

Effects of the HeartMate II continuous-flow left ventricular assist device on right ventricular function

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BACKGROUND: Continuous-flow devices have become the standard of care for mechanical circulatory support for end-stage heart failure patients because of improved survival and durability. The effects of these devices, such as the HeartMate II (HMII) left ventricular assist device (LVAD), on right ventricular (RV) function have not been evaluated in detail. This study evaluated the incidence of RV failure, alterations in RV function, severity of tricuspid regurgitation (TR), and cardiac hemodynamics after HMII implantation.

METHODS: Echocardiograms ($n = 22$) and right heart catheterizations ($n = 40$) were performed before and after 4 to 6 months of HMII support in 40 bridge-to-transplant patients. Right heart failure was defined as the requirement for inotropes and/or nitric oxide requirement after LVAD implantation for >14 days or the need for right-sided mechanical circulatory support.

RESULTS: Overall, RV failure after HMII implantation occurred in 2 of 40 patients (5%). Significant improvements occurred in cardiac index, with reductions in right atrial pressure, RV stroke work index, tricuspid annular motion, mean pulmonary artery pressure, and pulmonary vascular resistance after HMII support. There was a trend towards reduction in TR after LVAD support ($p = 0.075$).

CONCLUSIONS: The incidence of RV failure after support with continuous-flow devices such as the HMII is low. The favorable effects of the HMII on cardiac hemodynamics result in improved RV function, improved right- and left-sided hemodynamic profiles, and a reduction in TR severity. These findings may have important implications for LVAD patients needing longer-term support.

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Left ventricular assist devices (LVAD) offer an acceptable treatment strategy for end-stage heart failure patients.¹ The original first-generation LVADs were pulsatile pumps that enhanced cardiac output by mimicking the physiologic blood flow of the native heart. These pumps provided ex-

cellent hemodynamic support but were associated with significant patient comorbidity due to various factors, including the need for extensive surgical dissections to accommodate the large pump, large-caliber drivelines prone to the development of infections, and the need to change pumps within the first 2 years due to mechanical wear.

Continuous-flow devices offer a smaller and more durable pump, are technically easier to implant, and have wider applicability. The decreased morbidity associated with continuous-flow devices, especially the lower incidence of post-operative bleeding and device-related infections, may be due to their smaller size, the lack of need for a large

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pocket to house the pump, and the smaller driveline.² The absence of a large pre-peritoneal pocket, which was required with the larger pulsatile devices, has lessened the need for extensive dissection and reduced the incidence of post-operative bleeding, LVAD pocket hematomas, and the development of pocket infections. The new HeartMate II (HMII) LVAD (Thoratec, Pleasanton, CA), which incorporates continuous-flow rotary-pump technology, represents the next generation of devices.²

One of the main complications inherent after LVAD therapy begins is right ventricular (RV) failure, manifested by the need for prolonged inotropic support after LVAD placement and/or the need for right-sided mechanical circulatory support. RV failure is a major contributor of significant morbidity and mortality after LVAD placement. Patients with severe RV dysfunction are usually excluded from the institution of exclusively LV support; however, many of the conditions leading to the need for LV support may be associated with RV support, adversely effecting RV loading conditions and/or RV/LV mechanical coupling.

RV failure after LV support has begun may be exposed by the development or persistence of pulmonary artery hypertension, further impairment of RV contractility secondary to alterations in mechanical relationships between the RV and the “unloaded” LV, or further intrinsic impairment of RV contractility associated with the known susceptibility of the RV to myocardial preservation injury during circulatory arrest.

A number of studies have been designed to help predict those patients who are likely to present with RV failure after LVAD implantation.^{3–6} Predictors of RV failure have been identified as female gender, nonischemic heart failure etiology, increased right atrial pressure, low pulmonary artery pressure, and decreased RV stroke work index (RVSWI). Others have identified abnormal biochemical indicators such as elevated levels of bilirubin, creatinine, and aspartate aminotransferase, suggestive of pre-existing severe multiorgan dysfunction.

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.⁷ Moreover, most of these studies were done in patients who received pulsatile pumps rather than those in the current era in which continuous-flow pumps are being predominantly used, which might limit the usefulness and relevance of those studies.^{7,8}

Although the benefits of continuous-flow pumps on LV unloading and end-organ function have been well documented, the complex interactions of continuous-flow physiology on RV function and performance are less well known. Recently, changes in RV function during support with a centrifugal pump have been shown not to worsen during intermediate-term follow-up.⁹ However, the effect on RV function after 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 who might benefit

from institution of biventricular mechanical circulatory (BIVAD) support. Therefore, our objective was to study RV function after LVAD implantation by evaluating various hemodynamic and echocardiographic indicators as well as the incidence of RV failure after HMII placement.

Materials and Methods

The protocol for the study was approved by the United States Food and Drug Administration and by the University of Minnesota Institutional Review Board (IRB). Patient consent for data collection and for reporting was obtained by a standard informed consent process.

Patients

The study population included 40 bridge-to-transplant (BTT) patients who received the HMII device from June 2005 through May 2008 at the University of Minnesota Medical Center, Fairview, as part of a prospective, multicenter study evaluating the use of the HMII LVAD as BTT therapy. Patients with end-stage heart failure who were on our transplant waiting list were eligible for study enrollment. Detailed inclusion and exclusion criteria are listed in the supplementary appendix, available with the referenced article in the *New England Journal of Medicine* (at www.nejm.org).¹⁰

HeartMate II

The HMII consists of an internal blood pump with a percutaneous lead that connects the pump to an external system driver and power source. The pump has an implant volume of 63 ml and generates up to 10 liters/min of flow at a mean pressure of 100 mm Hg. Details of HMII function and the implantation technique have been described elsewhere.^{3,11}

Device management

According to our local practice at the University of Minnesota, the revolutions/min (rpm) rate of the HMII is set to provide adequate cardiac output and achieve optimal LV decompression, while maintaining a pulsatility index 3.5 to 4. In addition, the fixed-rate speed of the HMII is usually adjusted to maximize LV decompression and to improve cardiac output, simultaneously allowing for at least a 1:3 ratio of aortic valve opening. We optimize the rpm speed, both hemodynamically and echocardiographically, at the time of LVAD placement, before the patient is discharged from the hospital (ie, after admission for LVAD placement) and if clinical events such as new symptoms or suction events warranted further adjustment.

The 40 study patients were receiving standard heart failure therapy, including antiarrhythmic therapy (our usual practice). Anticoagulation involved a combination of warfarin and aspirin. After LVAD placement, we did not change defibrillator and biventricular pacing settings. All

patients underwent a standard post-operative rehabilitation program.

Hemodynamic profiles

Hemodynamic measurements before and after LVAD implantation (139.3 ± 60.7 days) were obtained in 40 patients, including mean right atrial pressure (mRAP), RV stroke work (RVSW), RV stroke work index (RVSWI), mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), transpulmonary gradient (TPG), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and cardiac index (CI).

RV failure was defined as the need for intravenous inotropic support or use of inhaled nitric oxide for >14 days after LVAD placement, or the need for right-sided mechanical circulatory support after LVAD placement.

Echocardiography

Echocardiographic data were obtained in 22 patients before and after LVAD implantation (202 ± 86.2 days). A graded-system for tricuspid regurgitation (TR) severity was used: 0, none; 1, mild; 1.5, mild-moderate; 2.0, moderate; 2.5, moderate-severe; 3.0, severe.

Two-dimensional lateral tricuspid annular plane systolic excursion (TAPSE) was assessed in the apical 4-chamber view at end-diastole and end-systole to determine RV systolic function, as previously described.^{12,13} Echocardiography was interpreted by a single cardiologist blinded to clinical data with a minimum of 2 measurements per parameter.

Statistical analysis

Continuous data are presented as mean \pm standard deviation and compared with analysis of variance or the *t* test as indicated. Results were considered statistically significant for values of $p \leq 0.05$.

Results

Patients

The mean age was 52.9 ± 13.4 years, and men comprised 67.5% of the study population. Ischemic cardiomyopathy was present in 23 (57.5%) and acute myocardial infarction in 5 (12.5%). The average baseline ejection fraction before LVAD implantation was $17 \pm 8\%$. All patients received the HMII LVAD device as BTT. The overall mean duration of HMII support in the BTT group was 193.2 ± 139.9 days. The baseline characteristics of the 40 BTT patients are summarized in Table 1.

RV failure

Severe RV failure requiring intravenous inotropes and/or nitric oxide or placement of a RV assist device (RVAD)

Table 1 Patient Demographics

Variable	Mean \pm SD, or No. (%)
Patients, total	40
Age, years	52.9 ± 13.4
Male gender	26 (65)
Etiology of heart failure	
Ischemic	24 (60)
Non-ischemic	16 (40)
Left ventricular ejection fraction, %	17.2 ± 8
Diabetes	14 (35)
Hypertension	16 (40)
Hyperlipidemia	15 (38)
Peripheral vascular disease	3 (8)
COPD	8 (20)
Baseline creatinine, mg/dl	1.6 ± 0.7

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

occurred in 2 of the 40 patients (5%). Both required CentriMag Levitronix (Waltham, MA) RVAD placement for immediate RV failure, which occurred immediately after HMII placement, and the RVAD was explanted in both 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 after LVAD placement but was not eligible for a transplant owing to the development of postoperative paraplegia. No additional patients required prolonged inotropic support or nitric oxide for any period of time. Thus, the overall incidence of RV failure was 5%, as defined by RVAD requirement or inotropic and/or nitric oxide support >14 days.

An additional patient who required temporary RVAD support was not included here because he had RV failure requiring RVAD support even before HMII placement. This patient did not meet inclusion criteria for the study, and an exemption was obtained from the IRB. He was a 23-year-old man who was transferred from an outside hospital with acute cardiogenic shock with multisystem organ failure and required urgent placement of biventricular support with CentriMag Levitronix devices. After failure to wean temporary biventricular support, he underwent placement of a HMII LVAD; he required RVAD support with the CentriMag device postoperatively.

Mortality

In the total cohort of 40 patients, 37 (86 %) were alive or underwent transplantation within 6 months. Of the 3 deaths, one was secondary to multisystem organ failure, including RV dysfunction and sepsis, the second was secondary to pump dysfunction, and the third was secondary to thrombosis of the aortic root and ventricular fibrillation.

Hemodynamic data

After HMII implantation, there was significant unloading of both the right and left side of the heart manifested by

Table 2 Hemodynamic and Echocardiographic Variables Before and After Left Ventricular Assist Device Implant

Variables	No.	Pre-LVAD	Post-LVAD	<i>p</i> -value
Tricuspid regurgitation	22	2.5 ± 1.1 (mild-mod)	2.0 ± 1.1 (mild)	0.075
TAPSE, mm ^a	22	11.7 ± 3.9	8.6 ± 2.5	<0.005
RAP, mm Hg ^a	40	13.7 ± 5.3	7.71 ± 5.6	<0.001
RVSW, mL × mm Hg ^a	40	1105 ± 630	893 ± 500	0.03
RVSWI, mL × mm Hg/m ^{2a}	40	553 ± 287	448 ± 252	0.04
MPAP, mm Hg ^a	40	37.4 ± 8.0	23.3 ± 7.1	<0.001
PVR, Wood U ^a	40	3.7 ± 1.8	2.1 ± 0.8	<0.001
TPG, mm Hg ^a	40	12.7 ± 4.9	9.4 ± 3.2	<0.001
PCWP, mm Hg ^a	40	24.5 ± 5.7	12.9 ± 6.23	<0.001
Cardiac output, liters/min ^a	40	3.8 ± 1.24	4.9 ± 1.3	<0.001
Cardiac index, liters/min/m ^{2a}	40	1.9 ± 0.5	2.5 ± 0.5	<0.001

LVAD, left ventricular assist device; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSW, right ventricular stroke work; RVSWI, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient.

^aAll *p*-values are significant for these variables, *p* < 0.05.

reductions in right- and left-sided filling pressures as well as augmentation of cardiac output. The baseline mean RAP was 13.7 ± 5.3 mm Hg, PCWP was 24.5 ± 5.7 mm Hg, and CO was 3.8 ± 1.2 liters/min. After HMII support (mean duration of 139.3 ± 60.7 days), the mean RAP and PCWP decreased significantly to 7.7 ± 5.6 mm Hg (*p* < 0.001) and 12.9 ± 6.2 mm Hg (*p* < 0.001), respectively, with an increase in CO to 4.9 ± 1.3 liters/min (*p* < 0.001; Table 2; *n* = 40). The baseline RVSW was 1105 ± 631 ml × mm Hg and RVSWI was 553.8 ± 286 ml × mmHg/m²; after HMII support, RVSW decreased to 893 ± 500 ml × mm Hg (*p* = 0.03) and RVSWI to 448.1 ± 252 ml × mm Hg/m² (*p* = 0.04; Table 2; *n* = 40). The decrease in the RVSWIs suggests that, in the context of the unloaded RV, the RV does not need to contract as vigorously to provide adequate right- to left-sided forward flow to sustain the significant increase in CO.

Echocardiographic data

Generally, the RV free wall is often difficult to visualize on conventional 2-dimensional echocardiography. Thus, we did not estimate RV ejection fraction as a measure of RV function. Instead, the TAPSE measured in the apical 4-chamber view, which was much better visualized, was used as a validated proxy of RV function in this study.^{12,13} The mean TAPSE before 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; Table 2). Individual changes in TAPSE before and after implant are shown in Figure 1. The decrease in TAPSE observed is consistent with our hemodynamic data demonstrating a decrease in RVSW and RVSWI after LVAD support, reinforcing the concept that the RV contractile requirements required to sustain an augmented cardiac output are reduced in the unloaded heart.

We also analyzed the effect of the HMII on TR severity. After 202 ± 86.5 days of LVAD support, there was a trend toward improvement in TR severity after LVAD compared

with before LVAD implantation (2.5 ± 1.1, mild-moderate vs 2.0 ± 1.1, mild; *p* = 0.07; *n* = 22). Individual changes in severity of TR before and after implant are shown in Figure 2. None of these patients had tricuspid valve annuloplasty at the time of HMII implantation.

Discussion

RV failure is a significant cause of increased morbidity and death after LVAD implantation.¹⁴ During the initial clinical trials with continuous-flow pumps, there were concerns that the continuous unloading mechanism of the LV by these pumps might 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 after LVAD implantation and/or the need for RVAD insertion at our institution was 5%, which is lower than compared with previous reports.^{15,16} Further, we observed a significant decrease in both right- and left-sided filling pressures after HMII support compared with baseline. Other hemodynamic

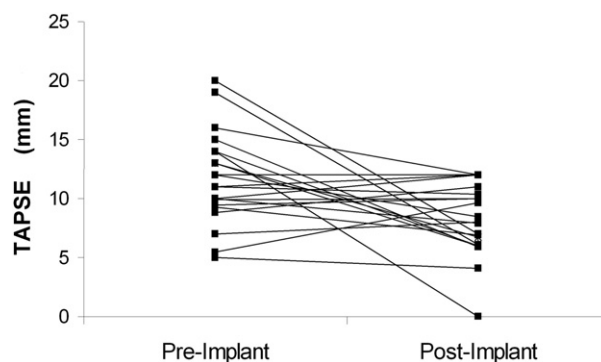


Figure 1 Individual changes are shown in tricuspid annular plane systolic excursion (TAPSE) values pre-implant and at 202 ± 86.2 days post-implant.

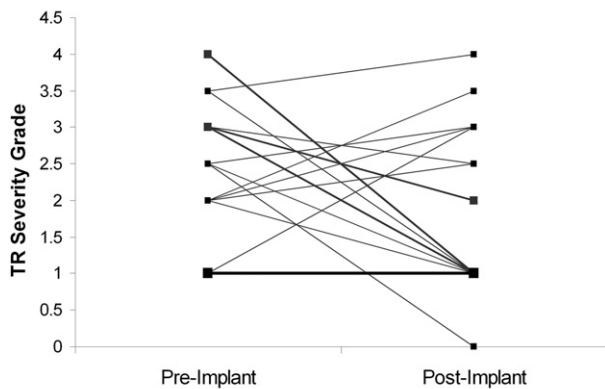


Figure 2 Individual changes are shown in the severity of tricuspid regurgitation (TR) pre-implant and at 202 ± 86.2 days post-implant.

indices of RV function such as RVS_W and RVS_{WI} also significantly decreased.

Echocardiographic parameters of RV function demonstrated a significant reduction in TAPSE as well as a trend towards improvement of TR severity after LVAD support. 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.¹⁶

It is important to note that the reductions of RVS_W, RVS_{WI}, and TAPSE that were seen after HMII implantation were in the setting of the unloaded heart with augmented cardiac output. A reduction in these parameters associated with increased right- and left-sided filling pressures would certainly suggest worsening RV function. However, given significant reductions in PCWP during LVAD support along with augmented CO, a decrease in RVS_W, RVS_{WI} 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.^{17–19}

In a review by Santamore and Gray,⁷ 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. 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 pre-load. It should be noted the primary benefit to RV function after LVAD placement is from a reduction in the secondarily elevated pulmonary artery pressures and its subsequent favorable effect on RV function and performance. Research showing patients supported with an LVAD alone demonstrated less structural remodeling in the RV than when

supported with BIVADs confirmed that the favorable changes seen in RV function are primarily a result of the hemodynamic benefits of LV unloading.²⁰

The low incidence of RV failure at our institution after HMII implantation that is associated with a significant decrease in RVS_{WI} differs from previous studies demonstrating a significant association with a decreased RVS_{WI} and post-LVAD RV failure and/or RVAD use.^{4,5} Several differences may account for this discrepancy. First, we studied exclusively BTT patients who received the newer-generation HMII axial continuous-flow pump as part of a multicenter trial with strict inclusion and exclusion criteria. Specifically, the trial excluded patients at high risk of needing an RVAD after HMII implantation.¹⁰ Second, the patient populations may have been different because most of the patients in our study were in New York Heart Association functional class IV with decompensated heart failure rather than patients presenting in acute cardiogenic shock with multiorgan dysfunction.

There is a paucity of evidence in the literature regarding the effects of the HMII on tricuspid insufficiency.^{21,22} Our observations after 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 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 moderate or severe TR at the time of LVAD placement predicted an increased risk of RV failure after LVAD and have recommended BIVAD or the total artificial heart for these patients. It remains unclear at this time whether to intervene surgically on TR in patients undergoing only LVAD placement, although our recommendations based on this study as well as our overall clinical outcomes suggests that at least moderate TR should be left alone.

The issue of pulmonary hypertension assumes importance when the efficacy of continuous-flow devices is evaluated. Previous studies showed a lesser degree of LV unloading with continuous-flow (vs pulsatile) devices but a similar degree of pressure unloading under resting conditions.^{23,24} Other end points, such as exercise performance, cellular recovery, and end-organ function, have also been shown to be similar for the 2 types of devices.^{25–27} Concerns have remained, however, about the ability of partial unloading of the LV 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),²⁸ 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. 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.

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 step-wise and systematic improvements in patient selection, better pre-operative optimization, improved operative techniques, and better post-operative management, such as improved optimization of RV function in the post-operative period. The absence of a large pre-peritoneal pocket, which was required with the larger pulsatile devices, has lessened the need for extensive dissection and reduced the incidence of post-operative bleeding. The reduced transfusion requirements after HMII placement may also have a beneficial effect on RV function after LVAD placement.

Our study has several limitations. This was a single-center retrospective study that would need to be verified prospectively, and it was limited by its relatively small number of patients. We also did not have a comparison group of patients treated with pulsatile devices. However, all of our HMII patients underwent LVAD placement over a relatively short period (approximately 3 years), so the surgical techniques and perioperative treatment protocols were consistent for this group. Tricuspid annular motion and the degree of TR were not obtained in all 40 patients who had hemodynamic measurements due to poor acoustic windows. One cardiologist interpreted echocardiographic data, but the reader was blinded to the data, and echocardiographic measurements were repeated at a minimum of 2 times as acoustic windows would allow.

In conclusion, the incidence of RV failure after HMII implantation at our institution is relatively 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 after LVAD implantation and up to almost 6 months of LVAD support. After HMII placement, there is a significant reduction in right- and left-sided filling pressures, augmentation of cardiac output, and in this context, reduction of RVSW, RVSWI, and TAPSE, suggesting a lusitropic effect on the RV. 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.

Disclosure statement

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