Risk Factors Predictive of Right Ventricular Failure After Left Ventricular Assist Device Implantation

Stavros G. Drakos, MD[a,b,c], Lindsay Janicki, MS[a,b], Benjamin D. Horne, PhD[a], Abdallah G. Kfoury, MD[a,b], Bruce B. Reid, MD[a,b], Stephen Clayson, MD[a], Kenneth Horton, RCS[a], Francois Haddad, MD[d], Dean Y. Li, MD, PhD[b], Dale G. Renlund, MD[a,b], and Patrick W. Fisher, DO, PhD[a,e,*]

Right ventricular failure (RVF) after left ventricular assist device (LVAD) implantation appears to be associated with increased mortality. However, the determination of which patients are at greater risk of developing postoperative RVF remains controversial and relatively unknown. We sought to determine the preoperative risk factors for the development of RVF after LVAD implantation. The data were obtained for 175 consecutive patients who had received an LVAD. RVF was defined by the need for inhaled nitric oxide for ≥48 hours or intravenous inotropes for >14 days and/or right ventricular assist device implantation. An RVF risk score was developed from the β coefficients of the independent variables from a multivariate logistic regression model predicting RVF. Destination therapy (DT) was identified as the indication for LVAD implantation in 42% of our patients. RVF after LVAD occurred in 44% of patients (n = 77). The mortality rates for patients with RVF were significantly greater at 30, 180, and 365 days after implantation compared to patients with no RVF. By multivariate logistic regression analysis, 3 preoperative factors were significantly associated with RVF after LVAD implantation: (1) a preoperative need for intra-aortic balloon counterpulsation, (2) increased pulmonary vascular resistance, and (3) DT. The developed RVF risk score effectively stratified the risk of RV failure and death after LVAD implantation. In conclusion, given the progressively growing need for DT, the developed RVF risk score, derived from a population with a large percentage of DT patients, might lead to improved patient selection and help stratify patients who could potentially benefit from early right ventricular assist device implantation. **(Am J Cardiol 2010;105:1030–1035)**

Implantation of a left ventricular assist device (LVAD) has proved to be a successful treatment option for patients with end-stage heart failure, as either a bridge to transplantation (BTT) or permanent ("destination") therapy (DT).[1–4] However, a significant proportion of patients who undergo implantation with an LVAD develop significant right ventricular failure (RVF) that adversely affects the outcome.[5–10] In medically nonresponsive patients, implantation of a right ventricular assist device (RVAD) might be necessary.[5–11] It appears, however, that early planned institution of biventricular mechanical circulatory support results in improved outcomes compared to delayed conversion of an LVAD to biventricular mechanical support.[12,13] However, the determination of which patients under consideration for advanced therapy with an LVAD are at a greater risk of developing intraoperative or early postoperative RVF remains controversial and relatively unknown. Hence, the aim of the present study was to attain a better understanding of the perioperative risk factors that are predictive of postoperative RVF in patients receiving an LVAD as BTT or DT. Moreover, we sought to define a novel risk score model derived from a large, single-center population with a large number of both DT and BTT patients.

Methods

The analysis was performed using a prospectively collected database from a large-volume, single center of 175 LVAD patients who underwent implantation from 1993 to 2008. The patients underwent implantation with the HeartMate XVE (n = 82, 47%), HeartMate VE (n = 42, 24%), HeartMate 1000 IP (n = 17, 10%), HeartMate II (n = 25, 14%; all devices manufactured by Thoratec, Pleasanton, California) or the Novacor device (n = 9, 5%; World Heart, Oakland, California). The LVADs were placed as BTT in 58% of the patients and as DT in 42% of the population. RVF was defined by the need for RVAD implantation, the need for inhaled nitric oxide for ≥48 hours, or the need for intravenous inotrope therapy for >14 consecutive days.

Clinically relevant data were collected from the patient population, ≤24 hours before implantation, within a 2-week period to determine the clinical and hemodynamic predictors for RVF after LVAD implantation. The clinical vari-

[a]Cardiovascular Department, Intermountain Medical Center, Salt Lake City, Utah; [b]University of Utah School of Medicine, Salt Lake City, Utah; [c]Third Cardiology Department, University of Athens, Athens, Greece; [d]Stanford University Medical School, Palo Alto, California; and [e]The Mechanical Circulatory Support Program, Ochsner Clinic Foundation, New Orleans, Louisiana. Manuscript received September 5, 2009; revised manuscript received and accepted November 16, 2009.

*Corresponding author: Tel: (801) 209-7630; fax: (504) 842-4184.
E-mail address: pwfisher@stanfordmedalumni.org (P.W. Fisher).

0002-9149/10/$ – see front matter
doi:10.1016/j.amjcard.2009.11.026

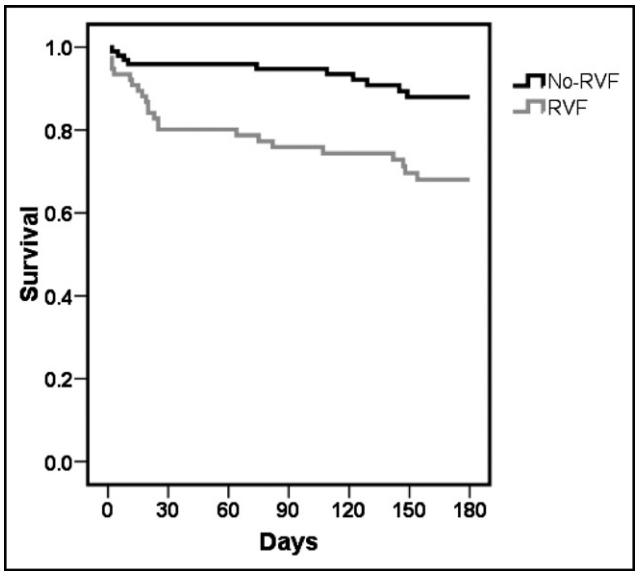

Figure 1. Survival curves 6 months after LVAD for patients with RVF compared to those without.

ables obtained before LVAD implantation included demographics, medications, preimplant inotrope dependency, preoperative intra-aortic balloon pump, intubation, and comorbidities. The preoperative laboratory data included sodium, hemoglobin, white blood cell count, platelets, uric acid, total cholesterol, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, creatinine, blood urea nitrogen, and so forth. The hemodynamic data included measurements of the right atrial pressure, right ventricular systolic pressure, systolic pulmonary artery pressure, mean pulmonary artery pressure, and diastolic pulmonary artery pressure, pulmonary capillary wedge pressures, cardiac output, cardiac index, pulmonary vascular resistance and systemic vascular resistance. The right ventricular stroke work was calculated using the equation: right ventricular stroke work = cardiac output/[heart rate × (mean pulmonary artery pressure − right atrial pressure) × 0.0136]. Before LVAD implantation, 2-dimensional echocardiography with pulsed, continuous wave, and color flow Doppler was obtained. The measurements obtained included left ventricular ejection fraction and fractional shortening, left and right atrial area, left ventricular internal dimensions at end-diastole and end-systole, intraventricular septum, and left ventricular posterior wall dimensions.

Univariate analysis was performed using the Student *t* test for continuous variables and the chi-square test for the categorical variables to perform between-group comparisons for those patients with RVF and those without. For all analyses, $p \leq 0.05$ was considered statistically significant and a univariate predictor of RVF after LVAD implantation. Backward and forward step-wise multivariate logistic regression analyses were performed for all variables according to groupings of related variables. Nominal statistical significance was set at $p \leq 0.05$, with other variables included for $p < 0.10$, with an odds ratio >1.5 or <0.67 or for those parameters with substantial confounding effects (change in the regression β coefficient $>10\%$) on variables included using the first 2 criteria. A RVF risk score was created by rounding the exponentiated regression model coefficients to the nearest 0.5. The risk score thresholds were determined using recursive partitioning according to data from the receiver operating characteristic curve of the RVF risk score's ability to predict patients' RVF status. The area under the curve was calculated using a receiver operating characteristic curve of the RVF risk score. Kaplan-

Table 1
Preoperative clinical characteristics

Variable	RVF		p Value
	Yes (n = 77)	No (n = 98)	
Age (years)	58.2 ± 12.9	56.5 ± 14.4	0.417
Therapy			0.171
Bridge to transplantation	52%	62%	
Destination therapy	48%	37%	
Men	79%	87%	0.185
Body surface area (m^2)	2.00 ± 0.32	2.06 ± 0.27	0.249
Body mass index (kg/m^2)	27.4 ± 6.3	27.3 ± 5.6	0.89
Obesity (body mass index ≥30 kg/m^2)	34%	23%	0.132
Etiology			0.516
Ischemic	42%	37%	
Nonischemic	58%	63%	
Preoperative intra-aortic balloon counterpulsation	49%	31%	0.012
Preoperative intubation	43%	26%	0.016
Diabetes mellitus	23%	28%	0.531
Previous sternotomy	42%	45%	0.713
Smokers*	45%	41%	0.464

Data are presented as mean ± SD or %.
* Included both past and current smokers.

Table 2
Preoperative medications and laboratory data

Variable	RVF		p Value
	Yes (n = 77)	No (n = 98)	
Angiotensin-converting enzyme inhibitor	22%	34%	0.084
β Blocker	26%	21%	0.504
Intravenous inotropes	87%	79%	0.147
Angiotensin receptor blocker	9%	9%	0.502
Aldosterone	27%	27%	0.934
Allopurinol	9%	8%	0.844
Statin	22%	24%	0.681
Platelets (k/mm^3)	178.8 ± 95.9	212.2 ± 101.8	0.029
Lymphocyte	11.7 ± 7.4	12.8 ± 9.0	0.452
Uric acid (mg/dl)	8.2 ± 3.4	8.4 ± 3.2	0.811
Cholesterol (mg/dl)	117.7 ± 43.6	149.8 ± 50.2	0.019
Albumin (g/dl)	3.3 ± 0.7	3.3 ± 0.7	0.663
Total bilirubin (mg/dl)	1.8 ± 1.8	1.3 ± 1.1	0.05
Alanine aminotransferase (U/L)	212.1 ± 570.9	130.2 ± 286	0.227
Aspartate aminotransferase (U/L)	258.4 ± 720.2	157.5 ± 360.8	0.115
Creatinine (mg/dl)	1.8 ± 1.0	1.6 ± 0.8	0.176
Blood urea nitrogen (mg/dl)	34.4 ± 20.5	31.3 ± 19.4	0.315

Data are presented as mean ± SD or %.

Table 3
Preoperative hemodynamic measurements

Variable	RVF		p Value
	Yes (n = 77)	No (n = 98)	
Systolic blood pressure (mm Hg)	108.1 ± 17.6	107.6 ± 13.3	0.834
Diastolic blood pressure (mm Hg)	62.3 ± 11.4	63.0 ± 10.1	0.651
Heart rate (beats/min)	95.2 ± 14.5	96.0 ± 14.8	0.738
QRS >120 ms	68%	59%	0.297
Right atrial pressure (mm Hg)	11.6 ± 6.2	9.5 ± 5.1	0.023
Pulmonary artery systolic pressure (mm Hg)	48.9 ± 13.1	51.0 ± 14.6	0.381
Pulmonary artery diastolic pressure (mm Hg)	25.6 ± 7.2	24.4 ± 8.4	0.375
Mean pulmonary artery pressure (mm Hg)	34.5 ± 10.9	34.4 ± 10.6	0.921
Pulmonary capillary wedge pressure (mm Hg)	21.9 ± 7.5	21.8 ± 8.4	0.909
Pulmonary vascular resistance (Wood units)	3.6 ± 2.0	2.9 ± 1.8	0.485
Cardiac output (L/min)	4.5 ± 1.4	4.7 ± 1.7	0.451
Cardiac index (L/min/m^2)	2.2 ± 0.5	2.3 ± 0.9	0.415
Right ventricular stroke work (mm × Hg × ml/beat)	14.9 ± 7.8	17.4 ± 8.6	0.08

Data are presented as mean ± SD or %.

Table 4
Preoperative echocardiographic measurements

Variable	RVF		p Value
	Yes (n = 77)	No (n = 98)	
Ejection fraction (%)	21.1 ± 6.8	20.3 ± 6.7	0.456
Fractional shortening (%)	10.8 ± 6.8	10.1 ± 7.0	0.572
Left ventricular end-diastolic diameter (cm)	6.0 ± 1.1	6.5 ± 0.9	0.003
Left ventricular end-systolic diameter (cm)	5.4 ± 1.2	5.9 ± 1.1	0.007
Intraventricular septum (cm)	1.2 ± 0.3	1.1 ± 0.2	0.283
Left ventricular posterior wall (cm)	1.2 ± 0.3	1.1 ± 0.2	0.306
Left atrial area (cm^2)	28.4 ± 9.7	28.9 ± 6.8	0.738
Right atrial area (cm^2)	22.6 ± 6.6	22.6 ± 6.4	0.962

Data are presented as mean ± SD or %.

Meier survival curves were generated, and post-LVAD survival between those patients with and without RVF were analyzed using the log-rank test for linear trend. The analysis was conducted for 30-day, 6-month, and 1-year survival. Post-LVAD survival was defined as current LVAD support at the cutoff date for the study or successful cardiac transplantation. All data were analyzed using Statistical Package for Social Sciences, version 15.0 (SPSS, Chicago, Illinois) and are expressed as the mean ± SD, unless otherwise specified. The institutional review board approved the study, and all patients provided informed consent for collection of data used in the present study.

Results

Of the 175 patients analyzed, 77 (44%) experienced RVF after LVAD implantation. Of the 77 patients who were diagnosed with RVF, 45 (58%) were treated medically with either inotropes or inhaled nitric oxide, and 32 (42%) required the placement of an RVAD after LVAD implantation. The survival rate between the non-RVF and RVF groups was 96% versus 80% at 30 days (p = 0.0012), 90% versus 70% at 180 days (p = 0.0011; Figure 1), and 83% versus 62% at 365 days (p = 0.002).

Table 1 displays the preoperative clinical characteristics of those patients whose postoperative care was complicated by RVF compared to those who were free of RVF. The preoperative medications and laboratory values are listed in Table 2. Tables 3 and 4 summarize the preoperative hemodynamic and echocardiographic parameters. Independent variables or those with significant confounding effects that were retained after multivariate analysis (Table 5) were

Table 5
Multivariate predictors for right ventricular failure (RVF)

Variable	Odds Ratio	p Value
Full model		
Destination therapy	3.31	0.005
Inotrope dependency	2.47	0.08
Obesity (body mass index ≥30 kg/m^2)	1.99	0.08
Intra-aortic balloon counterpulsation	3.88	0.002
Pulmonary vascular resistance		
≤1.7 Wood unit	1.0	
1.8–2.7 Wood unit	1.95	0.22
2.8–4.2 Wood unit	3.01	0.045
≥4.3 Wood unit	4.14	0.012
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	0.49	0.054
β Blocker	1.60	0.258
Model with variables not included in full model*		
Left ventricular end-diastolic diameter	0.73	0.13
Left ventricular end-systolic diameter	0.77	0.19
Right atrial pressure	1.03	0.442
Right ventricular stroke work†	0.94	0.09
Bilirubin	1.17	0.261
Platelets	0.998	0.221
Intubation	1.944	0.208
Left ventricular ejection fraction	1.01	0.727

* Results for variables not included in primary model when they were added to the full model.

† Not included in primary model owing to concerns of model overfitting.

Table 6
Right ventricular risk score strata

Risk Score	Patients (n)	RVF
≤5.0	36	4 (11%)
5.5–8.0	48	18 (37%)
8.5–12	72	40 (56%)
≥12.5	18	15 (83%)

The risk score was calculated as the sum of the points assigned for the existence of each of the 8 perioperative variables. Destination therapy patients were given 3.5 points; intra-aortic balloon counterpulsation, 4 points; pulmonary vascular resistance, quartile 1 (≤1.7 Wood units), 1 point; quartile 2 (1.8–2.7 Wood units), 2 points; quartile 3 (2.8–4.2 Wood units), 3 points; and quartile 4 (≥4.3 Wood units), 4 points; inotrope dependency, 2.5 points; obesity, 2 points; angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker, −2.5 points; and β blocker, 2 points.

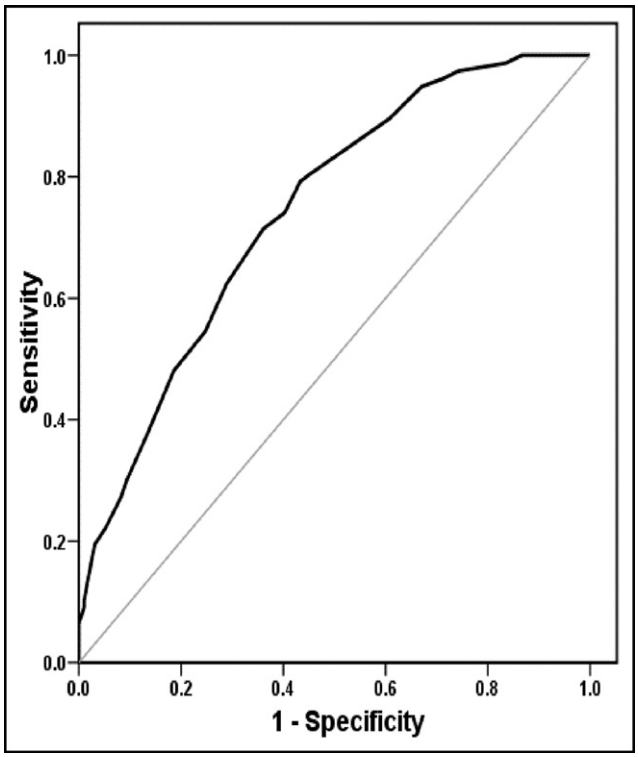

Figure 2. Receiver operating characteristic of right ventricular risk score.

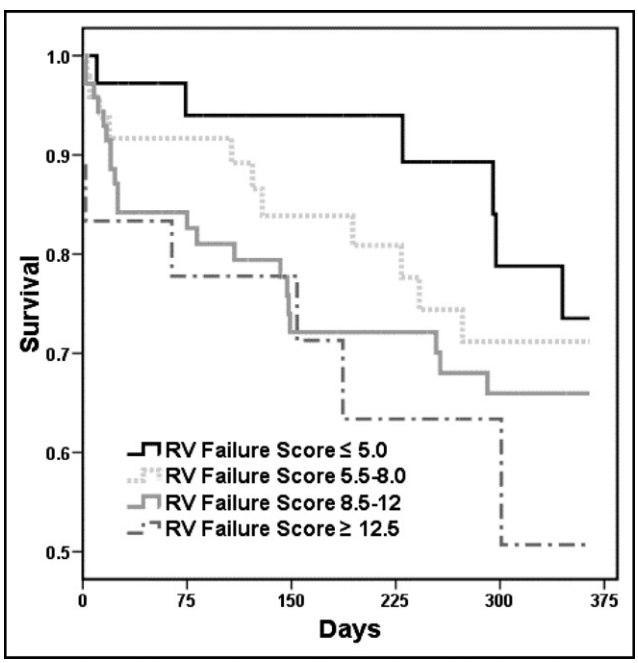

Figure 3. Survival curves 1 year after LVAD for each RVF risk score strata.

entered as factors of the RVF risk score. The risk score was calculated as the sum of the points assigned for the existence of each of 8 perioperative variables (Table 6). The risk score was then broken into 4 categories: ≤5.0, 5.5 to 8, 8.5 to 12, and ≥12.5 points (Table 6). Of the 36 patients who did not develop RVF, 32 (89%) had a right ventricular risk score of ≤5.0. Of the 18 patients with a risk score of ≥12.5 points, 15 (83%) developed RVF after LVAD implantation. The area under the curve for the risk score was 0.743 ± 0.037 (Figure 2). A comparison with a recently published risk score[8] was also undertaken. By application of that risk score's point values for vasopressor requirement, aspartate aminotransferase ≥80 IU/L, creatinine ≥2.3 mg/dl, and bilirubin ≥2.0 mg/dl to risk in this study population, an area under the curve of 0.61 ± 0.04 was found, considerably lower than the 0.73 reported by Matthews et al.[8]

Kaplan-Meier survival analyses were performed to compare the survival among the 4 different risk score categories (≤5.0, 5.5 to 8, 8.5 to 12, and ≥12.5 points). The corresponding 30-day survival rates after LVAD were 97%, 92%, 85%, and 83% for those categories (log-rank for linear trend $p = 0.029$). The corresponding survival rates at 180 days after LVAD were 94%, 85%, 75%, and 72% for the 4 categories ($p = 0.009$). The corresponding survival rates at 365 days were 83%, 77%, 71%, and 61% ($p = 0.046$; Figure 3). The generated survival curves indicated an increased rate of mortality for patients with a greater risk score for RVF. Furthermore, the survival analysis showed that RVF is predictive of survival and is independent of the RVF risk score. RVF had a hazard ratio of 1.83 (95% confidence interval 1.15 to 2.91; $p = 0.010$) in a Cox regression model with both RVF risk score and RVF entered as covariates.

Discussion

RVF in the early postoperative period after LVAD implantation remains a major cause of morbidity and mortality.[5–11] In the present study, we demonstrated a substantial mortality rate associated with perioperative RVF in patients receiving an LVAD for end-stage heart failure. Furthermore, our results have clearly delineated the significant decrease in survival at 30, 180, and 365 days after LVAD implantation using our risk score model. The subgroup with a risk score of ≥12.5 had substantially lower survival at 1 year compared to the subgroup with a risk score of 8.5 to 12.

In general, risk score models predicting patients at risk of RVF after LVAD implantation might prove to be an additional, yet essential, tool for physicians and surgeons in guiding appropriate patient selection. Matthews et al[8] have recently made a notable attempt at defining a risk score in identifying patients who are poor candidates for permanent LVAD therapy. However, the lack of a significant number of patients in their study population who received an LVAD as DT made their risk score model limited, at least in terms of its universal applicability in the clinical setting in which patients receiving LVAD as DT for treatment of end-stage heart failure have been constantly increasing.[1,14–16] To our knowledge, the present study is the first to address the preoperative risk stratification for RVF development that included a large percentage of DT patients. In our study, 42% of the 175 patients received an LVAD as DT. In contrast, only 6% of patients reported in the study by Matthews et al[8] had received an LVAD for DT. This difference is becoming even more important, noting that in our population, DT was identified as a strong independent predictor of RVF after LVAD implantation. The risk score model of Matthews et al[8] was not reproducible when applied to our patient cohort. The area under the curve derived from ap-

plying their risk score model to our patient population was 0.61 versus the 0.73 reported in their investigation.[8] In addition, we used a statistical approach similar to that of Matthews et al,[8] with one major exception: in our investigation, dichotomization of continuous variables was avoided owing to the loss of statistical power inherent with this approach. Nevertheless, no single model thus far has demonstrated complete or total applicability and practicality in the clinical setting. The challenge lies in determining which patients are likely to benefit from an LVAD and are less likely to experience major adverse events such as RVF in the early postoperative period. These questions remain elusive.[15–17]

The independent predictors of RVF after LVAD implantation, as defined in our study, were not astounding. For example, it is plausible that the patient with increased pulmonary vascular resistance cannot tolerate the increased volume load imposed to the right ventricle after LVAD implantation because of the abrupt LVAD-induced increased cardiac output. It might also be that a large proportion of patients with high pulmonary vascular resistance have fixed irreversible pulmonary hypertension that prevented them from deriving benefit from the anticipated LVAD-induced right ventricular afterload reduction. We have previously shown that the reversibility of pulmonary hypertension is a crucial factor in determining how well the nonfailing donor right ventricle compensates after cardiac transplantation.[18]

Another significant risk factor identified in our analysis was the need for preoperative intra-aortic balloon pump. These patients might be more prone to develop RVF merely because of the critical nature of the end-stage heart failure in this subgroup. Most intriguingly, we found that patients selected for DT therapy had a greater likelihood of RVF after LVAD implantation. Many possibilities could explain this finding. For instance, it might be that in this particular cohort of patients, those selected for DT therapy were more ill, had a greater number of co-morbidities, or were selected for treatment later in the disease process. Another explanation might be, in part, the selection bias. For example, patients receiving an LVAD for BTT likely undergo greater scrutiny because of the universal meticulous pretransplant evaluation, including the identification of pulmonary hypertension and its degree of reversibility.[18] Because RVF is a major etiology for primary graft failure in the cardiac allograft recipient, patients receiving an LVAD for BTT are less likely to have major co-morbidities that would place them at risk of RVF in the early postoperative period after cardiac transplantation.[19]

Inotrope dependency was associated in our study with an increased likelihood of RVF after LVAD implantation. A plausible explanation for this finding was that these patients had a more advanced stage of disease compared to the patients who were not inotrope dependent preoperatively. In addition, a continuous infusion of inotropic agents for a prolonged period before LVAD implantation might induce tolerance, resulting in a less efficacious response when challenged with higher doses,[20,21] especially in the intraoperative or early postoperative period when hemodynamic instability could develop.

The risk score thresholds were chosen post hoc using recursive methods; thus, external verification of those thresholds and additional validation of the proposed risk score in other populations is required. In addition, the diverse approaches in the clinical treatment of these patients in the early preoperative, intraoperative, and postoperative care have introduced confounding factors that are difficult to track with respect to their potential effect on outcome. Our study population included only those from a single-center population; therefore, it is not clear how reproducible our risk score model would be when applied to other institutions. Another inherent problem in all studies published on this subject has been the appropriate determination of the presence of RVF, especially given that the inotropic support agent used and infusion duration is highly operator and center dependent, which has introduced operator-dependent bias into the definition. We matched our criteria closely to that defined by other investigators for direct comparison purposes.[8] Our specific choice for defining RVF in the present study was done for clinical applicability and, more so, for consistency with recent and future major studies in this arena.

1. Rose E, Gelijns A, Moskowitz A, Heitjan D, Stevenson L, Dembitsky W, Long J, Ascheim D, Tierney A, Levitan R, Watson J, Meier P, Ronan N, Shapiro P, Lazar R, Miller L, Gupta L, Frazier O, Desvigne-Nickens P, Oz M, Poirier V. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;345:1435–1443.
2. Deng M, Edwards L, Hertz M, Rowe A, Keck B, Kormos R, Naftel D, Kirklin J, Taylor D. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report—2005. *J Heart Lung Transplant* 2005;24:1182–1187.
3. Frazier O, Rose E, Oz M, Dembitsky W, McCarthy P, Radovancevic B, Poirier V, Dasse K. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg* 2001;122:1186–1895.
4. Drakos S, Kfoury A, Long J, Stringham J, Gilbert E, Moore S, Campbell B, Nelson K, Horne B, Renlund D. Effect of mechanical circulatory support on outcomes after heart transplantation. *J Heart Lung Transplant* 2006;25:22–28.
5. Dang N, Topkara V, Mercando M, Kay J, Kruger K, Aboodi M, Oz M, Naka Y. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. *J Heart Lung Transplant* 2006;25:1–6.
6. Furukawa K, Motomura T, Nosé Y. Right ventricular failure after left ventricular assist device implantation: the need for an implantable right ventricular assist device. *Artif Organs* 2005;29:369–377.
7. Kavarana M, Pessin-Minsley M, Urtecho J, Catanese K, Flannery M, Oz M, Naka Y. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. *Ann Thorac Surg* 2002;73:745–750.
8. Matthews J, Koelling T, Pagani F, Aaronson K. The right ventricular failure risk score a preoperative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. *J Am Coll Cardiol* 2008;51:2163–2172.
9. Morgan J, John R, Lee B, Oz M, Naka Y. Is severe right ventricular failure in left ventricular assist device recipients a risk factor for unsuccessful bridging to transplant and post-transplant mortality. *Ann Thorac Surg* 2004;77:859–863.
10. Ochiai Y, McCarthy P, Smedira N, Banbury M, Navia J, Feng J, Hsu A, Yeager M, Buda T, Hoercher K, Howard M, Takagaki M, Doi K, Fukamachi K. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. *Circulation* 2002;106(Suppl 1):I198–I202.
11. Fitzpatrick JR III, Frederick JR, Hsu VM, Kozin ED, O'Hara ML, Howell E, Dougherty D, McCormick RC, Laporte CA, Cohen JE, Southerland KW, Howard JL, Jessup ML, Morris RJ, Acker MA, Woo

YJ. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. *J Heart Lung Transplant* 2008;27:1286–1292.
12. Fitzpatrick JR III, Frederick JR, Hiesinger W, Hsu VM, McCormick RC, Kozin ED, Laporte CM, O'Hara ML, Howell E, Dougherty D, Cohen JE, Southerland KW, Howard JL, Paulson EC, Acker MA, Morris RJ, Woo YJ. Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of a left ventricular assist device to a biventricular assist device. *J Thorac Cardiovasc Surg* 2009;137:971–977.
13. Copeland JG, Smith RG, Bose RK, Tsau PH, Nolan PE, Slepian MJ. Risk factor analysis for bridge to transplantation with the CardioWest total artificial heart. *Ann Thorac Surg* 2008;85:1639–1644.
14. Kirklin J, Naftel D, Stevenson L, Kormos R, Pagani F, Miller M, Ulisney K, Young J. INTERMACS database for durable devices for circulatory support: first annual report. *J Heart Lung Transplant* 2008; 27:1065–1072.
15. Lietz K, Long J, Kfoury A, Slaughter M, Silver M, Milano C, Rogers J, Naka Y, Mancini D, Miller L. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;116:497–505.
16. Drakos SG, Charitos EI, Nanas SN, Nanas JN. Ventricular-assist devices for the treatment of chronic heart failure. *Expert Rev Cardiovasc Ther* 2007;5:571–584.
17. Holman W, Kormos R, Naftel D, Miller M, Pagani F, Blume E, Cleeton T, Koenig S, Edwards L, Kirklin J. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. *J Heart Lung Transplant* 2009;28:44–50.
18. Drakos S, Kfoury A, Gilbert E, Horne B, Long J, Stringham J, Campbell B, Renlund D. Effect of reversible pulmonary hypertension on outcomes after heart transplantation. *J Heart Lung Transplant* 2007;26:319–323.
19. Drakos S, Kfoury A, Gilbert E, Long J, Stringham J, Hammond E, Jones K, Bull D, Hagan M, Folsom J, Horne B, Renlund D. Multivariate predictors of heart transplantation outcomes in the era of chronic mechanical circulatory support. *Ann Thorac Surg* 2007;83:62–67.
20. Unverferth D, Blanford M, Kates R, Leier C. Tolerance to dobutamine after a 72 hour continuous infusion. *Am J Med* 1980;69:262–266.
21. Tohmeh J, Cryer P. Biphasic adrenergic modulation of beta-adrenergic receptors in man: agonist-induced early increment and late decrement in beta-adrenergic receptor number. *J Clin Invest* 1980;65:836–840.