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The incidence, risk factors, and outcomes associated with late right-sided heart failure in patients supported with an axial-flow left ventricular assist device

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BACKGROUND: Early right-sided heart failure (RHF) after left ventricular assist device (LVAD) implantation is associated with increased mortality, but little is known about patients who develop late RHF (LRHF). We evaluated the incidence, risk factors, and clinical impact of LRHF in patients supported by axial-flow LVADs.

METHODS: Data were analyzed from 537 patients enrolled in the HeartMate II (HM II; Thoratec/St. Jude) destination therapy clinical trial. LRHF was defined as the development of clinical RHF accompanied by the need for inotropic support occurring more than 30 days after discharge from the index LVAD implant hospitalization. Clinical variables, quality of life, rehospitalizations, and survival were compared between patients with and without LRHF.

RESULTS: LRHF developed in 41 patients (8%), with a median time to LRHF of 480 days. A higher preoperative blood urea nitrogen and increased central venous pressure–to–pulmonary capillary wedge pressure ratio were independent predictors of LRHF. The Michigan and HMII RHF risk scores were both associated with an increased likelihood of LRHF ($p < 0.05$). Patients with LRHF had worse quality of life according to the Kansas City Cardiomyopathy Questionnaire (61 ± 26 vs 70 ± 21; $p < 0.05$), poorer

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functional capacity by 6-minute walk distance (275 ± 189 m vs 312 ± 216 m; $p < 0.05$), and more rehospitalizations (6 vs 3; $p < 0.001$). LRHF was associated with decreased survival ($p < 0.001$).
CONCLUSIONS: LRHF is an important complication in patients with LVADs and is associated with worse quality of life, reduced functional capacity, more frequent hospitalizations, and worse survival compared with those without LRHF.
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Heart failure (HF) affects nearly 6 million Americans, accounts for more than 1 million annual United States hospitalizations, and is a progressive disorder that is usually fatal.[1] During the past 20 years, substantial advances in the field of mechanical circulatory support with the use of durable, left ventricular assist devices (LVADs) have resulted in significant, progressively improved survival in patients with advanced HF who are not eligible for or are too sick to wait to receive a heart transplant.[2,3] Despite the survival advantage afforded by LVADs to carefully selected patients with advanced HF, an increasing emphasis within the LVAD clinical community and among the regulatory authorities is being placed on a variety of other relevant post-LVAD outcome measures, particularly minimizing the frequency of adverse events and hospital readmissions, while maximizing quality of life (QOL) and maintaining excellent overall survival.[4]

Among the recognized complications of LVAD therapy is right-sided HF (RHF) occurring early after LVAD implantation. The reported incidence varies among studies, but early RHF (ERHF) is estimated to occur in 15% to 25% of all LVAD implants,[5] and this complication is associated with worse short-term and long-term survival.[6,7] However, an increasingly recognized and problematic clinical phenomenon is the development of RHF that occurs "late" after LVAD implantation (LRHF).[8] Yet, in contrast to ERHF, very few studies have addressed this vexing clinical problem of LRHF in the LVAD-supported patient.[9,10] Furthermore, although LRHF is a concern in all patients who receive an LVAD, it may be of particular importance in those implanted as destination therapy (DT), who are effectively ineligible for heart transplantation and thus have few therapeutic options when LVAD-associated complications such as LRHF occur.

In this study, we sought to determine the incidence, timing, risk factors, and clinical outcomes associated with LRHF in a large cohort of DT patients supported by a durable, axial-flow LVAD.

Methods

Study design and definitions

The data from this study were derived and analyzed from the prospective, multicenter HeartMate II DT clinical trial conducted across 38 United States centers.[3] Detailed inclusion and exclusion criteria for the trial have been previously reported.[3] The primary focus of this study was to define and better understand the features, risk factors, and outcomes associated with the clinical complication of LRHF in the LVAD-supported patient compared with those

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patients who do not develop ERHF or LRHF. To do so, the following definitions were used for the present analysis:

Patients were determined to have suffered LRHF if they experienced all of the following criteria:

1. They met the clinical trial definition of right ventricular dysfunction associated with symptoms of RHF, including hepatic congestion, peripheral edema, and jugular venous distension.
2. The RHF was severe enough to warrant readmission to the hospital accompanied by the initiation of inotropes.
3. The readmission occurred more than 30 days after discharge from the index LVAD implant hospitalization in an effort to avoid capturing cases that may be more consistent with early RHF.

ERHF was defined by:

1. The presence of right ventricular dysfunction associated with symptoms of RHF, including hepatic congestion, peripheral edema, and jugular venous distension.
2. The requirement of either the implant of a right ventricular assist device or the extended use of inotropes for more than 14 consecutive days post-LVAD implant or the need to reinitiate inotropes after 14 days post-implant but before 30 days after hospital discharge.
3. Despite the ERHF syndrome, the patient survived to at least 30 days after hospital discharge.

By default, those patients who did not meet the definitions of ERHF or LRHF were defined as having no RHF.

Study sample

The study sample was derived from the 637 patients who received an HMII LVAD in the HMII DT trial.[3] After excluding 51 patients who developed ERHF but did not survive 30 days after hospital discharge and 49 patients who died during the index hospitalization but not related to ERHF, we arrived at a final sample size of 537 patients who served as the cohort for the present study (Figure 1). The analysis also excluded patients who received the XVE device (Thoratec/St. Jude) or who received an HMII as an exchange for an XVE. We were careful to include only patients who survived to hospital discharge to avoid potentially biasing the analyses because, by definition, all patients with LRHF survived to hospital discharge. This also allowed us to evaluate the association between ERHF and LRHF events. Requiring a window of at least 30 days after hospital discharge before diagnosing LRHF was also important to exclude those patients more likely to have experienced an ERHF syndrome but not immediately identified. A clinical

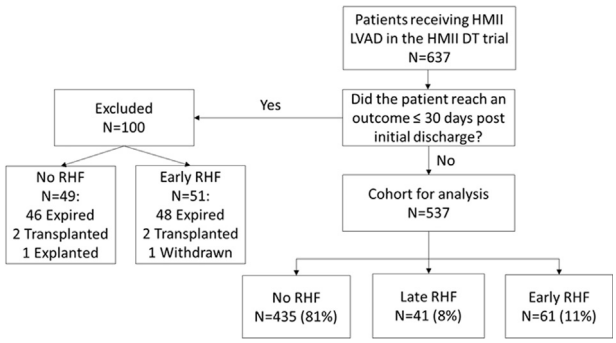

Figure 1 The HeartMate II (HMII) DT (destination therapy) trial enrolled 637 patients. After applying the defined inclusion criteria, which required patients to be alive by 30 days after discharge from the index hospitalization, 100 patients were excluded (49 who died during the index hospitalization unrelated to right-sided heart failure [RHF] and 51 who developed early RHF but died before 30 days after discharge) resulting in a final cohort of 537 patients. LVAD, left ventricular assist device.

events committee adjudicated all adverse events during the trial, including the outcome of RHF.

Variable selection

Baseline covariates analyzed included pre-operative demographic, laboratory, and other pertinent clinical data, including use of inotropes, vasopressors, intraaortic balloon pump, or mechanical ventilation. We also included invasive hemodynamic data (including right ventricular stroke work index and the pulmonary artery pulsatility index), echocardiographic data (including the qualitative degree of tricuspid regurgitation), and whether a concomitant tricuspid valve repair was performed during the LVAD implant. Previously defined composite risk scores for predicting early RHF, including the University of Michigan risk score and a risk score derived from the multivariate analysis of early RHF performed by Kormos et al[6] (HeartMate II RV Failure Risk Score) were also examined.[7,11]

Outcomes

In addition to survival, other important clinical outcomes measured included QOL and functional capacity assessments, which were evaluated before LVAD implantation (baseline) and at 1, 3, 6, 12, 18, and 24 months after implant. New York Heart Association Functional Classification at each of these time points was assessed independently by a physician, nurse, or other trained medical staff not directly involved with the patient's care at that time. Submaximal exercise performance was measured using the 6-minute walk distance (6MWD) measured in meters. HF-related QOL was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[12] An overall summary score is derived for the KCCQ by combining the individual domain scores, where the higher the score on the KCCQ, the higher the QOL. We also determined the time to first readmission, frequency of hospital readmissions, and days spent in the hospital as a result of readmissions.

Statistical analysis

Differences between baseline characteristics of patients with and without LRHF were evaluated with an independent samples *t*-test for normally distributed continuous variables, the Wilcoxon rank sum test for non-normal variables, or the Fisher exact test for categoric variables. For continuous variables, including the 6MWD and KCCQ, linear mixed-effects modeling was used to determine statistical significance. Post hoc comparisons were performed using the Scheffe test.

Stepwise multivariable logistic regression analyses were performed on univariable predictors of LRHF (entry criterion: $p < 0.10$, stay criterion: $p < 0.05$). Kaplan-Meier survival curves were created to evaluate survival, which was defined as continued LVAD support at the time of the last follow-up, LVAD explant due to recovery, or cardiac transplant. Survival between groups was analyzed by log-rank for linear trend. Unless otherwise specified, all continuous data are expressed as mean ± standard deviation. The level of statistical significance was set at $p < 0.05$. All statistical comparisons were 2-sided. Statistical analyses were done using SAS software (SAS Institute Inc., Cary, NC).

Results

The study cohort consisted of 537 patients (77% male) with a mean duration of support of 2.4 ± 1.5 years. There was no difference in days on LVAD support between those with LRHF and those with no RHF (834 ± 495 vs 895 ± 569 days; $p = 0.64$). Patients were a mean age of 63 ± 12 years, and the HF etiology was an ischemic cardiomyopathy in 59%. Pre-implant hemodynamic support included 77% of patients on inotropes and 19% supported by an intra-aortic balloon pump. Key baseline clinical characteristics of the patients at the time of LVAD implant, stratified by the development of LRHF or no RHF, are reported in Table 1.

Right-sided heart failure

A total of 41 patients developed LRHF (8%) while 435 patients (81%) did not develop RHF at any point following hospital discharge. ERHF developed in 61 patients (11%), but, interestingly, in only 4 of these patients did a LRHF syndrome subsequently occur. Among the 61 patients with ERHF, 12 required temporary right ventricular assist device support, with the remaining 49 patients requiring prolonged inotropic therapy for more than 14 consecutive days. The median time to development of LRHF was 480 days (range, 62–1,798 days) with 59% of the LRHF events developing more than 1 year post-LVAD implant (Figure 2).

Predictors of LRHF

Baseline demographic and clinical characteristics were generally similar between patients who did and did not develop LRHF, with a few notable exceptions (Table 1).

The difference between the groups in baseline use of intravenous vasoactive therapies, including vasopressor or inotropic support, baseline intraaortic balloon pump use, or the need for preoperative mechanical ventilation, was not statistically significant. There was also no significant difference in the presence of tricuspid regurgitation, presence of severe tricuspid regurgitation, or the proportion of patients undergoing concomitant tricuspid valve repair at the time of LVAD implant.

Table 1 Key Baseline Clinical Characteristics of Patients Who Did and Did Not Develop Late Right-Sided Heart Failure

Clinical variables[a]	No RHF (n = 435)	Late RHF (n = 41)	*p*-value[b]
Support duration, days	891 ± 567	834 ± 495	0.64
Age, years	63.3 ± 11.9	64.5 ± 13.5	0.25
Female	97 (22)	5 (12)	0.16
Body surface area, m^2	1.96 ± 0.28	2.07 ± 0.25	**0.02**
Body mass index, kg/m^2	26.9 ± 5.9	28.3 ± 5.5	0.13
Body mass index ≥ 30 kg/m^2	124 (29)	13 (32)	0.72
LV ejection fraction, %	16.8 ± 5.7	17.2 ± 4.9	0.48
Ischemic cardiomyopathy	254 (58)	25 (61)	0.87
Tricuspid regurgitation	234 (54)	27 (66)	0.14
Severe	45 (10)	4 (10)	1.00
Tricuspid valve repair	57 (13)	4 (10)	0.81
Aortic insufficiency	95 (22)	12 (29)	0.33
Mitral valve insufficiency	303 (70)	30 (73)	0.72
Aortic valve repair	37 (9)	2 (5)	0.56
Mitral valve repair	23 (5)	1 (2)	0.71
Pre-implant hemodynamic support			
Inotropes	325 (75)	35 (85)	0.18
Vasopressors	18 (4)	2 (5)	0.69
Intraaortic balloon pump	75 (17)	9 (22)	0.52
Ventilator support	13 (3)	1 (2)	1.00
Laboratory values			
Sodium, mEq/L	135.1 ± 4.2	134.7 ± 3.6	0.23
Blood urea nitrogen, mg/dl	31.8 ± 19.8	41.7 ± 40.0	**<0.05**
Creatinine, mg/dl	1.45 ± 0.54	1.59 ± 0.56	0.08
Albumin, g/dl	3.45 ± 0.57	3.35 ± 0.60	0.29
Aspartate aminotransferase, U/liter	40 ± 70	35 ± 18	0.77
Alanine aminotransferase, U/liter	43 ± 66	32 ± 35	0.07
Total bilirubin, mg/dl	1.18 ± 0.90	1.33 ± 0.71	0.06
Hemoglobin, g/dl	11.6 ± 1.9	11.4 ± 2.0	0.60
Platelet count, $10^3/\mu1$	211 ± 87	207 ± 93	0.53
White blood cell count, $10^3/\mu1$	7.7 ± 2.7	7.6 ± 2.6	0.71
International normalized ratio	1.34 ± 0.73	1.31 ± 0.25	0.13
Pre-implant hemodynamics			
Blood pressure, mm Hg			
Systolic	103 ± 15	106 ± 15	0.33
Diastolic	63 ± 11	60 ± 13	0.14
CVP, mm Hg	12.6 ± 6.5	13.6 ± 5.9	0.31
PAP, mm Hg			
Systolic	52.7 ± 13.9	54.3 ± 12.3	0.48
Diastolic	25.6 ± 8.1	25.6 ± 7.4	0.94
Mean	36.0 ± 9.5	36.3 ± 7.7	0.84
PVR, Wood units	3.46 ± 1.83	3.44 ± 2.01	0.70
PCWP, mm Hg	24.6 ± 8.8	23.9 ± 6.3	0.71
Cardiac index, liters/min/m^2	2.0 ± 0.6	2.1 ± 0.6	0.15
CVP-to-PCWP ratio	0.52 ± 0.26	0.62 ± 0.30	**<0.05**
PAP-to-CVP ratio	4.0 ± 3.9	3.3 ± 2.0	0.29
PA pulsatility index[c]	3.13 ± 3.74	2.75 ± 2.24	0.55
RVSWI, mm Hg/ml/m^2	556 ± 281	590 ± 302	0.43
Early RHF risk scores			
HMII RV Risk Score	1.16 ± 1.58	1.76 ± 1.56	**<0.01**
University of Michigan Risk Score	0.76 ± 1.58	1.23 ± 1.89	**<0.05**

CVP, central venous pressure; HMII, HeartMate II (Thoratec/St. Jude); LV, left ventricular; PA, pulmonary artery; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHF, right-sided heart failure; RV, right ventricular; RVSWI, right ventricular stroke work index.

[a]Continuous variables are shown as the mean ± standard deviation and categoric variables as number (%).

[b]Bold values are statistically significant ($p < 0.05$).

[c]Calculated as (PA systolic – PA diastolic)/CVP.

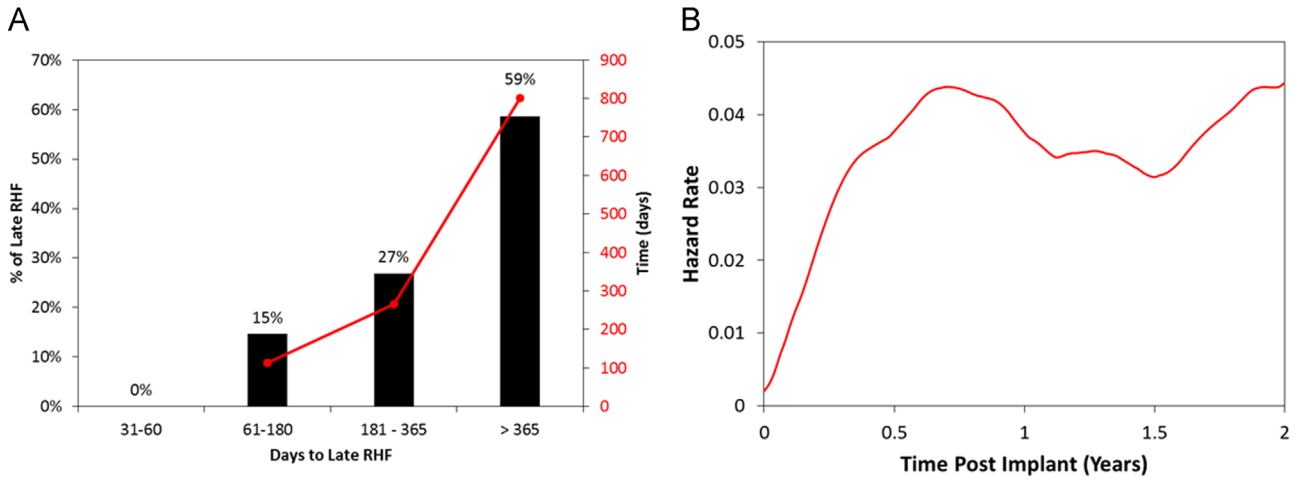

Figure 2 (A) The bar graph depicts the proportion of patients in whom late right-sided heart failure (RHF) developed at various intervals. The line graph depicts the average time to developing late RHF over time. Only a small percentage of late RHF developed before 180 days after left ventricular assist device implant, with most cases developing more than 1 year after implant. (B) A plot of the hazard function demonstrates the time course of developing late RHF. The rate of late RHF appears to peak between approximately 180 days and 1 year after left ventricular assist device implant and remains nearly constant thereafter.

Also notable was the absence of significant differences in baseline invasive hemodynamic values among the 2 cohorts with the exception of the right atrial pressure–to–pulmonary capillary wedge pressure (PCWP) ratio, which was higher among patients with LRHF than in those without RHF (0.62 ± 0.30 vs 0.52 ± 0.26; $p < 0.05$).

Among the measured laboratory values, baseline blood urea nitrogen (BUN) levels were higher in those who developed LRHF (41.7 ± 40 mg/dl vs 31.8 ± 19.8 mg/dl; $p < 0.05$), with a trend toward higher baseline serum creatinine in this cohort as well but no significant differences were seen in measured hematologic markers or laboratory values of hepatic function.

Given the theoretical concern that set pump speed might influence RV function over time, we collected data on the documented pump speed each month from baseline through 12 months after implant. No differences in pump speed were noted across time between patients with LRHF (9,386 ± 397 rpm) and without RHF (9,420 ± 445 rpm; $p = 0.47$).

One might speculate that the occurrence of ERHF that resolves might be predictive of subsequent LRHF, but this was not observed. Specifically, 6% of patients with ERHF developed LRHF compared with 8% of patients without ERHF who developed LRHF ($p = 0.81$). Also, among the 2 most notable risk-prediction models for ERHF are the HeartMate II and University of Michigan RV Risk Scores. Patients with LRHF had significantly higher HeartMate II and University of Michigan RV Risk Scores, respectively, compared with those with no RHF (Table 1).

Quality of life

Compared with patients without RHF, LRHF was associated with significantly worse QOL as reflected by reduced KCCQ scores from the first month after implantation through 24 months of support ($p = 0.009$, Figure 3). Baseline scores were similar. During the 24 months of support, the mean KCCQ score for patients with late RHF (51 ± 24) was lower than scores for patients without RHF (57 ± 26; $p = 0.009$).

Functional capacity

The baseline 6MWD was similar for patients with and without LRHF (192 ± 90 m vs 205 ± 130 m; $p =$ not significant). However, there were significant differences in the 6MWD between the 2 cohorts over time, and the mean 6MWD at 24 months was 265 ± 135 m for patients with LRHF compared with 373 ± 303 m for those without RHF ($p < 0.05$).

Hospitalizations

A comparison of clinically relevant variables surrounding hospitalizations between the 2 cohorts is reported in Table 2. Index hospital length of stay after LVAD implant was longer in patients who subsequently developed LRHF than in those without RHF (27 [range, 14–69] days vs 22 [range, 7–135]

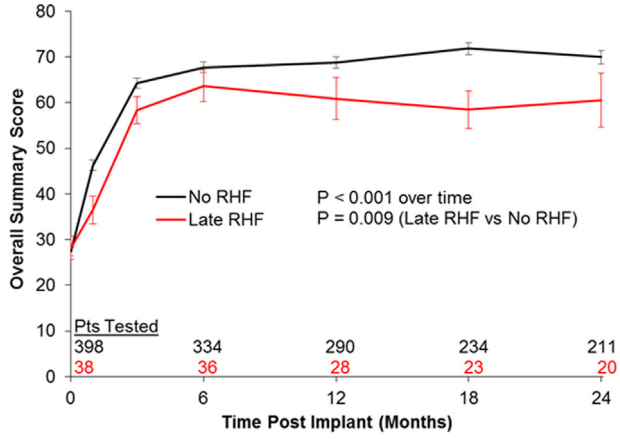

Figure 3 Quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire, was consistently lower at all measured times in those with late right-sided heart failure (RHF) compared with those without late RHF. The error bars show the standard deviation.

Table 2 Burden of Rehospitalizations in Patients Who Did and Did Not Develop Late Right-Sided Heart Failure

Parameter[a]	No RHF (n = 435)	Late RHF (n = 41)	p-value[b]
Patients rehospitalized	395 (91)	41 (100)	**<0.05**
Rehospitalizations, No.	3 (0–27)	6 (2–19)	**<0.01**
Days to first rehospitalization	92 (9–1,464)	96 (20–1,109)	0.75
Days of rehospitalization			
Total duration	27 (0–341)	62 (2–157)	**<0.01**
VAD-AE related	17 (0–288)	40 (0–154)	**<0.01**
Non–VAD-AE related	0 (0–137)	2 (0–89)	0.57
Days in the hospital (initial + rehospitalizations)	52 (7–397)	95 (17–194)	**<0.01**
Days out of the hospital	806 (0–2,610)	637 (111–2,182)	0.39

AE, adverse event; RHF, right-sided heart failure; VAD, ventricular assist device.
[a]Continuous data are presented as median (range) and categoric data as number (%).
[b]Bold values are statistically significant ($p < 0.05$).

days; $p < 0.05$). After discharge, compared with those without RHF, those who developed LRHF suffered more subsequent rehospitalizations (6 [range, 2–19] vs 3 [range, 0–27]; $p < 0.001$) and had a longer accumulated length of stay during those hospitalizations (62 [range, 2–157] days vs 27 [range, 0–341] days; $p < 0.001$). However, there was no difference in the time to the first rehospitalization between the 2 groups.

Survival

Long-term survival after LVAD implant was notably worse in those with LRHF compared with those without RHF, including at 1 year (78% ± 6% vs 84% ± 2%), 2 years (58% ± 8% vs 71% ± 2%), and 3 years (36% ± 8% vs 56% ± 3%; Figure 4A). Interestingly, a sub-group analysis of survival among ERHF patients compared with LRHF patients found worse survival among those with LRHF ($p = 0.01$; Figure 4B). When survival was analyzed from the time of diagnosis of LRHF rather than from the time of implant, survival was 38% ± 8% at 1 year and 22% ± 7% at 2 years (Figure 5). Despite this being a DT trial, 76 patients (14%) ultimately received a transplant, and the LVAD in 15 patients (3%) was explanted because of recovery.

Discussion

Major findings in this study of more than 500 patients receiving an axial-flow LVAD as DT include:

1. Nearly 10% of patients will develop LRHF severe enough to require rehospitalization and initiation of inotropes.
2. LRHF is associated with considerable morbidity, including lower QOL, worse exercise capacity, and more frequent rehospitalizations of prolonged durations.
3. LRHF is associated with reduced survival, worse even than those who develop ERHF after LVAD implant in those who survive to hospital discharge.

Epidemiology of LRHF

With increasing numbers of patients supported with durable LVADs for refractory left HF has come the observation that a RHF syndrome will develop in a considerable percentage of patients months to years after LVAD implant. Whereas the occurrence of early RHF after LVAD implant has been extensively studied,[6,7,13–16] only recently have published reports emerged attempting to characterize the phenomenon of LRHF in LVAD patients.[9,10] In 2010, Kormos et al[6] reported the incidence and risk factors of RHF after LVAD implant in the HeartMate II bridge-to-transplant trial. Although patients were stratified into "early" and "late" RHF cohorts, this was effectively a study of early RHF post-LVAD implant because "late" RHF was defined by the need to reinitiate inotropes more than 14 days after LVAD implant but during the same index implant hospitalization.[6] Importantly, however, predictors of RHF in this study served as the basis for the development of the HeartMate II RV failure risk score.[6,17]

More recently, Takeda et al[10] retrospectively analyzed their single-center experience of LRHF after LVAD implant, defined as the need for rehospitalization for RHF.[10] Although they found a similar 11% incidence of LRHF as we did in the present study, surprisingly, they found no difference in survival while on LVAD support between those with and without LRHF. One possible explanation for this discrepancy is that 50% of patients in that study received a heart transplant, perhaps limiting the ability to detect long-term differences in survival on LVAD support. Equally interesting is their observation of a significantly worse survival in those who received a transplant after LRHF occurred. This finding might lead one to speculate that their survival might have been poor had they remained on LVAD support and not received a transplant given the poor outcomes associated with LRHF as described in the current report with survival rates of only 38% at 1 year and 22% at 2 years (Figure 5). The present study's evaluation of the epidemiology of LRHF in LVAD-supported patients has also assessed and confirmed its association with worse QOL and functional capacity in addition to worse survival in these patients.

Mechanisms of LRHF

The potential mechanisms responsible for LRHF in LVAD patients warrant discussion. One possibility is that the alterations in several key physiologic domains occurring in an

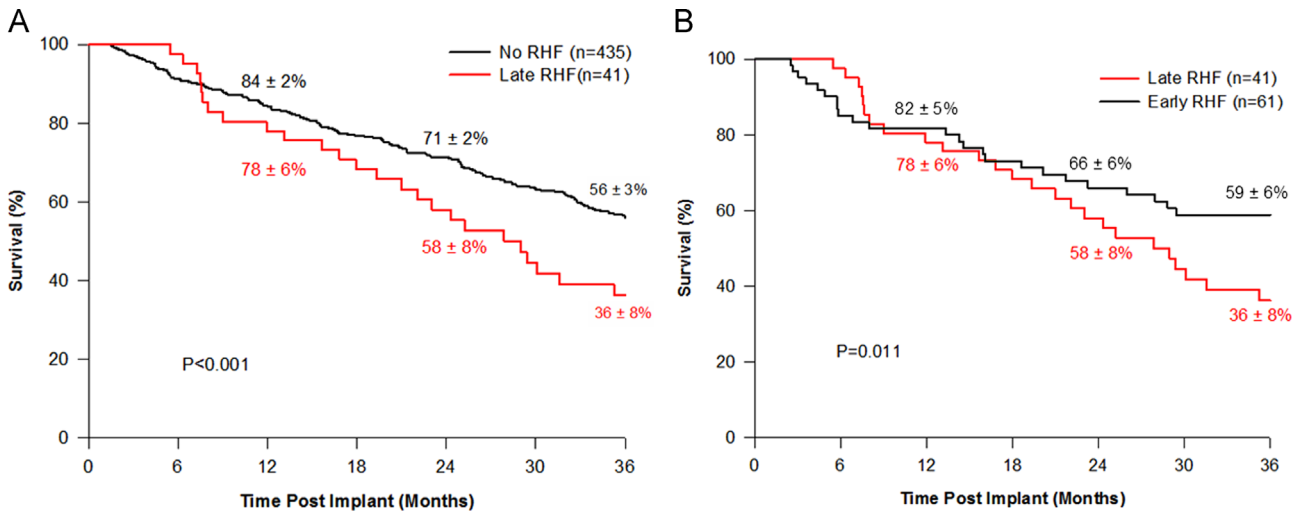

Figure 4 (A) The development of late right-sided heart failure (RHF) was associated with a significantly reduced survival, with a nearly 50% mortality at 2 years after implant. (B) Interestingly, long-term survival is worse in late RHF patients than in patients who develop an early RHF syndrome but ultimately survive to at least 30 days after hospital discharge.

LVAD-supported patient are sufficient to explain the worsening right-sided heart function over time. In the pre-implant period, most patients are in low cardiac output states[3,18]; after LVAD implant, cardiac output increases, which increases venous return to the "unsupported" RV, increasing RV wall stress and potentially contributing to eventual LRHF over time. In fact, elegant work detailing important differences in molecular and cellular changes occurring in the LV and RV, respectively, supports the clinical observations. Whereas prolonged LVAD support results in lower end-diastolic volumes, a reduction in myocyte hypertrophy, and an increased in SERCA-2a (sarco/endoplasmic reticulum Ca^{2+} adenosine 5'-triphosphatase) expression in the LV, such reverse remodeling does not occur in the RV.[19] In addition, many relevant biomarkers of residual cardiovascular stress, fibrosis, and inflammation remain elevated months after LVAD implant.[20]

Another important consideration is the effect on interventricular septal geometry and function. The chronic leftward shift of the LV septum may contribute to the development and/or worsening of tricuspid regurgitation.[21] Moreover, the importance of the septal contribution to RV function should not be underestimated, which may be diminished during durable LVAD support.[22,23] Finally, the extent of the theoretically favorable effect on RV function accompanying a reduction in pulmonary hypertension and RV afterload associated with LV unloading during LVAD support is unclear.[19] Whereas most pre-existing pulmonary hypertension will resolve over time in the LVAD-supported patient, a small percentage of patients may persist with an elevated pulmonary vascular resistance (and residual RV afterload) attributable to advanced pulmonary vascular remodeling from long-standing elevations in left atrial pressure.[24]

Our findings also support the likelihood that a component of LRHF in some patients is due to progression of their underlying, pre-implant RV dysfunction irrespective of the physiologic changes attributable to the LVAD itself. Supporting this assertion is our finding that LRHF was not any more likely to develop in those with ERHF after LVAD implant than in those without ERHF. Furthermore, the predictors of LRHF, namely a higher preoperative BUN, central venous pressure–to–PCWP ratio, and higher HeartMate II and Michigan RV failure risk scores, respectively, support the notion that many of these patients had significant, pre-existing RV dysfunction at the time of implant, which ultimately progressed to overt RHF over time.

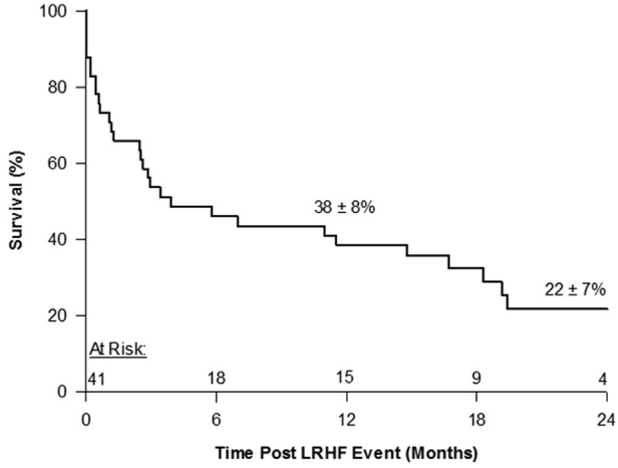

Figure 5 Survival is poor from the time late right-sided heart failure (RHF) is diagnosed, with a nearly 80% mortality at 2 years.

Management of LRHF

Our findings that patients with LRHF have significant impairments in QOL and exercise capacity, require frequent hospital readmissions, and have worsened survival all highlight the need to define the optimal approach to the prevention and management of LRHF. Independent predictors of LRHF found in this study, including an elevated BUN and central venous pressure–to–PCWP ratio, may to some extent help with patient selection regarding the decision to implant an LVAD at all and/or to help determine

whether up-front durable biventricular support should be considered. However, particularly in a DT patient population, implanting biventricular assist devices other than in highly select cases is largely impractical at the present time. Smaller devices, such as the HeartWare MVAD (HeartWare Inc.) and Circulite (HeartWare Inc.), which are currently under development or in clinical trials (clinicaltrials.gov NCT01831544 and NCT00878527), may one day allow for this strategy.

Presently, a more critical issue is how to best prevent or at least delay progression to LRHF in the LVAD-supported patient. We found that the median time to LRHF was 480 days post-LVAD implant, which raises the question about the best prevention strategies before the LRHF syndrome develops. Reinstituting, continuing, and/or uptitrating guideline-directed medical heart failure therapy, such as β-blockers, renin-angiotensin blockade, and aldosterone blockade, would seem to be logical given their indisputable benefits in patients with LV systolic heart failure, even with concomitant RV dysfunction before LVAD implant.[25] As in LV failure, neurohormonal upregulation also occurs in clinical settings of isolated RV failure.[26] Yet, until carefully designed studies are performed to prove their benefit, the judicious use of these agents should best be recommended case-by-case. The improvement in RV function associated with guideline-directed medical heart failure therapy in many patients with LV systolic HF may be largely a result in improvements in LV function with only indirect benefits on RV function.[27]

Other areas requiring further investigation include the effect of pacing strategies, including biventricular pacing on RV function after LVAD implant.[28] The use of pulmonary vasodilators, which may have benefits in select cases of ERHF after LVAD,[29] have yet to be shown beneficial in preventing or treating LRHF, although this requires further study, particularly as it might relate to patients with residual pulmonary hypertension.

Finally, once patients have recovered from the perioperative phase after LVAD implant and are demonstrating the benefits of adequate LV unloading, studies are needed to determine how to optimally tailor pump settings and loading conditions specifically to optimize RV performance. Many studies to date using advanced imaging, invasive hemodynamics, and ramp studies aim to balance LV unloading with aortic valve opening and other left-sided parameters. However, RV function is known to be an independent predictor of exercise capacity in patients with left-sided HF[30]; and, particularly in a DT population, our finding of reduced QOL and impaired exercise capacity in LRHF is arguably as important as its association with reduced survival. The emergence of speckle tracking and 3-dimensional echocardiography may be of particular value in evaluating for subtle but relevant changes in RV function during durable LVAD support, but this requires further study.[11]

Limitations

This study has several limitations that should be mentioned. First, our estimate of an approximate 8% incidence of LRHF is likely an underestimate of the total burden imposed by RHF because we restricted our definition to requiring both rehospitalization for RHF and of sufficient severity to need treatment with inotropes. Many more patients on LVAD support in this study could have had a less severe form or stage of LRHF, further highlighting the importance of this complication.

Also, this study included only patients with a HeartMate II axial-flow LVAD; thus, although these data can likely be extrapolated to other continuous-flow LVADs, including those using centrifugal flow, this remains speculative and requires confirmation. Finally, this study was restricted to patients implanted with a continuous-flow LVAD as DT, given that our aim was to evaluate true "late" RHF while on LVAD support, which would not be possible to fully evaluate in a bridge-to-transplant population. However, further study including patients who received an LVAD as bridge to transplant but who remain on long-term LVAD support is warranted.

Conclusions

This is the largest study to date to evaluate the clinically relevant complication of LRHF during LVAD support. LRHF is associated with significant morbidity highlighted by its association with recurrent hospitalizations, reduced QOL, and impaired exercise capacity. LRHF is also associated with reduced long-term survival. Optimal strategies to prevent and treat LRHF remain unclear at this time and underscore the need for future studies to directly address this complication.

Disclosure statement

J.D.R. has served as a consultant for HeartWare. C.P. has served as a consultant for HeartWare and Thoratec/St. Jude. S.J. has received speaker honoraria from Thoratec/St Jude. J.K. has received research support from Thoratec/St. Jude. P.E. has served as a consultant for Thoratec/St. Jude. K.S. is an employee of Thoratec/St. Jude. B.B. has served as a consultant for Medtronic. N.U. has served as a consultant for HeartWare, Thoratec/St. Jude, and Abiomed. M.K. has received research support from Thoratec/St. Jude and speaker honoraria from HeartWare. All of the authors have received travel support from Thoratec/St. Jude to participate in EMERG network research meetings.

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References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2014;129:e28-292.
2. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-43.
3. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.
4. U.S. Department of Health and Human Services. Serious adverse events with implantable left ventricular assist devices (LVADs): FDA

safety communication. August 2015. Available at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm457327.htm.
5. Rich JD. Right ventricular failure in patients with left ventricular assist devices. Cardiol Clin 2012;30:291-302.
6. Kormos RL, Teuteberg JJ, Pagani FD, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg 2010;139:1316-24.
7. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163-72.
8. MacGowan GA, Schueler S. Right heart failure after left ventricular assist device implantation: early and late. Curr Opin Cardiol 2012;27:296-300.
9. Kapelios CJ, Charitos C, Kaldara E, et al. Late-onset right ventricular dysfunction after mechanical support by a continuous-flow left ventricular assist device. J Heart Lung Transplant 2015;34:1604-10.
10. Takeda K, Takayama H, Colombo PC, et al. Late right heart failure during support with continuous-flow left ventricular assist devices adversely affects post-transplant outcome. J Heart Lung Transplant 2015;34:667-74.
11. Stainback RF, Estep JD, Agler DA, et al. Echocardiography in the management of patients with left ventricular assist devices: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2015;28:853-909.
12. Hu FB, Stampfer MJ, Solomon C, et al. Physical activity and risk for cardiovascular events in diabetic women. Ann Intern Med 2001;134:96-105.
13. Dang NC, Topkara VK, Mercando M, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant 2006;25:1-6.
14. Fitzpatrick JR 3rd, Frederick JR, Hsu VM, et al. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. J Heart Lung Transplant 2008;27:1286-92.
15. Kavarana MN, Pessin-Minsley MS, Urtecho J, et al. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. Ann Thorac Surg 2002;73:745-50.
16. Kukucka M, Stepanenko A, Potapov E, et al. Right-to-left ventricular end-diastolic diameter ratio and prediction of right ventricular failure with continuous-flow left ventricular assist devices. J Heart Lung Transplant 2011;30:64-9.
17. Kiernan MS, Sundareswaran KS, Pham DT, et al. Preoperative determinants of quality of life and functional capacity response to left ventricular assist device therapy [e-pub ahead of print]. J Card Fail http://dx.doi.org/%2010.1016/j.cardfail.2016.01.0062016, accessed April 22, 2016.
18. Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191-200.
19. Barbone A, Holmes JW, Heerdt PM, et al. Comparison of right and left ventricular responses to left ventricular assist device support in patients with severe heart failure: a primary role of mechanical unloading underlying reverse remodeling. Circulation 2001;104:670-5.
20. Ahmad T, Wang T, O'Brien EC, et al. Effects of left ventricular assist device support on biomarkers of cardiovascular stress, fibrosis, fluid homeostasis, inflammation, and renal injury. JACC Heart Fail 2015;3:30-9.
21. Piacentino V 3rd, Williams ML, Depp T, et al. Impact of tricuspid vaanlve regurgitation in patients treated with implantable left ventricular assist devices. Ann Thorac Surg 2011;91:1342-6; discussion 1346-7.
22. Palardy M, Nohria A, Rivero J, et al. Right ventricular dysfunction during intensive pharmacologic unloading persists after mechanical unloading. J Card Fail 2010;16:218-24.
23. Saleh S, Liakopoulos OJ, Buckberg GD. The septal motor of biventricular function. Eur J Cardiothorac Surg 2006;29(Suppl 1):S126-38.
24. John R, Liao K, Kamdar F, Eckman P, Boyle A, Colvin-Adams M. Effects on pre- and posttransplant pulmonary hemodynamics in patients with continuous-flow left ventricular assist devices. J Thorac Cardiovasc Surg 2010;140:447-52.
25. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:1810-52.
26. Nootens M, Kaufmann E, Rector T, et al. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension: relation to hemodynamic variables and endothelin levels. J Am Coll Cardiol 1995;26:1581-5.
27. Massie B, Kramer BL, Topic N, Henderson SG. Hemodynamic and radionuclide effects of acute captopril therapy for heart failure: changes in left and right ventricular volumes and function at rest and during exercise. Circulation 1982;65:1374-81.
28. Gopinathannair R, Birks EJ, Trivedi JR, et al. Impact of cardiac resynchronization therapy on clinical outcomes in patients with continuous-flow left ventricular assist devices. J Card Fail 2015;21:226-32.
29. Tedford RJ, Hemnes AR, Russell SD, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail 2008;1:213-9.
30. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995;25:1143-53.