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ORIGINAL RESEARCH

Echocardiographic Predictors of Adverse Outcomes After Continuous Left Ventricular Assist Device Implantation

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OBJECTIVES The purpose of the study was to identify echocardiographic predictors of adverse outcome in patients implanted with continuous-flow left ventricular assist devices (LVAD).

BACKGROUND Continuous flow LVAD have become part of the standard of care for the treatment of advanced heart failure. However, knowledge of echocardiographic predictors of outcome after LVAD are lacking.

METHODS Overall, 83 patients received continuous-flow LVAD (HeartMate II, Thoratec Corporation, Pleasanton, California) from February 2007 to June 2010. The LVAD database, containing various echocardiographic parameters, was examined to analyze their influence on in-hospital mortality, a compound cardiac event (in-hospital mortality or acute right ventricular [RV] dysfunction), and long-term mortality.

RESULTS Eight patients died before discharge (operative mortality 9.6%), and another 15 patients were considered to have acute RV dysfunction immediately after surgery. Patients with relatively small left ventricular end-diastolic diameters (<63 mm) had significantly higher risk for in-hospital mortality (odds ratio [OR]: 0.9; 95% confidence interval [CI]: 0.83 to 0.99; $p = 0.04$) or occurrence of the compound cardiac event (OR: 0.89; 95% CI: 0.84 to 0.95; $p < 0.001$). The most significant predictor of outcome was the decreased timing interval between the onset and the cessation of tricuspid regurgitation flow corrected for heart rate (TRDc), a surrogate for early systolic equalization of RV and right atrial pressure. Short TRDc predicted in-hospital mortality (OR: 0.85; 95% CI: 0.74 to 0.97; $p = 0.01$) and the compound cardiac event (OR: 0.83; 95% CI: 0.74 to 0.91; $p < 0.0001$). Multivariate analysis based on a logistic regression model demonstrated that the accuracy of predicting the 30-day compound adverse outcome was improved with the addition of echocardiographic variables when added to the commonly used hemodynamic or clinical scores. TRDc predicted long-term survival, with adjusted risk ratios of 0.89 for death from any cause (95% CI: 0.83 to 0.96; $p = 0.003$) and 0.88 for cardiac-related death (95% CI: 0.77 to 0.98; $p = 0.03$).

CONCLUSIONS The presence of either a relatively small left ventricle (<63 mm) or early systolic equalization of RV and right atrial pressure (short TRDc) demonstrated by echocardiography is associated with increased 30-day morbidity and mortality. Prediction of early adverse outcomes by echocardiographic parameters is additive to laboratory or hemodynamic variables. (J Am Coll Cardiol Img 2011;4:211–22) © 2011 by the American College of Cardiology Foundation

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Left ventricular (LV) assist device (LVAD) therapy for patients with advanced heart failure has been proven to improve survival over medical therapy (1). Continuous-flow LVAD have replaced pulsatile LVAD because they have been shown to have better patient survival and less device failure (2,3). However, there is still significant morbidity and mortality in patients treated with LVAD. It is important to identify risk factors for such adverse outcomes and modify current practice to reduce them (4). Pre-operative echocardiography has a major role in the management of patients with LVAD and is frequently used to assist in patient selection for LVAD therapy. Because LVAD therapy is effective in replacing LV function, we postulated that variables related to LV function may not be predictive of adverse outcomes after surgery. In contrast, other factors, especially those related to LV dimensions or to right ventricular (RV) function, may have a strong influence. We examined various pre-operative echocardiographic, hemodynamic, and clinical variables for their impact on mortality and RV dysfunction after surgery. We also examined different clinical scores (5–7) to determine whether they were additive to the echocardiographic parameters for the prediction of clinical outcomes.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
EROA = effective regurgitant orifice area
LV = left ventricular
LVAD = left ventricular assist device
LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter
MR = mitral regurgitation
NYHA = New York Heart Association
OR = odds ratio
RA = right atrial
RIMP = right index of myocardial performance
RV = right ventricular
TR = tricuspid regurgitation
TRDc = time of tricuspid regurgitation flow corrected for heart rate

METHODS

Patient population. We identified all 83 consecutive patients who received the HeartMate II continuous-flow LVAD (Thoratec Corporation, Pleasanton, California) for either destination or bridge to transplant therapy between February 2007 and June 2010. We defined operative mortality as death within 30 days of LVAD implantation or during the index hospitalization and acute right-heart failure as a need for an RV assist device or inotropic support for more than 7 days post-operatively.

Clinical and demographic data. Pre-operative clinical, echocardiographic, hemodynamic, and laboratory data as well as data concerning post-operative adverse events, right-heart failure, length of stay, and short-term and long-term mortality were abstracted from the medical records. Laboratory evaluations were all performed within 24 h before surgery. Echocardiographic examinations were performed in all patients, usually within the month before surgery (median 16 days, 25th and 75 percentiles 7 and 36 days). Hemodynamic catheterizations were performed in 80 of 83 patients (96.4%), usually within a week before surgery (median 4 days, 25th and 75th percentiles 2 and 9 days). The study protocol was reviewed and approved by the institutional review board at the Mayo Clinic in Rochester, Minnesota.

Echocardiographic measurements. Two-dimensional transthoracic echocardiography was performed in a standard manner. LV diameters and ejection fraction were measured as recommended (8). Right atrial (RA) pressure was estimated by the inferior vena cava diameter and its response to inspiration (9). RV function and tricuspid regurgitation (TR) and mitral regurgitation (MR) severity were qualitatively graded using a 4-point scale (normal, mild, moderate, or severe) using all views. The severity of TR was assessed using color flow imaging and vena contracta width (10). MR was quantitatively assessed using the proximal isovelocity surface area method whenever it was considered to be more than mild (11). RV function was assessed using tissue Doppler assessment of lateral tricuspid annular motion (12), systolic TR duration (13), and the right index of myocardial performance (RIMP) (14).

We corrected the time intervals of RV ejection time and the time between the onset and the cessation of TR flow (13) for heart rate using the correction formula time of TR flow corrected for heart rate (TRDc) = TR flow time/$\sqrt{}$RR, as previously suggested by others (Fig. 1C) (14,15).

Interobserver and intraobserver variability. Interobserver variability was determined by a second independent blinded observer who measured the echocardiographic variables in 15 randomly selected patients. Intraobserver variability was determined by having the first observer who measured the data in all patients remeasure the timing intervals in 15 patients at least 3 months apart. Interobserver and intraobserver variability were assessed using the Bland-Altman method and the within-subject coefficient of variation. The within-subject coefficient of variation (calculated as the ratio of the standard deviation of the measurement difference to the mean value of all measurements) provides a scale-free, unitless estimate of variation expressed as a percentage. We measured intraobserver and interobserver reproducibility for TRDc, RV ejection time corrected for heart rate, and RIMP and expressed them using the coefficient of variation. Values of $p < 0.05$ were considered statistically significant.

Statistical analysis. Unless otherwise specified, data are presented as mean ± SD or as percentages.

Comparisons between groups were performed using analysis of variance, Student *t* test, or the chi-square test as appropriate. To analyze independent determinants of the compound 30-day adverse event (in-hospital mortality or RV dysfunction), multivariate analysis based on a logistic regression model (with the combined end point as the dependent variable and the different echocardiographic variables as independent variables) was performed. Variables assessing echocardiographic predictors were entered first, and those measuring right-heart catheterization measurements or the different clinical scores were added consecutively to the models. The first entry criterion in the multivariate analysis was a univariate p value <0.05. To correct for possible overfitting of the model considering that we observed only 23 events, we selected only variables that supported our stated hypothesis that variables related to LV function or filling pressure would not be predictive of adverse outcomes after surgery but that factors related to LV dimensions or to RV function might have a strong influence. On the basis of those assumptions, we excluded MR effective regurgitant orifice area (EROA) and TR velocity from the model. To detect multicollinearity, we first used correlation factor analyses to determine if any pairs of predictor variables were highly correlated (correlation coefficients over 0.9) and therefore likely to result in multicollinearity. If any such pairs were found, 1 of the predictor variables was selected for inclusion in the final analysis and the other was ignored. The variable with the lowest p value was chosen to be included in the analysis. We then proceeded with multicollinearity diagnostic statistics and examined the variance inflation factor. Variance inflation factors exceeding 10 were regarded as indicating multicollinearity and were dropped from the model. Using these procedures, we excluded LV systolic diameter, RIMP, and TR minus RV ejection time from the model and were left with only 2 echocardiographic variables (LV end-diastolic diameter [LVEDD] and TRDc). Actuarial survival analysis was performed using the Kaplan-Meier method, and the results were compared between the pre-specified groups using log-rank analysis. Patients were censored for heart transplantation. All p values were 2 sided, and p values <0.05 were considered to indicate statistical significance. All data were analyzed using JMP version 8.0 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Baseline characteristics. Table 1 shows the baseline characteristics of the patients enrolled, both overall

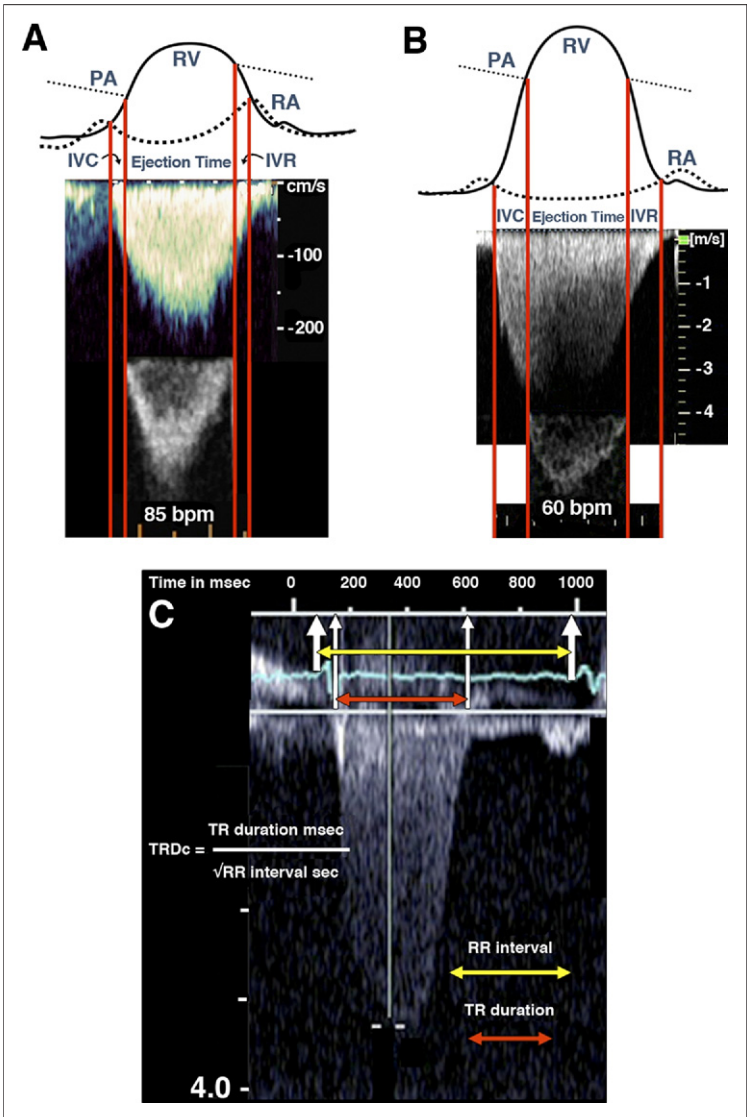

Figure 1. Duration of the TR Signal on Continuous-Wave Doppler

(A) A patient with short tricuspid regurgitation (TR) duration. The increased right atrial (RA) pressure causes the tricuspid valve to open earlier, on the steeper curve of the ventricular relaxation curve, thereby shortening the isovolumic relaxation (IVR) interval and TR flow duration. Furthermore, a reduction in diastolic pulmonary artery (PA) to end-diastolic right ventricular (RV) pressure difference shortens the "isovolumic contraction (IVC) time." **(B)** Prolonged TR duration in another patient with end-stage dilated cardiomyopathy. The TR signal has a higher peak velocity and systolic RV pressure. The pressure in the right ventricle at the time of pulmonary valve closure must fall from a higher point to reach the pressure of the right atrium, lengthening the IVR period. Furthermore, the increase in diastolic pulmonary pressure to end-diastolic RV pressure difference lengthens the IVC period. Note that the TR signal ends with a concave, prolonged contour consistent with a markedly delayed relaxation of the right ventricle. **(C)** Calculation of TR duration corrected for heart rate (TRDc). We first measured the time interval of the duration of the TR signal in milliseconds (**red arrow** = 450 ms). We then measured the RR interval in seconds using the electrocardiographic tracing (**yellow arrow** = 0.9 seconds). We then used the formula TRDc = TR duration/$\sqrt{}$RR interval (450/$\sqrt{}$0.9 = 473 ms).

Table 1. Baseline Characteristics of All Patients and Divided by Those With and Without Adverse 30-Day Cardiac Outcomes (In-Hospital Mortality, Need for RVAD, or Post-Operative Inotropic Support >168 H) Before LVAD Implantation

Characteristic	All Patients (n = 83)	Adverse Cardiac 30-Day Outcome (n = 23)	Normal 30-Day Outcome (n = 60)	p Value
Age (yrs)	62.9 ± 12.0	60.4 ± 10.0	64.2 ± 13.0	0.10
Men/women (%)	80.7/19.3	88/12	80/20	0.40
NYHA functional class				0.02
IIb	40%	26%	45%	
IV	60%	74%	55%	
Prior sternotomy (%)	51	48	53	0.60
Pre-operative IABP (%)	31	56	25	0.008
Pre-operative inotropic use (%)	74	65	68	0.40
Destination therapy (%)	67	52	70	0.04
Type of cardiomyopathy				0.006†
Ischemic heart disease	54%	31%	63%	
Dilated cardiomyopathy	34%	48%	32%	
Restrictive heart disease	10%	17%	7%	
Other	2%	4%	8%	
Heart rate (beats/min)	77.1 ± 14.0	78.9 ± 15.0	76.4 ± 15.0	0.50
Systolic blood pressure (mm Hg)	99.4 ± 14.0	102.2 ± 18.0	98.4 ± 13.0	0.30
Diastolic blood pressure (mm Hg)	62.4 ± 10.0	65.7 ± 10.0	63.7 ± 11.0	0.50
Hemoglobin (g/dl)	11.8 ± 2.0	11.5 ± 1.0	12.0 ± 2.0	0.30
Bilirubin (mg/dl)	1.2 ± 0.7	1.2 ± 0.9	1.2 ± 0.6	0.70
BUN (mg/dl)	31.0 ± 16.0	34.2 ± 19.0	29.7 ± 15.0	0.30
Creatinine (mg/dl)	1.4 ± 0.5	1.5 ± 0.6	1.4 ± 0.5	0.30
NT-BNP (pg/ml)	5,673 ± 5,229	6,570 ± 6,704	5,270 ± 4,499	0.50
Lietz-Miller score	9.7 ± 5.7	12.5 ± 6.5	8.5 ± 5.0	0.005
Matthews score	1.1 ± 2.2	2.0 ± 3.0	0.8 ± 1.7	0.03
Kormos score	1.8 ± 1.9	2.7 ± 2.4	1.4 ± 1.5	0.005
Echocardiography				
LV diastolic diameter (mm)	67.2 ± 9.0	61.2 ± 9.0	69.4 ± 9.0	0.0003
LV systolic diameter (mm)	60.8 ± 9.0	54.7 ± 9.0	63.2 ± 8.0	0.0006
Septal thickness (mm)	10.2 ± 2.0	11.3 ± 3.0	10.2 ± 3.0	0.20
Posterior wall thickness (mm)	9.8 ± 2.0	9.8 ± 1.0	10.0 ± 2.0	0.60
Ejection fraction (%)	19.7 ± 7.0	19.1 ± 11.0	20.1 ± 8.0	0.70
Cardiac output (l/min)	4.1 ± 1.0	4.0 ± 1.0	4.1 ± 1.0	0.80
Cardiac index (l/min/m^2)	2.2 ± 0.8	2.2 ± 1.0	2.2 ± 0.7	0.80
LA volume (cm^3)	133.0 ± 49.0	134.0 ± 34.0	132.6 ± 54.0	0.90
LA volume index (cm^3/m^2)	68.2 ± 27.0	66.9 ± 19.0	68.7 ± 30.0	0.80
E/e′ ratio*	27.5 ± 12.0	23.6 ± 10.0	28.8 ± 12.0	0.10
Deceleration time#	135.9 ± 30.0	126.8 ± 27.0	138.7 ± 31.0	0.20
TR velocity (m/s)	3.0 ± 0.6	2.8 ± 0.7	3.1 ± 0.6	0.03
Estimated RA pressure¶ (mm Hg)	14.9 ± 5.0	15.0 ± 5.0	14.8 ± 5.0	0.90
Tricuspid valve lateral annular velocity (m/s)	0.08 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.80
RV dysfunction > moderate	67%	68%	66%	0.90
RIMP	0.57 ± 0.2	0.43 ± 0.2	0.61 ± 0.2	0.003
TRDc‡ (ms)	466 ± 69	416 ± 56	486 ± 64	<0.0001
RV ejection time corrected‖ (ms)	302 ± 39	296 ± 40	306 ± 38	0.40
TR − RV ejection time§ (ms)	150 ± 56	109.6 ± 44.0	165.4 ± 53.0	0.0002
MR				0.02
None	8%	8%	8%	
Mild	30%	42%	26%	

(Continued on next page)

Table 1. Continued

Characteristic	All Patients (n = 83)	Adverse Cardiac 30-Day Outcome (n = 23)	Normal 30-Day Outcome (n = 60)	p Value
Moderate	23%	29%	22%	
Severe	39%	21%	44%	
MR EROA (PISA) (cm^2)	0.35 ± 0.15	0.23 ± 0.05	0.37 ± 0.16	0.05
TR				0.03
None	9%	6%	22%	
Mild	34%	23%	37%	
Moderate	13%	18%	12%	
Severe	44%	53%	29%	
TR vena contracta width (mm)	4.0 ± 2.0	4.9 ± 3.0	3.7 ± 2.0	0.05
Hemodynamic parameters				
Mean RA pressure (mm Hg)	15.4 ± 7.0	18.6 ± 8.0	14.1 ± 5.0	0.007
Mean PA pressure (mm Hg)	36.0 ± 9.0	33.6 ± 9.0	37.0 ± 9.0	0.15
PVR (Wood units)	4.2 ± 3.0	3.5 ± 3.0	4.4 ± 3.0	0.20
RV dP/dt	483 ± 207	442 ± 219	499 ± 202	0.30
Mean wedge pressure (mm Hg)	23.5 ± 7.0	23.5 ± 7.0	23.5 ± 7.0	0.90
Cardiac output (l/min)	3.9 ± 1.0	4.0 ± 1.0	3.8 ± 1.0	0.40
Cardiac index (l/min/m^2)	1.9 ± 0.5	2.0 ± 0.5	1.9 ± 0.5	0.60
Matching for NYHA functional class, destination therapy, type of cardiomyopathy, Lietz-Miller score, and mean RA pressure				
Age (yrs)	60.0 ± 11.5	59.8 ± 10.4	60.3 ± 12.8	0.90
Men/women	85%/15%	87%/13%	83%/17%	0.70
NYHA functional class				1.00
IIIb	23%	23%	23%	
IV	77%	77%	77%	
Destination therapy	56.5%	52.1%	60.8%	0.20
Type of cardiomyopathy				0.50
Ischemic heart disease	30%	22%	39%	
Dilated cardiomyopathy	46%	48%	44%	
Restrictive heart disease	13%	17%	9%	
Other	10%	13%	8%	
Lietz-Miller score	12.4 ± 5.2	12.4 ± 6.5	12.4 ± 3.6	0.90
Mean RA pressure (mm Hg)	18.1 ± 6.8	18.6 ± 8.3	17.6 ± 5.0	0.60

Data are expressed as mean ± SD or as (%). *Ratio of E velocity of mitral inflow to early diastolic relaxation tissue velocity of medial annulus. †P value for the difference in ratio of ischemic heart disease. ‡Interval between cessation and onset of TR flow divided by the square root of the RR interval. §Difference between TR flow time and RV ejection time. ‖Interval between the onset and cessation of RV outflow divided by the square root of the RR interval. ¶Estimation of RA pressure using the inferior vena cava method. #Deceleration time of early mitral inflow.
BUN = blood urea nitrogen; EROA = effective regurgitant orifice area; IABP = intra-aortic balloon pump; LA = left atrial; LV = left ventricular; LVAD = left ventricular assist device; MR = mitral regurgitation; NT-BNP = N-terminal brain natriuretic peptide; NYHA = New York Heart Association; PA = pulmonary artery; PISA = proximal isovelocity surface area; PVR = pulmonary vascular resistance; RA = right atrial; RIMP = right index of myocardial performance; RV = right ventricular; RVAD = right ventricular assist device; TR = tricuspid regurgitation; TRDc = tricuspid regurgitation duration corrected for heart rate.

and divided into 2 groups, those (23 patients) positive for the 30-day compound adverse outcome (operative mortality or acute RV dysfunction) and those (60 patients) considered to have normal 30-day outcomes. The mean age was 62.9 ± 12.4 years, and 80.7% were men. We calculated and included the clinical scores proposed by Lietz et al. (7), Matthews et al. (5), and Kormos et al. (6) for all patients (Table 1).

The parameters estimating LV systolic function and LV filling pressures were not different between the groups. LVEDD and left ventricular end-systolic diameter (LVESD) (61.2 ± 8.7 mm vs. 69.4 ± 8.8 mm, p = 0.0003, and 54.7 ± 9.3 mm vs. 63.2 ± 8.5 mm, p = 0.0006, respectively) were smaller in patients with adverse 30-day outcomes. TR was worse (TR vena contracta width 4.9 ± 2.5 mm vs. 3.7 ± 2.4 mm, p = 0.05), but the EROA of MR was smaller (0.23 ± 0.05 cm^2 vs. 0.37 ± 0.16 cm^2, p = 0.05) in patients with adverse outcomes.

TRDc was significantly shorter in patients with adverse outcomes (416 ± 56 ms vs. 486 ± 64 ms, p < 0.0001). The RV ejection period corrected for

heart rate was not different between the groups, so the derived sum of RV isovolumetric contraction time and isovolumetric relaxation time (calculated by subtracting RV ejection time from TR flow duration) was significantly shorter in patients with adverse outcomes (109.6 ± 44 ms vs. 165.4 ± 53 ms, p = 0.0002). The RIMP ratio was significantly decreased (pseudonormalized) in patients with adverse outcomes (0.43 ± 0.2 vs. 0.61 ± 0.2, p = 0.003).

The only difference in hemodynamic baseline characteristics was higher RA pressure (18.6 ± 8.3 mm Hg vs. 14.1 ± 5.5 mm Hg, p = 0.007) in patients with adverse 30-day outcomes. Lietz, Matthews, and Kormos scores (5–7) were significantly higher in patients with adverse outcomes as well (Table 1).

Thirty-day post-operative outcomes. Table 2 shows post-operative outcomes in all patients and divided into patients with and without 30-day adverse outcomes. Eight patients died before discharge (operative mortality 9.6%). The causes of death included multiple-organ failure in 2 patients, uncontrolled right-heart failure in 2, hyperperfusion brain injury in 2, sepsis in 1, and uncontrollable bleeding after argatroban treatment for heparin-induced thrombocytopenia in 1. The median length of stay after LVAD surgery was 17.5 days (25th and 75th percentiles 11 and 27.5 days), and the median duration of inotropic support was 114.5 h (25th and 75th percentiles 66.5 and 166.5 h). Post-operative LVAD flow (before discharge or death) and pulmonary artery pressure tended to be lower, but RA pressure (the last hemodynamic measurement before taking out the Swan-Ganz catheter) was significantly higher in patients with adverse outcomes, suggestive of RV dysfunction.

Echocardiographic predictors of adverse outcomes. Univariate analysis (Table 3) showed that none of the parameters related to LV function or filling pressure influenced the compound event or early mortality. Patients with relatively small ventricles had significantly higher risk for the compound event (prolonged inotropic support or death): LVEDD (odds ratio [OR]: 0.89; 95% confidence interval [CI]: 0.84 to 0.95) and LVESD (OR: 0.89; 95% CI: 0.83 to 0.95), p < 0.001 for both. A small ventricle was also associated with increased risk for

Table 2. Post-Operative 30-Day Outcomes and Hospital Courses of All Patients and Divided by Patients With and Without Adverse 30-Day Outcomes

Outcome	All Patients (n = 83)	Adverse 30-Day Outcome (n = 23)	Normal 30-Day Outcome (n = 60)	p Value
Operative mortality (%)	9.6	35.0	0.0	<0.0001
Cardiopulmonary bypass time (min)	103.3 ± 34.0	116.7 ± 33.0	98.0 ± 33.0	0.03
Post-operative red blood cell transfusion (U)	10.5 ± 10.0	15.9 ± 15.0	8.5 ± 6.0	0.002
Need for RVAD (%)	3.6	13.0	0.0	0.004
Infection (%)†	49	74	38	0.001
Bleeding (%)*	68	77	65	0.30
Prolonged intubation (%)#	23	73	5	<0.0001
Arrhythmia (%)¶	20	36	13	0.02
Acute renal failure (%)‡	16	36	8	0.004
Acute cerebral event (%)‖	12	32	5	0.002
Hepatic dysfunction (%)§	18	41	10	0.002
Thromboembolic event (%)**	11	14	10	0.60
Dialysis (%)	10	37	2	<0.0001
Mean RA pressure (mm Hg)††	12.8 ± 5.4	16.2 ± 5.4	11.6 ± 4.8	0.003
Mean PA pressure (mm Hg)††	26.8 ± 7.2	29.6 ± 9.4	25.7 ± 5.8	0.06
Pump flow (l/min)‡‡	5.1 ± 0.7	4.8 ± 0.7	5.2 ± 0.7	0.07
LOS (days)	17 (11, 27)	33 (23, 41)	15 (10, 23)	<0.0001
Duration of inotropic support (h)	114 (66, 166)	372 (247, 696)	76 (54, 120)	<0.0001
RV failure (%)	24	87	0	<0.0001
LOS > 30 days (%)	17	57	10	0.0002

Data are expressed as (%), as mean ± SD, or as median (25th percentile, 75th percentile). *Bleeding requiring blood transfusion >24 h after surgery. †Infection requiring intravenous antibiotics. ‡Renal failure requiring dialysis or increase in creatinine to >2 mg/dl or by >50% from baseline. §Liver enzymes > 300 U/l or bilirubin > 5.0 mg/dl after surgery. ‖Any stroke, brain hemorrhage, or hyperperfusion injury. ¶Hemodynamically significant arrhythmia or requiring cardioversion. #Mechanical ventilation for >1 week or need for tracheostomy. **Any embolic event after surgery. ††Hemodynamic data represent the last measurement before taking out the pulmonary artery catheter. ‡‡Pump flow by the LVAD monitor before discharge or death.
LOS = length of stay; other abbreviations as in Table 1.

Table 3. Univariate Analysis of Predictors of Short-Term Mortality or Compound 30-Day Adverse Event in Patients Undergoing LVAD Implantation

Variable	OR (95% CI) (Death or RV Failure)	p Value	Early Mortality	p Value
Echocardiography				
LV diastolic diameter (mm)	0.89 (0.84–0.95)	0.0003	0.9 (0.83–0.99)	0.04
LV systolic diameter (mm)	0.89 (0.83–0.95)	0.0007	0.9 (0.81–0.98)	0.01
Septal thickness (mm)	1.1 (0.94–1.34)	0.20	1.05 (0.77–1.33)	0.70
Posterior wall thickness (mm)	0.94 (0.71–1.2)	0.60	0.87 (0.6–1.3)	0.50
Ejection fraction (%)	0.98 (0.92–1.04)	0.70	0.93 (0.81–1.03)	0.20
Cardiac output (l/min)	0.96 (0.62–1.42)	0.80	1.14 (0.62–1.9)	0.60
Cardiac index (l/min/m^2)	0.93 (0.41–1.9)	0.80	0.91 (0.25–2.3)	0.90
LA volume (cc)	1.0 (0.99–1.01)	0.90	1.0 (0.98–1.02)	0.90
LA volume index (cc/m^2)	0.99 (0.97–1.02)	0.80	1.0 (0.96–1.03)	0.90
E/e′ ratio*	0.95 (0.89–1.01)	0.10	1.03 (0.95–1.12)	0.40
Deceleration time§	0.98 (0.96–1.01)	0.20	1.01 (0.98–1.05)	0.40
TR velocity (m/sec)	0.4 (0.16–0.92)	0.03	0.6 (0.2–2.1)	0.40
Estimated RA pressure¶	1.0 (0.91–1.11)	0.90	1.02 (0.9–1.2)	0.80
Tricuspid lateral annular velocity (m/sec)	0.97 (0.79–1.15)	0.80	0.96 (0.65–1.3)	0.90
RV dysfunction > moderate	1.1 (0.6–1.8)	0.80	0.5 (0.1–1.25)	0.15
RIMP (0.1 increase)	0.63 (0.44–0.85)	0.001	0.86 (0.57–1.2)	0.40
TRDc† for 10 ms	0.83 (0.74–0.91)	<0.0001	0.85 (0.74–0.97)	0.01
RV ejection time‖	0.99 (0.97–1.0)	0.30	0.97 (0.96–1.00)	0.056
TR − RV ejection time‡	0.78 (0.66–0.89)	<0.0001	0.85 (0.72–1.0)	0.05
MR EROA (PISA)	0.38 (0.1–0.9)	0.03	0.42 (0.08–1.16)	0.10
TR vena contracta width	1.2 (0.95–1.5)	0.10	1.2 (0.87–1.7)	0.30
Clinical and demographic				
Age	0.97 (0.94–1.0)	0.10	1.02 (0.96–1.11)	0.40
Gender (male)	1.7 (0.7–2.8)	0.40	1.6 (0.5–5.6)	0.60
NYHA functional class IV	2.7 (0.92–9.0)	0.07	0.77 (0.26–1.5)	0.40
Pre-operative IABP	2.0 (1.2–3.3)	0.007	1.9 (0.9–4.3)	0.08
Hemoglobin	0.86 (0.66–1.12)	0.30	0.82 (0.54–1.22)	0.30
Bilirubin	1.1 (0.6–2.2)	0.70	1.08 (0.3–2.7)	0.80
BUN	1.0 (0.98–1.04)	0.30	1.05 (1.01–1.1)	0.004
Creatinine	1.6 (0.6–4.3)	0.30	5.1 (1.3–22.8)	0.02
NT-BNP (per 100 pg/ml)	1.0 (0.98–1.01)	0.50	1.03 (1.01–1.06)	0.003
Lietz-Miller score	1.1 (1.04–1.25)	0.005	1.05 (0.92–1.2)	0.40
Matthews score	1.24 (1.01–1.55)	0.04	1.25 (0.94–1.6)	0.10
Kormos score	1.5 (1.1–2.1)	0.006	1.4 (1.0–2.1)	0.04
Right-heart catheterization				
Mean RA pressure (mm Hg)	1.1 (1.02–1.2)	0.007	1.07 (0.96–1.2)	0.20
Mean PA pressure (mm Hg)	0.96 (0.91–1.01)	0.10	0.97 (0.89–1.06)	0.60
PVR (WU)	0.88 (0.72–1.06)	0.20	0.78 (0.5–1.08)	0.15
RV dP/dt	0.99 (0.99–1.0)	0.30		
Mean wedge pressure (mm Hg)	0.99 (0.93–1.07)	0.90	1.01 (0.9–1.13)	0.80
Cardiac index (lit/min/m^2)	1.3 (0.5–3.5)	0.60	1.5 (0.33–6.6)	0.60
Univariate analysis in the matched group				
LV diastolic diameter (mm)	0.88 (0.8–0.95)	0.0007	1.07 (0.98–1.19)	0.09
LV systolic diameter (mm)	0.89 (0.82–0.96)	0.003	1.08 (0.99–1.19)	0.06
RIMP (0.1 increase)	0.64 (0.4–0.93)	0.02	1.0 (0.65–1.56)	0.90
TRDc† for 10 ms	0.82 (0.69–0.93)	0.001	1.14 (0.99–1.36)	0.06
TR − RV ejection time‡	0.97 (0.95–0.99)	0.001	1.12 (0.94–1.36)	0.20

*Ratio of E velocity of mitral inflow to early diastolic relaxation tissue velocity of medial annulus. †Interval between cessation and onset of TR flow divided by the square root of the RR interval. ‡Difference between TR flow time and RV ejection time. §Deceleration time of early mitral inflow. ‖Interval between the onset and cessation of RV outflow divided by the square root of the RR interval. ¶Estimation of RA pressure using the inferior vena cava method.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

in-hospital mortality (OR: 0.9; 95% CI: 0.83 to 0.99; and OR: 0.9; 95% CI: 0.81 to 0.98), for every increase in LVEDD and LVESD ($p < 0.05$ for both). To define which LV diameter should be considered relatively small and carrying increased risk after LVAD surgery, we dichotomized LVEDD at the 25th (LVEDD < 60 mm), 33rd (60 mm < LVEDD < 63 mm), 50th (63 mm < LVEDD < 67 mm), 66th (67 mm < LVEDD < 71 mm), 75th (67 mm < LVEDD < 74 mm), and above (LVEDD > 74 mm) percentiles. We then calculated the risk for the compound cardiac event for each group. We found that the risk for adverse outcomes almost tripled when LVEDD decreased below 63 mm (the risk for adverse outcomes was 64%, 60%, 25%, 13%, 14%, and 20%, respectively, from the smallest to the largest quartile; $p = 0.005$).

In contrast, the EROA of MR had a positive impact on outcome (OR: 0.38; 95% CI: 0.1 to 0.9;

$p = 0.03$ for every increase in EROA by 1 cm^2). The most significant predictor of the clinical outcome was TRDc. Short TRDc was predictive of the compound 30-day outcome (OR: 0.83; 95% CI: 0.74 to 0.91; $p < 0.0001$) and in-hospital mortality (OR: 0.85; 95% CI: 0.74 to 0.97; $p = 0.01$).

The derivatives of TR flow time, including the shortened sum of isovolumic contraction and relaxation, and RIMP were all predictors of worst compound 30-day outcome but not of early mortality (Table 3).

Multivariate analysis based on logistic regression using only echocardiographic parameters demonstrated that the accuracy of predicting the 30-day compound adverse outcome was maximal when incorporating LVEDD and TRDc (Table 4). RA pressure and all the clinical scores were predictive of the combined event on univariate analysis (Table 3) and marginally increased the C-index of the echocardiographic logistic model (from 0.81 for echocardiography alone to 0.83) (Table 4).

To further evaluate whether the proposed echocardiographic variables retained their predictive value after adjusting for the other baseline differences between the groups (New York Heart Association [NYHA] functional class, the percentage of destination therapy, etiology of heart disease, Lietz-Miller score, and right-heart pressure), we matched each subject in the group positive for the 30-day compound adverse outcome with a patient from the group considered to have normal 30-day outcomes for age, gender, and all baseline differences (Table 1).

We found that the predictive value of LVEDD (OR: 0.88; 95% CI: 0.8 to 0.95; $p = 0.0007$), LVESD (OR: 0.89; 95% CI: 0.82 to 0.96; $p = 0.003$), TRDc (OR: 0.82; 95% CI: 0.69 to 0.93; $p = 0.001$), TR − RV ejection time (OR: 0.97; 95% CI: 0.95 to 0.99; $p = 0.001$), and RIMP (OR: 0.64; 95% CI: 0.4 to 0.93; $p = 0.02$) for the combined 30-day adverse end point remained significant (Table 3) even after the matching process.

Intraobserver and interobserver variability. Comparison of intraobserver timing intervals showed good agreement between measurements: TRDc (mean difference 0.71 ± 15.4 ms, $r = 0.97$, $p = 0.86$), RV ejection time corrected for heart rate (mean difference −0.1 ± 9.8 ms, $r = 0.98$, $p = 0.97$), and RIMP (mean difference 0.003 ± 0.066, $r = 0.95$, $p = 0.86$). The Bland-Altman plot showed a random scatter of points around 0, indicating no systematic bias or measurement error proportional to the measurement value. Measurement variability (within-subject coefficient of variation and 95% CI of the Bland-Altman method) for measurements of intraobserver differences was as follows: TRDc, 3.3% and ±8.9 ms; RV ejection time corrected for heart rate, 3.2% and ±5.6 ms; and RIMP, 10.1% and ±0.04.

Comparison of interobserver timing intervals showed good agreement as well: TRDc (mean difference −3.7 ± 25.6 ms, $r = 0.92$, $p = 0.60$), RV ejection time corrected for heart rate (mean difference 5.0 ± 10.0 ms, $r = 0.97$, $p = 0.10$), and RIMP (mean difference −0.04 ± 0.12, $r = 0.84$, $p = 0.30$). Measurement variability for measurements of interobserver differences was as follows: TRDc, 5.0% and ±14.8 ms; RV ejection time corrected for heart rate, 3.3% and ±5.8 ms; and RIMP, 17% and ±0.06.

Long-term mortality. The mean follow-up duration after surgery was 270.1 ± 262.8 days. Eighteen patients (21.7%) died and 11 patients had their

Table 4. Multivariate Analysis of Predictors of Compound 30-Day Adverse Event (In-Hospital Mortality, Need for RVAD, or Prolonged Inotropic Support) in Patients Undergoing LVAD Implantation

	Echocardiography Alone	Adjusted for RA Pressure	Adjusted for Lietz-Miller Score	Adjusted for Matthews Score	Adjusted for Kormos Score
LV diastolic diameter	0.06	0.06	0.05	0.08	0.08
TRDc*	0.001	0.006	0.005	0.001	0.01
RA pressure		0.6			
Lietz-Miller score			0.09		
Matthews score				0.2	
Kormos score					0.6
p Value	<0.0001	<0.0001	<0.0001	0.0001	0.0001
Hosmer-Lemeshow	0.98	0.97	0.5	0.7	0.7
C-index	0.81	0.83	0.83	0.83	0.83

*Interval between onset and cessation of TR flow divided by the square root of the RR interval.
Abbreviations as in Table 1.

LVAD explanted for heart transplantation during the follow-up period. The causes of death in patients surviving the index hospitalization were traumatic head injury in 3, hemorrhagic stroke in 2, and unexplained sudden death in 2; 1 patient decided to withdraw support. The actuarial survival rate was 77.4 ± 5.5% and 62.6 ± 9.2% at 1 and 2 years, respectively.

TRDc and its derivative RV ejection time − TR flow time were the only echocardiographic predictors of long-term survival, with adjusted risk ratios for death from any cause of 0.89 (95% CI: 0.83 to 0.96; p = 0.003) and 0.9 (95% CI: 0.82 to 0.99; p = 0.03), respectively. Of note, neither RA pressure nor any of the clinical scores predicted long-term mortality in our models. We defined cardiovascular mortality as mortality related to intractable heart failure or arrhythmic death. TRDc was predictive of cardiac-related death (OR: 0.88; 95% CI: 0.77 to 0.98; p = 0.03) but not of noncardiac causes of death (OR: 0.92; 95% CI: 0.82 to 1.04; p = 0.20).

The echocardiographic parameters were first dichotomized at the 10th, 25th, 33rd, 50th, 66th, 75th, and 90th percentiles, and the percentile value with the lowest p value was chosen as the threshold for the Kaplan-Meier analyses.

The dichotomization took place at the 50th percentile for TRDc (461 ms). TRDc <461 ms was a strong predictor of mortality, with an adjusted OR of 2.3 (95% CI: 1.3 to 4.9; p = 0.03) compared with a longer TRDc. The 2-year survival rate was significantly lower in those with TRDc <461 ms (28.8 ± 21.1%) compared with patients with longer TRDc (85.7 ± 8.5%) (Fig. 2). We compared NYHA functional class and 6-min walking distance 3 months after LVAD surgery in patients with prolonged or short TRDc before surgery. More patients were in NYHA functional class III or IV 3 months after surgery among those with TRDc <461 ms before surgery compared with patients with prolonged TRDc (58.8% vs. 19.2%, p = 0.008). There was a trend for decreased 6-min walking distance in patients with pre-operative TRDc <461 ms (278 vs. 366.2 m, p = 0.10) 3 months after surgery.

The dichotomization for LVEDD took place at the 33rd percentile (63 mm), and we classified patients as having relatively small left ventricles (LVEDD ≤ 63 mm) or larger left ventricles (LVEDD > 63 mm). Although a small increase in mortality could be appreciated, the survival curves coalesced after 18 months (Fig. 3).

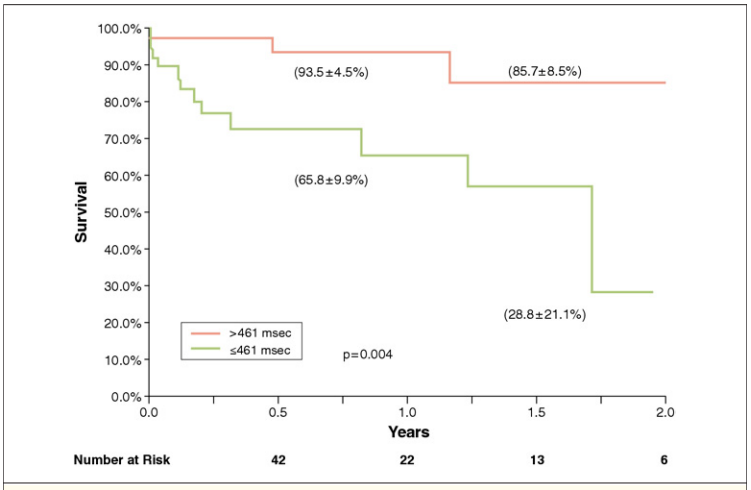

Figure 2. Kaplan-Meier Estimates of the Mean ± SE Rates of Overall Survival Among Patients After LVAD Surgery According to the TRDc

The 1-year and 2-year survival rates were low in patients with tricuspid regurgitation duration corrected for heart rate (TRDc) <461 ms and markedly improved in patients with longer TRDc. Values in parentheses are survival rates at 1 and 2 years. LVAD = left ventricular assist device.

DISCUSSION

This study is among the first to report echocardiographic predictors of outcomes after LVAD surgery. We found that early adverse events were predicted by the presence of a relatively small left ventricle and shorter TR flow duration at the time of LVAD therapy. It was interesting to note that none of the LV functional parameters influenced

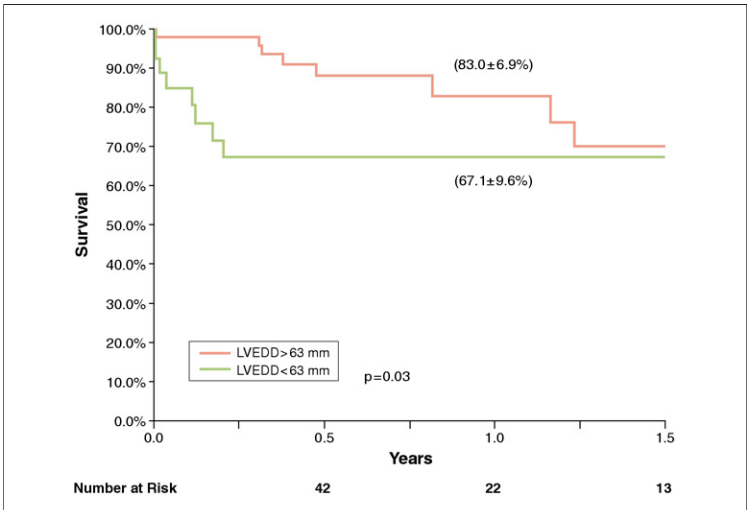

Figure 3. Kaplan-Meier Estimates of the Mean ± SE Rates of Overall Survival Among Patients After LVAD Surgery According to LV Diameter

Although an increase in early mortality could be appreciated, the survival curves coalesced after 18 months. Values are survival rates at 1 year. LV = left ventricular; LVAD = left ventricular assist device.

outcomes. However, it is not surprising, given how effective an LVAD is in replacing LV function. Long-term mortality was predicted by a short TRDc (or its derivatives) as well.

LV diameter. A relatively small LV internal dimension (<63 mm) was found to pose an early postoperative problem. In patients with LVAD, an increase in revolutions per minute may cause a diminution of the LV cavity, shifting the interventricular septum to the left. This in turn impairs RV output, diminishing the LV cavity even further. This worsening spiral, sometimes referred to as the "suck-down event," may cause the septum to encroach upon the inflow cannula, resulting in ventricular arrhythmias or drastically decreasing LVAD preload. We believe that a relatively smaller left ventricle may increase the risk for such events. To minimize this risk, our practice in setting the speed early post-operatively is to use a ramped speed study using echocardiographic guidance before discharge. We generally use a fixed speed setting that falls midway between the minimal and maximal speeds on the basis of changes in ventricular dimensions, the position of the interventricular septum, and the frequency of aortic valve opening.

Patients with relatively small, hypertrophic left ventricle may present unique issues during surgery. In 2 patients, we had to perform a limited myomectomy of mid-septal muscle away from the septum to relieve the inflow tract to the pump. It is reassuring to note that the impact of a relatively small ventricle (<63 mm) on outcomes is short lived and that the actuarial survival after more than 18 months is comparable with that in patients with larger left ventricles (Fig. 3). We believe that the size of the left ventricle should not be considered a contraindication to this sometimes crucial therapy. However, LVAD implantation in patients with relatively small left ventricles should be considered higher risk surgery and be performed only at centers with high volume and expertise.

Predictors of RV dysfunction and mortality. RV dysfunction is very common in patients with severe LV failure and was shown to contribute to perioperative mortality (2,3,7) as well as decreased long-term survival.

In the present study, TRDc was found to be the strongest echocardiographic predictor of short-term and long-term outcomes.

An increased RIMP ratio was previously shown to predict outcomes in patients with primary pulmonary hypertension and restrictive and dilated cardiomyopathy (13,14,16). Evidence of a prolonged RV systole (corresponding to the duration of holosystolic TR, including the periods of isovolumic contraction and relaxation), was shown to predict adverse outcomes in patients with heart failure (13). To our surprise, we found that in our patient population, a short (pseudonormalized) duration of TR was the best predictor of total and cardiac mortality.

There are a few principal differences between our patients and the patients described by others (13,14,16). First, all patients in our study had end-stage heart failure (NYHA functional class IIIb or IV). Second, 44% of our patients had severe TR before LVAD surgery.

During the early phases of RV dysfunction, as the rate of contraction and relaxation decreases, the isovolumic contraction and relaxation periods become prolonged. Furthermore, the pulmonary artery pressure usually increases because of increased LV filling pressure. The increase in end-diastolic pulmonary pressure without a concomitant increase in end-diastolic RV pressure results in increased isovolumic contraction time because the pressure in the right ventricle must rise to a higher point to reach the pressure in the pulmonary artery immediately after tricuspid valve closure (Fig. 1B). Furthermore, the increase in pulmonary artery systolic pressure results in an equal rise in RV systolic pressure, so once the pulmonary valve has closed the pressure in the right ventricle must fall from a higher point to reach the pressure of the right atrium, increasing isovolumic relaxation and holosystolic periods even further (Fig. 1B). The increase in the systolic and isovolumic period is expected as long as the RV end-diastolic pressure and RA pressure are within normal limits and ejection time is preserved. In patients with extreme heart failure, RV peak systolic pressure may decrease secondary to the markedly diminished contractility and stroke volume. The ejection period usually shortens (evidence of decreased stroke volume), and the end-diastolic pulmonary artery pressure and end-systolic RV pressure may fall. Furthermore, end-diastolic RV pressure and end-systolic RA pressure (V wave) increase, decreasing the pressure differences from the time of tricuspid valve closure to pulmonary valve opening and pulmonary valve closure to tricuspid valve opening, respectively (Fig. 1A). Those changes in pressure difference shorten isovolumic contraction, isovolumic relaxation, and the holosystolic time interval (Fig. 1A). One should also note that although they are called isovolumic indexes, there are in fact large changes of ventricular volume during these time intervals, when tricuspid valve insufficiency flow is significant Thus, the main

determinant of "isovolumic relaxation time" may cease to be the rate of ventricular relaxation (14,16,17) but may be determined by the end-systolic RA pressure (V wave), causing the tricuspid valve to open earlier, on the steeper curve of ventricular relaxation, thereby shortening the "isovolumic" relaxation interval and the derived holosystolic period even further (Fig. 1A).

To analyze the significance of each of the Doppler time events, we compared them with the hemodynamic indexes in 20 patients in whom the echocardiographic and hemodynamic evaluations were performed <48 h apart (Table 5). A short TR flow duration was correlated with high RA pressure and a low RV to RA pressure difference, implying markedly increased RA pressure and reduced systolic pressure generation, consistent with a right ventricle working on the "flat portion" of its Frank-Starling curve and advanced RV diastolic dysfunction (Table 5).

In conclusion, we believe that the TRDc is a U-shaped risk factor in patients with right-heart disease. Increased duration is a risk factor in the early stages of disease (evidence of impaired relaxation), but a "pseudonormalized" TRDc, reflecting increased RV filling pressure, implies advanced RV failure and predicts the worst outcome. Of interest, we have shown that patients after LVAD surgery with prolonged TR duration have excellent 2-year survival (85.7 ± 8.5%) and 3-month functional outcomes, most probably related to the recovery of RV function.

Increase in Lietz-Miller, Matthews, and Kormos scores were associated with a higher prevalence of 30-day mortality or severe RV dysfunction. This is consistent with previous studies (7,18–21). Our overall Lietz-Miller, Matthews, and Kormos scores were 9.7 ± 5.7, 1.1 ± 2.2, and 1.8 ± 1.9, respectively, with only a minority of patients stratified as high risk. This is probably one of the reasons for our low perioperative mortality. It also seems to imply a progress in our patient selection process, positively influenced by the introduction of the scores. Importantly, echocardiographic analysis has added value to clinical and hemodynamic risk assessment in patients requiring LVAD. We believe that the most important factor in reducing the morbidity and mortality of LVAD therapy may be a timely institution of surgery before the development of profound RV dysfunction, evidenced by early equalization of RV and RA pressure.

Study limitations. Because of the relatively small number of patients, some potentially important risk factors might not have been entered into the multivariate analysis model. The results of the present study were based on a retrospective analysis, which carries limitations associated with the data source. Given the exploratory nature of the results and the relatively limited number of patients in the multivariate model, validation in larger patient samples will be required. Our use of TR flow to define the RV holosystolic period includes the time equivalent to the sum of isovolumic contraction, isovolumic relaxation periods, and ventricular contraction, but not the electromechanical delay. Regurgitant flow may end before tricuspid valve closure, thereby underestimating the duration of systole. However, this is likely not a substantial phenomenon.

CONCLUSIONS

Early mortality and need for prolonged inotropic support after LVAD surgery seem to be predominantly determined by a relatively smaller left ven-

Table 5. Correlation of Hemodynamic Parameters With Echocardiographic Doppler–Derived Time Variables

Hemodynamic Variable	Correlation With TRDc	Correlation With RV Ejection Time Corrected	Correlation With RIMP	Correlation With TR Time − RV Ejection Time	Correlation With Peak TR Velocity
RA V-wave	−0.39	−0.2	−0.55†	−0.71‡	0.02
RA A-wave	−0.2	−0.37	−0.3	−0.6†	0.13
RA mean pressure	−0.46*	0.03	−0.54*	−0.67‡	−0.06
RV systolic pressure	0.51*	−0.39	0.52*	0.23	0.71‡
RV diastolic pressure	0.02	−0.41	0.16	−0.003	0.14
PA mean pressure	0.39	0.02	0.22	0.08	0.61†
RV dP/dt	−0.05	−0.13	−0.36	−0.48*	0.5‡
Stroke volume	0.18	0.68‡	−0.15	0.2	0.25
RV PP	0.72‡	−0.36	0.85‡	0.83‡	0.83‡
PVR	0.45*	−0.37	0.64†	0.42	0.46*
PAP-RA mean	0.74‡	0.01	0.65†	0.62†	0.68‡

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
PAP = pulmonary artery pressure; PP = pulse pressure; other abbreviations as in Table 1.

tricle (<63 mm) and the degree of RV dysfunction, reflected by rapid equalization of RV and RA pressure (TRDc < 461 ms). Prediction of early adverse outcomes is improved by echocardiographic parameters when added to the previously suggested clinical scores or invasive hemodynamic variables. Patients with no evidence of early equalization of RV and RA pressure during systole are expected to have excellent short-term and long-term outcome after LVAD surgery. Given the extensive model and exploratory nature of the results, validation in larger patient samples is required.

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