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Right Ventricular Failure—A Continuing Problem in Patients with Left Ventricular Assist Device Support

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Abstract The discrepancy between the limited availability of donor hearts and the ever-increasing number of patients with heart failure has led to the increasing use of left ventricular assist devices (LVAD) as a bridge to transplant. One of the main complications inherent following institution of LVAD therapy is right ventricular (RV) failure, manifested by the need for inotropic and/or nitric oxide support >14 days after LVAD implant and/or the need for right-sided mechanical circulatory support. RV failure is a major contributor of significant morbidity and mortality after LVAD placement. The complex pathophysiology of RV failure, which could potentially be related to RV myocardial dysfunction, interventricular dependence, and RV afterload, has led to inconsistencies in predicting risk factors for RV dysfunction. Several strategies have evolved over the years of experience with mechanical circulatory support that have aimed to avoid as well as reduce the incidence of RV failure. It is imperative that patients who definitely need biventricular support are identified. Despite the numerous risk factors identified in many studies as well as the development of risk factor profile scores, this continues to be a challenging problem. However, the lower incidence of RV failure following LVAD in the current era is encouraging, suggesting a favorable relationship between RV unloading and function, and continuous-flow physiology.

Keywords Ventricular assist devices · Right ventricular function · Heart failure

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Introduction

Cardiac transplantation remains the gold standard for the treatment of patients with advanced end-stage heart failure, although its widespread application is limited by severe donor shortages. The discrepancy between the limited availability of donor hearts and the ever-increasing number of patients with heart failure has led to the increasing use of left ventricular assist devices (LVAD) as a bridge to transplant (BTT) [1–4]. The use of mechanical circulatory support as BTT has evolved to become the standard of care in most cardiac transplant programs. Success with those devices for BTT led to their successful use as an alternative altogether to a transplant, i.e., as destination therapy [5, 6].

One of the main complications inherent following institution of LVAD therapy is right ventricular (RV) failure, manifested by the need for prolonged inotropic and/or nitric oxide support after LVAD implant and/or the need for right-sided mechanical circulatory support. RV failure is a major contributor of significant morbidity and mortality after LVAD placement [7]. Patients with severe right ventricular dysfunction are usually excluded from the institution of exclusively left ventricular support; however, many of the conditions leading to the need for left ventricular support may be associated with right ventricular support, adversely effecting right ventricular loading conditions and/or right/left ventricular mechanical coupling. There have been a number of previous studies designed to help predict those patients at high likelihood of developing RV failure following LVAD implantation [8–11]. These previous studies have identified female gender, nonischemic heart failure etiology, increased right atrial pressure, low pulmonary artery pressure, and decreased RV stroke work index to be predictors of RV failure. Others have identified abnormal biochemical parameters such as elevated bilirubin, creatinine, and aspartate aminotransferase,

suggestive of pre-existing severe multiorgan dysfunction [12]. Unfortunately, the complex pathophysiology of RV failure, which could potentially be related to RV myocardial dysfunction, interventricular dependence, and RV afterload has led to inconsistencies in predicting risk factors for RV dysfunction as we will discuss later [13]. Moreover, the majority of these studies were done using pulsatile pumps as opposed to the current era in which continuous-flow pumps are being predominantly used, which might limit usefulness and relevance of those studies [13, 14].

While the benefits of continuous-flow pumps on LV unloading and end-organ function has been well documented, the complex interactions of continuous-flow physiology on RV function and performance are less well known [15]. Recently, changes in RV function during support with a centrifugal pump have been shown not to worsen during intermediate term follow up [16]. However, the effect on RV function following HeartMate II (HMII) implantation, a continuous-flow pump with axial-flow technology, has not been investigated in detail. A better understanding of changes in RV function during LVAD support can lead to altered selection of patients, such as predicting those patients that might benefit from institution of biventricular mechanical circulatory support. Therefore, the objective of this review is to discuss the changes in RV function after LVAD support, identify risk factors for RV failure, and evaluate the clinical significance of the development of RV failure after LVAD support.

Pathophysiolgic Basis of Right Ventricular Failure During LVAD Support: Role of Ventricular Interdependence

It was originally thought that abnormalities of right ventricular function were directly related to primarily pathological conditions affecting the right ventricle such as myocardial pathology, volume overload, or obstruction to outflow. However, studies performed several decades ago have shed light on the phenomenon of interventricular dependence, whereby mechanical factors influence the other ventricle because of the close anatomic association between them [17]. It has been clearly shown that a significant portion of right ventricular developed pressure and volume outflow depends on left ventricular function [17, 18]. In addition, sudden changes in the left ventricular volume will result in immediate changes in right ventricular pressure and volume. The various factors that contribute to ventricular interdependence include transseptal pressure gradients, septal motion, and ventricular wall function.

Several studies have evaluated the above changes in biventricular function, and especially right ventricular function in hearts supported by an LVAD. In a review by Santamore and Gray, a summary of various studies revealed a consistent RV response of decreased RV afterload, increased compliance, and decreased contractility to LV unloading by an LVAD [13]. Mandarino et al. suggested that changes in RV cross-sectional shape may be a contributing factor in the development of RV dysfunction during LVAD support. Based on echocardiographic studies, they measured the RV area and perimeter in patients before and after LVAD support and demonstrated that a tendency of the RV to develop a more circular shape in some patients that may result in worsening RV function [19]. A majority of the studies have focused on the hemodynamic changes, which consist of a reduction in RV afterload and RV preload, thus contributing to improved RV myocardial efficiency despite the overall impairment of global RV contractility. Moon et al. demonstrated in an animal model that with full LVAD support, LV end-diastolic volume decreased, RV end-diastolic volume increased, and RV end-diastolic pressure decreased. Despite a significant leftward septal shift, the RV pressure, volume, and dimension changes showed an increase in RV compliance [20]. In another animal model, Farrar et al. showed significant reductions on RV peak systolic pressure and mean pulmonary arterial pressure, indicating a reduced afterload. Further, end-diastolic volume, stroke volume, and ejection fraction were unchanged in response to the reduced afterload [21].

Thus, during LVAD support, global RV contractility is impaired due to leftward septal shift, but RV myocardial efficiency is maintained by a decrease in RV afterload and an increase in RV preload. It should be noted that the primary benefit to RV function following LVAD placement is from a reduction in the secondarily elevated pulmonary artery pressures and its subsequent favorable impact on RV function and performance. It has been shown that patients supported with an LVAD alone demonstrate less structural remodeling in the RV than when supported with BIVADs, confirming that the favorable changes seen in RV function are primarily a result of the hemodynamic benefits of LV unloading [22].

University of Minnesota Experience

In this section, we summarize our experience with RV failure in the continuous-flow pump era and attempt to evaluate changes in RV function following support with the HM II [23]. This included all patients receiving the HeartMate II device at the University of Minnesota as a bridge-to transplant between June 2005 and May 2008. Severe RV failure requiring either prolonged intravenous inotropes and/or nitric oxide, or placement of a right ventricular assist device (RVAD) occurred in two (5%) out of 40 patients requiring LVAD support. Both patients required CentriMag Levitronix RVAD placement for im-

mediate right ventricular failure (which occurred immediately after HMII placement). In both patients, the RVAD was explanted within 1 week after placement. Both patients survived more than 6 months: one is awaiting a heart transplant. The other patient survived almost 2 years following LVAD placement, but was not transplant eligible owing to the development of postoperative paraplegia. It should be noted that no additional patients required prolonged inotropic support or nitric oxide post-VAD. Thus, the overall incidence of RV failure in our experience (as defined by RVAD requirement or inotropic support >14 days) was 5%.

An additional patient who required temporary RVAD support was not included here as he had RV failure requiring RVAD support even prior to HMII placement. He was a 23-year-old male that was transferred from an outside hospital with acute cardiogenic shock with multi-system organ failure and required urgent placement of biventricular support with CentriMag Levitronix devices. Following failure to wean temporary biventricular support, he underwent placement of a HMII LVAD; he required RVAD support with the CentriMag device postoperatively [23].

Hemodynamic Data

Following HMII implantation, there was significant unloading of both the right and left side of the heart manifested by reductions in right- and left-sided filling pressures as well as augmentation of cardiac output. The baseline (prior to LVAD placement) central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) was 13.7±5.3 mmHg, 24.5±5.7 mmHg, and 3.8±1.2 L/min respectively. Following HMII support (mean duration of 139.3±60.7 days), the CVP and PCWP decreased significantly to 7.7±5.6 mmHg ($p<0.001$) and 12.9±6.2 ($p<0.001$), respectively, with an increase in CO to 4.9±1.3 L/min ($n=40$, $p<0.001$). The baseline RV stroke work (RVSW) and RV stroke work index (RVSWI) was 1,105±631 mL mmHg and 553.8±286 mL mmHg/m^2; following HMII support, these decreased to 893±500 mL mmHg ($p=0.03$) and 448.1±252 mL mmHg/m^2 ($p=0.04$) respectively ($n=40$). The decrease in the RV stroke work indices suggest that, in the context of the unloaded right ventricle, the RV does not need to contract as vigorously to provide adequate right- to left-sided forward flow to sustain the significant increase in cardiac output [23].

Echocardiographic Data

Generally, the RV free wall is often difficult to visualize on conventional 2-D echocardiography. Thus, we did not estimate RV ejection fraction as a measure of RV function. Instead, the tricuspid annular plane systolic excursion (TAPSE) measured in the apical four-chamber view (which was much better visualized) was used as a validated proxy of RV function in this study [24–26]. The mean TAPSE prior to LVAD implantation was 11.7±3.9 mm; after 202±86.5 days of LVAD support, the TAPSE decreased to 8.6±2.5 mm ($p<0.005$; $n=22$). The decrease in TAPSE observed is consistent with our hemodynamic data demonstrating a decrease in RVSW and RVSWI following LVAD support reinforcing the concept that the RV contractile requirements required to sustain an augmented cardiac output are reduced in the unloaded heart.

It previously has been shown that the severity of tricuspid regurgitation (TR) may predict RV function following LVAD implantation [27]. Thus, we also analyzed the effect of the HMII on TR severity. Following 202±86.5 days of LVAD support, there was a trend toward improvement in TR severity post-LVAD compared with pre-LVAD implantation (2.5±1.1, mild–moderate vs. 2.0±1.1, mild; $p=0.07$; $n=22$). None of these patients had TV annuloplasty at the time of HMII implantation [23].

Risk Factors for RV Failure

There have been a number of previous studies designed to help predict those patients at high likelihood of developing RV failure following LVAD implantation which have identified female gender, nonischemic heart failure etiology, preoperative need for intra-aortic balloon pump support, increased right atrial pressure, low pulmonary artery pressure, and decreased RV stroke work index to be predictors of RV failure. Others have identified abnormal biochemical parameters such as elevated bilirubin, creatinine, and aspartate aminotransferase, suggestive of pre-existing severe multiorgan dysfunction [6, 8–12, 28–30] (Table 1). Numerous studies have suggested that patients with an etiology of non ischemic cardiomyopathy are at significantly higher risk for RV failure, as both the RV and LV are involved in the disease process [10]. Unfortunately, the complex pathophysiology of RV failure, which could potentially be related to RV myocardial dysfunction, interventricular dependence, and RV afterload has led to inconsistencies in predicting risk factors for RV dysfunction [13]. Moreover, the majority of these studies were done using pulsatile pumps as opposed to the current era in which continuous-flow pumps are being predominantly used, which might limit usefulness and relevance of those studies [13, 14].

Kormos et al. studied the risk factors for RV failure in a large cohort of almost 500 patients receiving the HMII continuous-flow LVAD as part of a multicenter clinical trial [29]. By multivariate analysis, the following variables were predictive of RV failure: a central venous/pulmonary

Table 1 Literature review of risk factors for RV failure

Study	No. of patients	Type of VAD	Risk factors (multivariable)
Fukamachi et al. [10][a]	100	Pulsatile	Younger age
			Smaller patients
			Myocarditis
			Female gender
			Decreased RVSWI
			Decreased Mean PAP
Kavarana et al. [8][a]	69	Pulsatile	Decreased RVSWI
			Increased bilirubin
Ochiai et al. [9]	245	Pulsatile	Pre-LVAD circulatory support
			Female gender
			Nonischemic etiology
Dang et al. [11]	108	Pulsatile	Elevated CVP
Patel et al. [28]	77	Pulsatile (55%) Continuous (45%)	Preop IABP
Matthews et al. [12]	197	Pulsatile (84%)	Vasopressor requirement
		Continuous (16%)	AST>80 IU/L,
			Bilirubin>2.0 mg/Dl
			Creatinine>2.3 mg/dL
Fitzpatrick et al. [30][b]	266	Pulsatile (>90%)	Cardiac index <2.2 $L min^{-1} m^{-2}$
			RVSWI<0.25 $mmHg/m^2$
			Severe preop RV dysfunction
			Creatinine 1.9 mg/dL
			Previous cardiac surgery
			Systolic BP <96 mmHg
Kormos et al. [29]	484	Continuous	CVP/PCWP ratio >0.63
			Preop ventilator support
			Blood urea nitrogen >39 mg/dL
Drakos et al. [6]	175	Pulsatile (86%)	Preop IABP
		Continuous (14%)	Increased PVR
			Destination therapy

[a] Only included univariate analysis

[b] Included patients with planned biventricular support

RVSWI right ventricular stroke work index, *PAP* pulmonary artery pressure, *CVP* central venous pressure, *IABP* intra-aortic balloon pump, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance

capillary wedge pressure ratio of greater than 0.63, need for preoperative ventilator support, and a blood urea nitrogen level greater than 39 mg/dL. Variables that were significant by univariate analysis in addition to the latter included an elevated white blood cell count, increased CVP, and decreased RV stroke work index. The value of using the CVP/PCWP as opposed to an elevated CVP alone is that patients with a CVP level that approaches the left-sided filling pressures may be at the highest risk for the development of RV failure after LVAD placement.

Clinical Implications

A thorough knowledge of risk factors is important as it may help in selecting patients who will benefit from biventricular as opposed to isolated left ventricular assist device support. This is of significant clinical relevance as it has been shown that a planned placement of biventricular support results in superior outcomes when compared with patients receiving LVAD support with delayed institution of RVAD support [30].

Recent studies involving the use of continuous-flow pumps have suggested a reduced need for RVAD support; however, the mortality for patients requiring RVAD support remains high even in the current era. It was previously suggested that the increased mortality in patients requiring biventricular support is related to the direct use of either the additional RVAD or the BIVADs [31]. However, it is clear that the multiple risk factors for RV failure that have been identified from multiple studies are the same risk factors that lead to increased mortality after LVAD use itself. In the recent analysis of RV failure in 484 patients receiving the HMII LVAD, 6% required an RVAD, 7% required extended inotropic support, and an additional 7% required late inotropic support. Importantly, the survival (either transplanted, recovery, or ongoing device support) of patients with RV failure was significantly reduced as compared with patients without RV failure (71% vs. 89%) [29].

The development of RV failure after LVAD implantation is also associated not only with reduced success of bridging to transplant but also with increased post-transplant mortality. The multicenter pivotal study as well as single center studies has reported a significantly reduced incidence of RV failure after HMII implantation [2, 3, 29]. The development of RV failure following LVAD implantation is sometimes associated with an increased urgency for transplantation and thereby a tendency to use suboptimal donors for transplant. The lower incidence of RV failure seen with the HMII LVAD might also have contributed to the improved post-transplant survival being reported in the continuous-flow pump era [32].

Perioperative Strategies for RV Dysfunction and Failure in the LVAD Patient

Several strategies have evolved over the years of experience with mechanical circulatory support that have aimed to avoid as well as reduce the incidence of RV failure. It is imperative that patients who definitely need biventricular support are identified. Despite the numerous risk factors identified in many studies as well as the development of risk factor profile scores, this continues to be a challenging problem. It is important that each potential LVAD candidate be carefully evaluated for the risk of developing RV failure after LVAD placement. It should be also realized that though the initial biochemical, hemodynamic, and echocardiographic profile of a patient at admission may suggest the need for biventricular support, many of these risk factors may be favorably modified by a variety of strategies that may result in the subsequent avoidance of severe RV failure after LVAD placement. Such strategies include delaying LVAD implant until the patient's hemodynamics are optimized using therapies such as aggressive diuretic therapy, ultra-filtration, and temporary intra-aortic balloon pump use. In some patients, even the use of temporary biventricular mechanical circulatory support can be used to improve the RV function, thereby making the patient a candidate for isolated permanent LVAD support.

In some patients, the development of intra and postoperative bleeding and the subsequent transfusion requirements might predispose to RV failure or worsen an already borderline functioning RV. Thus, optimization of a patient's coagulation profile in the preoperative period is critically important. These might include delaying LVAD implant if a patient has recently received anticoagulant therapy and administration of vitamin K therapy appropriately. The need for careful and meticulous intraoperative hemostasis is also essential [33].

There has been a misconception that the presence of pulmonary hypertension is a risk factor for RV failure after LVAD placement. However, it is in fact a low PA pressure that suggests a higher risk for RV failure as the poor RV contractile function is unable to generate adequate PA pressures [34]. In some patients undergoing LVAD placement, there is a need for aggressive pulmonary vasodilator therapy such as nitric oxide that may reduce RV afterload, thereby favorably influencing RV function [35].

Our own observations following HMII implantation showed a trend towards a reduction in TR severity as loading conditions improved. This finding suggests that TR severity of moderate grade or less would not need to be corrected by either tricuspid valve repair or replacement at the time of HMII implantation, although this would need to be confirmed in larger, prospective studies. Other investigators have shown that the presence of moderate or severe TR at the time of LVAD placement predicted an increased risk of RV failure post-LVAD and have recommended BIVAD or the total artificial heart for these patients [30]. It remains unclear at this time regarding whether to intervene surgically on TR in patients undergoing only LVAD placement, though our recommendation based on this study as well as our overall clinical outcomes suggest that at least moderate TR should be left alone. However, some investigators do practice a more aggressive approach to performing a tricuspid valve annuloplasty in patients undergoing LVAD placement. They suggest that the diminished RV function requires an increased RV end-diastolic pressure to maintain comparable forward flow; this increased RV end-diastolic pressure can cause tricuspid valve chordal tethering and worsen tricuspid regurgitation [24].

It is important that following institution of continuous-flow LVAD support following termination of cardiopulmonary bypass, that the speed of the pump is not increased too rapidly, which may result in LV "suck-down", worsening septal shift and further impairing RV function. We advocate close monitoring of both RV and LV size by echocardiography following institution of LVAD support in the operating room. While continuous monitoring with transechocardiography (TEE) is unavailable in the intensive care unit, careful attention to avoidance of too high LVAD speeds is important and can usually be monitored with other available hemodynamic and LVAD parameters such as CVP, pulsatility index, and end-organ function such as urine output. If warranted, based on clinical suspicion, TEE can be performed to more carefully assess degree of LV decompression and RV function in the LVAD patient at the bedside.

Most cases of RV dysfunction in the operating room can usually be managed by using a combination of pulmonary vasodilator therapy and adequate inotropic support and sometimes temporarily supporting the heart with cardiopulmonary bypass. These patients are usually treated for prolonged duration in the postoperative period with inotropic therapy and nitric oxide or epoprostenol. Recent-

ly, the use of sildenafil has been shown to be a useful adjunctive therapy in the management of such patients [36]. If severe RV dysfunction does develop in the operating room despite aggressive measures such as adequate inotropic support, use of nitric oxide, etc., then immediate use of a temporary RVAD is mandatory. It has been shown that delayed placement of RVAD in such patients is associated with poorer outcomes as opposed to early placement in the operating room [30].

Summary

RV failure is a significant cause of increased morbidity and mortality following LVAD implantation [7]. During the initial clinical trials with continuous-flow pumps, there were concerns that the continuous unloading mechanism of the LV by these pumps may contribute to an increased risk of RV failure because of the leftward shift of the interventricular septum. However, the incidence of RV failure, defined as the need for inotropic and/or nitric oxide support >14 days post-LVAD implantation and/or the need for RVAD insertion at our institution was 5%, which is lower than compared with previous reports [12, 28, 29]. Further, we observed a significant decrease in both right- and left-sided filling pressures following HMII support compared with baseline. Other hemodynamic indices of RV function such as RVSW and RVSWI also significantly decreased [23]. Echocardiographic parameters of RV function demonstrated a significant reduction in TAPSE as well as a trend towards improvement of TR severity following LVAD support [23]. A comparison of right heart dysfunction between the pulsatile HM XVE and the axial-flow HMII at another center showed the overall incidence to be similar, although the need for RVAD support as well as inotropic use was less than with the HMII LVAD [28].

It is important to note that the reductions of RVSW, RVSWI, and TAPSE, which were seen following HMII implantation, were in the setting of the unloaded heart with augmented cardiac output. Certainly, a reduction in these parameters associated with increased right- and left-sided filling pressures would suggest worsening RV function. However, given significant reductions in CVP and PCWP during LVAD support along with augmented CO, a decrease in RVSW, RVSWI, and TAPSE would suggest that the unloaded RV does not need to contract as vigorously to maintain adequate blood flow to the left side of the heart. In essence, the unloading provided by the HMII has a lusitropic effect on the RV. Our findings are consistent with previous experimental data demonstrating that as a result of LV decompression with an LVAD, a decrease in RV contractility is observed despite improved RV afterload conditions due to the RV and LV systolic ventricular interactions secondary to changes in LV geometry [19–21]. During LVAD support, global RV contractility is impaired due to leftward septal shift, but RV myocardial efficiency is maintained by a decrease in RV afterload and an increase in RV preload. It should be noted that the primary benefit to RV function after LVAD placement is from a reduction in the secondarily elevated PA pressures and its subsequent favorable effect on RV function.

The issue of pulmonary hypertension assumes importance when evaluating the efficacy of continuous-flow devices. Previous studies showed a lesser degree of left ventricular unloading with continuous-flow (vs. pulsatile) devices but a similar degree of pressure unloading under resting conditions [37, 38]. Other endpoints (such as exercise performance, cellular recovery, and end-organ function) have also been shown to be similar for the two types of devices [15, 39, 40]. However, concerns have remained about the ability of partial unloading of the left ventricle to favorably influence altered pulmonary hemodynamics in end-stage heart failure patients. As a result of this lack of definitive evidence, at least until recently [37, 41], concerns have lingered about the efficacy of circulatory support provided by continuous-flow (vs. pulsatile) devices. However, recent reports using continuous-flow devices other than the HMII have demonstrated their efficacy in ameliorating pulmonary hypertension [41, 42]. It is because these continuous-flow pumps have demonstrated excellent pressure and volume unloading effects on the LV that the favorable effects on the hemodynamic and echocardiographic indices of RV function have been realized.

It should also be noted that these improvements seen with the newer devices in the current era, such as a low incidence of RV failure, may be secondarily related to lessons learned from earlier experiences (with pulsatile devices) that have led to stepwise and systematic improvements in patient selection, better preoperative optimization, improved operative techniques, and better postoperative management such as improved optimization of right ventricular function in the postoperative period. The absence of a large preperitoneal pocket (which was required with the larger pulsatile devices) has lessened the need for extensive dissection and reduced the incidence of postoperative bleeding. The reduced transfusion requirements following HMII placement may also have a beneficial effect on RV function following LVAD placement.

In conclusion, the incidence of RV failure following LVAD in the current era is low, suggesting a favorable relationship between RV unloading and function and continuous-flow physiology. Further, there is significant improvement in RV function based on several hemodynamic and echocardiographic indices following LVAD implantation and up to almost 6 months of LVAD support.

These findings may have important implications for patients with end-stage heart failure with moderate degrees of RV dysfunction requiring longer-term support. Further, these favorable findings on RV function during LVAD therapy are another reason to support the increasing use of continuous-flow devices. Despite this, the development of RV failure is associated with worse clinical outcomes in spite of major advances in the understanding of the pathophysiology of RV failure. Further attempts and studies to refine patient selection, optimization of RV function prior to LVAD support, earlier identification of patients for planned biventricular support, and the treatment of unanticipated RV failure after LVAD support will facilitate continued and widespread use of mechanical circulatory support for patients with advanced heart failure.

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