trends may enable the clinician to intervene pharmacologically and reverse the tide. If such interventions are unsuccessful, delayed RVAD implantation will be necessary.

Once the patient has been stabilized hemodynamically and end-organ perfusion is acceptable, efforts should be made to wean inhaled nitric oxide and prostacyclins to facilitate weaning from mechanical ventilatory support. Inotropes also should gradually be weaned with close monitoring of central venous and pulmonary artery pressures, as well as cardiac output. Central venous pressures between 10 to 15 mm Hg, mean systemic arterial pressures between 70 to 80 mm Hg, and normal cardiac indices are reasonable goals. Oral pulmonary and systemic vasodilators may be used to facilitate weaning of intravenous therapies. In patients with an RVAD, daily weaning trials with close monitoring of the aforementioned hemodynamic variables should be considered. Direct visualization of right ventricular function, septal position, and left ventricular loading by transthoracic or transesophageal echocardiography also may be used while weaning RVAD flows. Once mechanical support of the right ventricle no longer is necessary based on clinical and hemodynamic evaluation, the patient should be taken to the operative suite with adequate anticoagulation and RVAD support should be weaned off. Hemodynamics and right ventricular function then should be observed for a period of time before committing to explant.

Risk Factor Stratification and Patient Selection

As previously mentioned, a significant number of patients who undergo implantation of an LVAD will develop significant RVF. The resultant hemodynamic compromise may result in adverse clinical outcomes including increased mortality, length of hospitalization, and intensive care stay [4, 6–8, 10•]. Identifying patients who are at the greatest risk for developing RVF and the optimal management of these patients is less clear. Numerous preoperative variables have been shown to be predictive of RVF in patients undergoing LVAD implantation (Table 1). In addition, several risk models have been developed in an effort to identify patients at risk of developing RVF after LVAD implantation [10•, 15•, 21•]. Such models may help identify a group of patients who would benefit from planned use of BiVADs, a strategy that has demonstrated improved clinical outcomes when compared to delayed use of RVADs in patients undergoing LVAD implantation [15•].

Fitzpatrick et al. [9•] reviewed the preoperative characteristics of 266 patients undergoing LVAD implantation at a single center. Of these patients, 99 (37%) required BiVAD placement. They compared 36 variables and identified 23 with statistically significant differences by univariate analysis. Of those, cardiac index of 2.2 L/min/m^2 or less; right ventricular stroke work index of 2.5 mm Hg/L/m^2 or less; severe preoperative right ventricular dysfunction; previous cardiac surgery; preoperative creatinine of 1.9 mg/dL or greater; and systolic blood pressure of 96 mm Hg or less were predictive of the need for BiVAD by multivariate analysis. A risk-score equation with potential scores ranging from 0 to 98 was developed based on these variables. A risk score over 50 was predictive of the need for BiVAD with a sensitivity and specificity of 83% and 80%, respectively.

Drakos et al. [21•] looked at 175 consecutive patients in a single center who underwent implantation of a LVAD; 58% were placed as BTT and 42% as DT. RVF (defined as the need for inhaled nitric oxide for ≥48 h, use of intravenous inotropes for >14 days, or RVAD implantation) was developed postoperatively by 77 patients (44%). A risk score was developed as the sum of points assigned to eight preoperative variables. All of these variables either were independently predictive of RVF or had significant confounding effects that were retained after multivariate analysis. These preoperative variables included the use of an intra-aortic balloon pump, pulmonary vascular resistance of 4.3 or more Woods units, DT, inotrope dependency, use of an angiotensin converting–enzyme inhibitor or angiotensin II–receptor blocker, use of a β-blocker, and obesity. Scores were broken down into four categories. Four patients (11%) with risk scores in the lowest category developed RVF, compared to 15 patients (87%) with risk scores in the highest category. For these two categories, 1-year survival rates were 83% and 61%, respectively. The authors also found development of RVF was a predictor of survival independent of the risk score [21•].

Kormos et al. [32] evaluated the incidence of, risk factors associated with, and outcomes associated with RVF in a large population of patients undergoing implantation of the HMII as BTT. In the 484 patients enrolled in the trial, 98 patients (20%) developed RVF (defined as requiring ≥14 days of continuous inotropic support [35 patients], RVAD implantation [30 patients], or late initiation of inotropic support after the 14th day [33 patients]). At 180 days, more patients without RVF survived to transplant, recovery, or continued device support than those patients with RVF (89% vs 71%, $P<0.001$). In multivariate analysis, a central venous pressure/pulmonary capillary wedge pressure ratio greater than 0.63, preoperative ventilator support, and blood urea nitrogen greater than 39 were identified as significant predictors of right heart failure. The incidence of RVF in this

study population appears lower than previously reported [4, 5]. The authors postulated that such disparities may be related to better patient selection and preoperative management [32].

There are several recurring themes in the aforementioned studies. The incidence of RVF after LVAD implantation is significant, and the presence of RVF is associated with higher rates of mortality and longer lengths of hospitalization. Unfortunately, consistent identification of preoperative predictors of RVF has proven more difficult. Such disparities likely stem from the fact that most of the data are from retrospective single-center studies with small enrollment. In addition, numerous types of LVADs and varying definitions of RVF were used.

Conclusions

Advances in pharmacologic and device therapy have resulted in a growing population of patients with advanced heart failure. Cardiac transplantation remains the gold standard for many of these patients; however, the number of available donors is limited. LVADs have been shown to improve mortality when used as BTT or DT. However, the incidence of RVF in patients implanted with LVADs is considerable and has a significant impact on clinical outcomes. Current options for long-term right ventricular support are lacking. Although planned used of BiVADs may result in improved clinical outcomes when compared to delayed use of RVADs, consistent identification of patients at risk for the development of RVF has proven difficult. In the future, continued development and prospective validation of risk models predictive of RVF is paramount. In addition, the need for an implantable RVAD which provides long-term support of the right ventricle is crucial to address the needs of the growing population of patients with advanced heart failure.

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