ADULT

Cluster analysis of preoperative echocardiographic findings and outcomes following left ventricular device implantation

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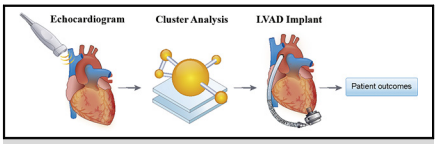
ABSTRACT

Objective: To investigate whether preoperative echocardiography findings determine postoperative continuous-flow left ventricular assist device outcomes.

Methods: From January 2003 to June 2017, 490 patients received a durable, continuous-flow left ventricular assist device. Two-step clustering of parameters including heart rate and preoperative echocardiographic findings (ie, left ventricular [LV] ejection fraction, right ventricular [RV] function, aortic insufficiency, mitral regurgitation [MR], tricuspid regurgitation [TR]) was performed and identified 5 distinct clusters associated with LV failure: group 1: moderate right ventricular dysfunction (RVD), severe MR and mild TR (n = 110); group 2: severe RVD, severe MR and TR (n = 64); group 3: moderate RVD and severe aortic insufficiency (n = 16); group 4: mild RVD and mild valvular pathology (n = 163); and group 5: moderate-severe RVD and mild valvular pathology (n = 137). Silhouette measure of cohesion and separation demonstrated satisfactory separation at 0.6.

Results: Group 2 had the greatest Interagency Registry for Mechanically Assisted Circulatory Support Level 1 (25%, $P = .010$), preoperative right atrial pressure (11 ± 5 mm Hg, $P < .001$), incidence of postoperative right ventricular failure (RVF; 20%, $P = .001$), delayed closure of the sternum (61%, $P = .002$), postoperative permanent dialysis (6%, $P = .04$), rate of tricuspid valve repair (n = 52; 81%, $P < .001$), and lowest RV stroke work index (489 ± 228 cc mm Hg/m^2/beat, $P < .001$). RVF in groups 1, 3, 4, and 5 was 6%, 0%, 4%, and 9%, respectively. No differences in incidence of heart transplantation ($P = .400$) or survival ($P = .535$) were found. Severe TR predicted RVF in those with moderate-severe preoperative RVD ($P = .001$, odds ratio 3.9).

Conclusions: Clustering demonstrated the importance of preoperative TR in predicting RVF. Combined severe LV and RV failure with severe MR and TR portends the worse prognosis. (J Thorac Cardiovasc Surg 2019;157:1851-60)



Cluster groups of pre-cfLVAD echocardiographic findings associated with surgical outcome.

Central Message

Atrioventricular valve insufficiency contributes to heart failure after cfLVAD. Pharmacologic and mechanical support may be expected.

Perspective

Cluster analysis defined severe biventricular dysfunction with severe regurgitation of both atrioventricular valves as highly predictive of right heart failure post-cfVLAD compared with lesser degrees of valve pathology. In addition to ventricular function, dual valvular regurgitation in series has important implications. This knowledge can promote early use of pharmacologic and/or mechanical support.

See Commentaries on pages 1861 and 1863.

Because of the shortage of suitable donor hearts for transplantation, durable mechanical circulatory support devices have become the prevailing surgical treatment for medically refractive advanced heart failure. An important challenge to successful durable, continuous-flow left ventricular assist device (cfLVAD) therapy is postoperative right ventricular failure (RVF), which occurs in 29.8% to 38.5% of patients

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Received for publication June 6, 2018; revisions received Oct 23, 2018; accepted for publication Nov 14, 2018; available ahead of print Feb 7, 2019.

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0022-5223/$0.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

https://doi.org/10.1016/j.jtcvs.2018.11.099

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Abbreviations and Acronyms

AI	= aortic insufficiency
AV	= aortic valve
cfLVAD	= continuous-flow left ventricular assist device
INTERMACS	= Interagency Registry for Mechanically Assisted Circulatory Support
LV	= left ventricle/ventricular
LVAD	= left ventricular assist device
MR	= mitral regurgitation
OR	= odds ratio
PVR	= pulmonary vascular resistance
RV	= right ventricle
RVAD	= right ventricular assist device
RVD	= right ventricular dysfunction
RVF	= right ventricular failure
RVSWI	= right ventricular stroke work index
TR	= tricuspid regurgitation
TV	= tricuspid valve

following implant.[1,2] RVF is associated with increased complications such as multiorgan failure, postoperative bleeding, poor oxygenation, as well as thromboembolic issues.[3] Severe RVF requiring right ventricular assist device (RVAD) support leads to greater hospital mortality, and even if successful RVAD weaning occurs, these patients are still impacted by a greater incidence of subsequent heart failure.[4] Although RVF risk-prediction models have been developed to facilitate patient selection for left ventricular assist device (LVAD) therapy,[5] these models are only modestly sensitive in identifying postoperative RVF, with a 60% positive predictive value based on several well-established prediction score paradigms.[6]

Although many patients with heart failure have associated single or multivalvular heart disease,[7] the large majority of studies have focused on single valvular lesions when evaluating their impact on postoperative outcomes, including the effects on right ventricular (RV) function. RVF pathophysiology post-cfLVAD implant is very complex and unlikely to be fully explained by a single valvular lesion. Recent studies have refocused on the impact of mitral regurgitation (MR) on RVF in the setting of LVAD implantation. Taghavi and colleagues[8] observed that mitral valve surgery at the time of LVAD implant leads to a greater decrement in mean pulmonary artery pressures and pulmonary vascular resistance (PVR) compared with cfLVAD implantation without concomitant valve repair. Cowger and colleagues[9] also described aortic insufficiency (AI) in patients with cfLVAD can worsen MR and adversely impacting RV function.

This study uses an unsupervised statistical clustering technique without pre-existing investigator biases to categorize preoperative LVAD echocardiographic assessment of valvular disease, ventricular contractility, and heart rate. We hypothesize that multivalvular disease increases the risk of RVF following LVAD implantation.

PATIENTS AND METHODS

Patients

This study with a waiver of informed consent was approved by the University of Michigan institutional review board (institutional review board no. HUM00135533). We conducted a retrospective review of prospectively collected data from the University of Michigan Mechanical Circulatory Support Registry (institutional review board no. HUM00020274) on 490 consecutive patients who underwent durable cfLVAD implantation from January 1, 2003, to June 1, 2017. RVF was defined as (1) a central venous pressure >18 mm Hg with a cardiac index <2.0 L/min/m^2 without elevation of pulmonary capillary wedge pressure >18 mm Hg; or (2) requirement for an RVAD; or (3) requirement for pulmonary vasodilator (eg, inhaled nitric oxide) or inotrope therapy for >1 week following LVAD implantation; in the absence of tamponade, ventricular arrhythmias, or pneumothorax.[10] Only postoperative RVF occurring during the index hospitalization following cfLVAD implantation was considered in the primary endpoint. The decision for using a RVAD was determined by the need for high-dose inotropes and vasopressors for hemodynamic support and/or when maximal pharmacologic circulatory support was reached without maintaining adequate hemodynamics for peripheral perfusion as a result of RVF.

Follow-up

Survival data were available for all 490 patients who underwent cfLVAD implantation and obtained through detailed clinical follow-up in the Mechanical Circulatory Support Registry and medical records. Patients were censored at the time of heart transplantation, device explant for cardiac recovery, device de-activation (without replacement), or for transfer of care to another institution. Longest follow-up was 12.8 years, with a total follow up of 998.0 patient years. Mean follow up was 2.04 ± 2.11 years with a median follow up of 1.31 (interquartile range 2.24) years. Preoperative echocardiographic assessment was obtained within 30 days of cfLVAD implantation. Right ventricular dysfunction (RVD) was graded as follows: 0 – normal, 1 – mild, 2 – moderate, and 3 – severe RVD. Tricuspid regurgitation (TR), MR, and AI was graded as: 0 – none, 1 – trace, 2 – mild, 3 – moderate, and 4 – severe. The primary end point was postoperative RVF. Secondary end points included operative mortality, readmissions, stroke, as well as the combined end point of LVAD survival and survival to heart transplant.

Statistical Methods

The Pearson χ^2 test or Fisher exact test along with binary comparisons was used to analyze categorical variables. An independent Student *t* test was used to compare continuous variables. Analysis of variance with post hoc Tukey testing or the Kruskal–Wallis method with post hoc Dunn–Bonferroni testing was performed for comparison of continuous variables across multiple groups. Logistic regression was performed to determine the relationship between RVF with TR, MR, and AI severity and degree of RVD. Kaplan–Meier survival analysis with Mantel–Cox statistics was used to analyze survival data. A 2-step cluster analysis was performed that used independent variables in the algorithm consisting of LV ejection fraction, RVD, AI, MR, TR, and heart rate. Using the log-likelihood distance, small subclusters were formulated from the cases by building a modified cluster feature tree to group similar cases together in nodes based on threshold distance as determined by variable mean and variance. The

second step then further aggregated the previously determined subclusters using Bayesian hierarchical clustering. The final optimal number of clusters was then determined by comparing the minimum intercluster distance among the hierarchically defined cluster possibilities with acceptance of the one with the widest separation.[11-14] All statistics were performed using Statistical Package for the Social Sciences software (SPSS Inc, version 24, Chicago, Ill).

RESULTS

Study Population Characteristics

Study population characteristics are presented in Table E1. These characteristics were consistent with patients with advanced heart failure. The majority of study population was male (78.4%) with a mean age of 55.2 ± 13.2 years. Baseline hemodynamics included a mixed venous oxygen saturation of 55.6 ± 8.8%, cardiac index of 2.3 ± 0.6 L/min/m^2, and right ventricular stroke work index (RVSWI) of 599.3 ± 260.0 g/m/m^2/beat (Table E2). Baseline echocardiography data demonstrated an LV ejection fraction of 15.4 ± 5.7%, moderate-severe RVF in 52.0%, severe AI in 3.3%, severe MR in 33.3%, severe TR in 13.7%, and a mean heart rate of 88.42 ± 17.76 (Table E2).

Unsupervised Statistical Categorization of Preoperative Echocardiographic Parameters

Of the 495 patients who had cfLVAD implantation in the registry, 490 patients had complete echocardiographic data to be included in our cluster analysis. Two-step cluster analysis resulted in 5 distinct groups of echocardiographic findings (Table 1) with an excellent degree of separation (silhouette cluster of cohesion and separation = 0.6), indicating that the cluster groups are distinct. Characteristics of the categories included left ventricular (LV) failure with group 1: moderate RVD, severe MR, and mild TR (n = 110); group 2: severe RVD, severe MR and TR (n = 64); group 3: moderate RVD, moderate MR, mild-moderate TR, and severe AI (n = 16); group 4: mild RVD and mild valvular pathology (n = 163); and group 5: moderate-severe RVD and mild valvular pathology (n = 137). A video discussion of the individual clusters is included with this article (Video 1).

Association of Cluster Grouping and Pre-cfLVAD Acuity of Illness

Whereas group 2 (biventricular failure and atrioventricular valve regurgitation) had the greatest proportion of patients assigned to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 1 profile (25.0%, $P = .090$), group 3 (with severe AI) had the greatest number of patients demonstrating progressive hemodynamic decline on inotropes and assigned to INTERMACS level 2 (37.5%). Patients in 2 group 2 largely consisted of those receiving device support for bridge to heart transplant indication (78.1%, $P = .002$, Table 2), and was also the youngest group with the lowest incidence of hypertension, diabetes, and hyperlipidemia ($P < .05$, Table 3). Groups 2 and 5 with biventricular failure had the greatest requirement for preoperative temporary circulatory support at 14.1% and 14.6%, respectively (Table 2, $P = .012$), and the greatest heart rate at 93.9 ± 19.9 bpm and 94.2 ± 17.7 bpm, respectively ($P < .001$). No difference in the frequency or duration of intra-aortic balloon pump use was demonstrated between the groups ($P > .05$, Table 2). Preoperative (Table 4) right atrial pressure was greatest in group 2 ($P < .001$) accompanied by the lowest RVSWI ($P = .002$), and the lowest mixed venous oxygen saturation ($P = .023$). Group 2 (Table 4) also had a greater alkaline phosphatase level ($P = .094$) and the greatest total bilirubin ($P < .001$), suggesting this group has the worse hepatic dysfunction and greater degree of preoperative hypoperfusion.

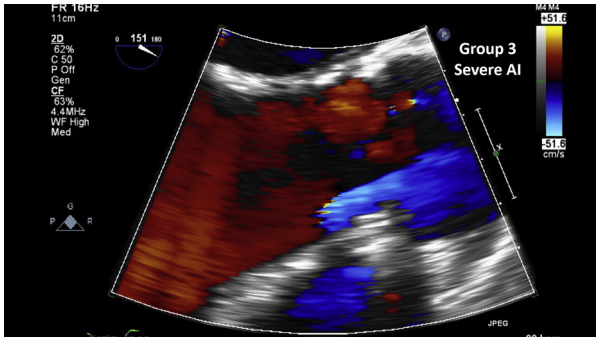
Operative Features

As expected, the majority of aortic valve (AV) interventions during cfLVAD implantation were performed in group 3 (100%, $P < .001$), and this group accounted for the longest cardiopulmonary bypass times (123.8 ± 35.1 minutes, $P < .001$). Most of the tricuspid valve (TV) procedures were performed in groups 2 and 3 (81.3% and 62.5%, respectively, $P < .001$), which displayed the greatest incidence of baseline severe TR. Mitral valve interventions only occurred in 1 patient in our series. AV intervention included AV replacement (25%, n = 4/16) and repair with the Park stitch (75%, n = 12/16). All tricuspid valve

TABLE 1. Segregated groups using unsupervised cluster analyses

Cluster	1 (n = 110)	2 (n = 64)	3 (n = 16)	4 (n = 163)	5 (n = 137)	*P* value
LVEF, %	14.52 ± 4.77	13.52 ± 4.75	13.44 ± 5.98	17.60 ± 6.80	14.43 ± 4.54	<.001
Moderate-severe RVD	59 (53.6%)	51 (79.7%)	10 (62.5%)	7 (4.3%)	128 (93.4%)	<.001
Severe AI	0 (0%)	0 (0%)	16 (100%)	0 (0%)	0 (0%)	<.001
Severe MR	110 (100%)	45 (70.3%)	6 (37.5%)	2 (1.2%)	0 (0%)	<.001
Severe TR	0 (0%)	64 (100%)	3 (18.8%)	0 (0%)	0 (0%)	<.001
Heart rate	90.06 ± 17.27	93.92 ± 19.90	85.75 ± 14.48	80.58 ± 14.47	94.18 ± 17.74	<.001

All nominal data expressed as presented as n and percentage of total population and compared with Pearson χ^2 or Fisher exact test. Continuous data expressed as mean ± standard deviation with comparisons calculated with one-way analysis of variance. *LVEF*, Left ventricular ejection fraction; *RVD*, right ventricular dysfunction; *AI*, aortic valve insufficiency; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation.



VIDEO 1. An overview of the preoperative echocardiographic categories as determined by cluster analysis and its association with subsequent clinical outcomes. It also discusses the study implications for left ventricular assist device management strategies. Video available at: https://www.jtcvs.org/article/S0022-5223(18)33246-X/fulltext.

interventions were repairs with an annuloplasty. The one mitral valve intervention was repair with an edge-to-edge Alfieri stitch placed through the LV apex.

More cfLVAD with axial design were placed in groups 1 and 2 at 61.8% and 75.0%, respectively. The other groups had comparable numbers of centrifugal and axial devices. Group 2 had the lowest number of redo-sternotomies (15.6%, $P = .001$) and greatest use of delayed closure of the sternum to manage coagulopathy or RVF (60.9%, $P = .002$, Table 5).

Postoperative Outcomes

There was no difference in length of intensive care unit stay, hospital stay, or days of readmission between the groups ($P > .05$, Table 5). Group 2 had the greatest incidence of postoperative RVF (20.3%, $P = .001$), need for RVAD use (17.2%, $P = .001$), as well as the longest median duration of nitric oxide use (3 days [interquartile range 1.0], Table 5). This group also had the greatest incidence of new postoperative permanent dialysis (6.3%, $P = .041$, Table 5). No difference in 30-day operative mortality, LVAD survival, or survival to heart transplantation was observed among groups ($P > .05$, Table 5). The Kaplan–Meier combined LVAD survival and survival to heart transplantation was also comparable ($P = .565$, Figure 1).

Tricuspid Valve Regurgitation and RVF

Using regression analysis, severe TR predicted postop RVF in the total study population ($P < .001$, odds ratio [OR] 3.8) as well as in those with moderate-severe RVD ($P = .001$, OR 3.9). Despite the baseline presence of severe MR (100%) and moderate-severe RVD (53%) in group 1 (in the absence of severe TR), postoperative RVF was relatively low at 5.5%. Group 5 had a 93.4% incidence of moderate-severe RVD at baseline with no other associated valvular lesions. Importantly, in the absence of severe TR, RVF post-cfLVAD in group 5 was also comparable at 8.8%. Interestingly, in group 2, with a baseline incidence of 100% severe TR and a significant number of patients with severe MR (70%), the RVF rate was markedly greater at 20.3%, even when taking into consideration an 80% moderate-severe RVD incidence. In group 2, the RVF rate in those with and without MR was 22.2% (n = 10/45) and 15.8% (n = 3/19), respectively ($P = .560$). For the

TABLE 2. Operative indication, preoperative mechanical support, and operative parameters

Cluster	1 (n = 110)	2 (n = 64)	3 (n = 16)	4 (n = 163)	5 (n = 137)	*P* value
Bridge to transplant	75 (68.2%)	50 (78.1%)	8 (50%)	85 (52.1%)	82 (59.9%)	.002
Destination	35 (31.8%)	14 (21.9%)	8 (50%)	78 (47.9%)	55 (40.1%)	.002
Temporary circulatory support	4 (3.6%)	9 (14.1%)	0 (0%)	12 (7.4%)	20 (14.6%)	.012
Temporary circulatory support duration, d, mean	7.75 ± 2.75	3.56 ± 1.33	0 (0%)	5.08 ± 1.98	5.70 ± 4.00	.135
IABP	55 (50%)	33 (51.6%)	8 (50%)	71 (43.6%)	75 (54.7%)	.416
IABP duration, d, mean	2.36 ± 2.46	2.15 ± 2.50	1.88 ± 1.46	2.25 ± 2.38	2.51 ± 2.57	.922
Redo-sternotomy	22 (20.0%)	10 (15.6%)	5 (31.3%)	62 (38.0%)	33 (24.1%)	.001
Centrifugal pump	42 (38.2%)	16 (25.0%)	8 (50.0%)	73 (44.8%)	60 (43.8%)	.059
Axial pump	68 (61.8%)	48 (75.0%)	8 (50.0%)	90 (55.2%)	77 (56.2%)	.059
Cardiopulmonary bypass, min	80.45 ± 28.62	97.91 ± 34.44	123.75 ± 35.09	79.78 ± 33.46	83.93 ± 28.95	<.001
Concomitant surgery						
Valve procedure	45 (40.9%)	52 (81.3%)	16 (100.0%)	47 (28.8%)	56 (40.9%)	<.001
AV procedure	4 (3.6%)	0 (0%)	16 (100.0%)	9 (5.5%)	4 (2.9%)	<.001
TV procedure	39 (35.5%)	52 (81.3%)	10 (62.5%)	39 (23.9%)	53 (38.7%)	<.001
Mitral valve procedure	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	.484

All nominal data expressed as presented as n and percentage of total population and compared with Pearson χ^2 or Fisher exact test. Continuous data expressed as mean ± standard deviation with comparisons calculated with one-way analysis of variance. Median test was used to analyze temporary circulatory support duration and IABP duration. *IABP*, Intra-aortic balloon pump; *AV*, aortic valve; *TV*, tricuspid valve.

TABLE 3. Patient demographics, comorbidities, and presentation

Cluster	1 (n = 110)	2 (n = 64)	3 (n = 16)	4 (n = 163)	5 (n = 137)	*P* value
Age, y	54.77 ± 12.98	51.50 ± 15.32	59.48 ± 8.67	57.50 ± 11.94	53.90 ± 13.56	.010
Male	82 (74.5%)	43 (67.2%)	13 (81.3%)	133 (81.6%)	113 (82.5%)	.087
Height, cm	173.72 ± 9.58	172.37 ± 13.10	173.56 ± 10.77	174.94 ± 9.17	175.57 ± 8.89	.219
Weight, kg	82.56 ± 22.65	80.99 ± 25.61	84.33 ± 16.54	88.78 ± 20.81	86.38 ± 19.77	.010
Body mass index, kg/m^2	27.80 ± 9.37	27.05 ± 6.61	27.92 ± 4.17	28.93 ± 6.09	27.97 ± 5.94	.059
Hypertension	46 (41.8%)	17 (26.6%)	8 (50.0%)	99 (60.7%)	64 (46.7%)	<.001
Diabetes	33 (30.0%)	12 (18.8%)	6 (37.5%)	67 (41.1%)	49 (35.8%)	.023
Stroke or transient ischemic attack	10 (9.1%)	8 (12.5%)	4 (25.0%)	26 (16.0%)	12 (8.8%)	.132
Carotid disease	10 (9.1%)	1 (1.6%)	0 (0%)	15 (9.2%)	9 (6.6%)	.201
Hyperlipidemia	59 (53.6%)	26 (40.6%)	14 (87.5%)	118 (72.4%)	77 (56.2%)	<.001
Atrial fibrillation	17 (15.5%)	16 (25.0%)	5 (31.3%)	38 (23.5%)	33 (24.1%)	.359
Dialysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	.630
Implantable cardioverter defibrillator	94 (85.5%)	55 (85.9%)	15 (93.8%)	136 (83.4%)	106 (77.4%)	.265
Cardiac resynchronization therapy	58 (56.3%)	32 (56.1%)	11 (78.6%)	82 (50.6%)	51 (38.6%)	.008
INTERMACS						
1	15 (13.6%)	16 (25.0%)	1 (6.3%)	14 (8.6%)	26 (19.0%)	.010
2	37 (33.6%)	22 (34.4%)	6 (37.5%)	22 (13.5%)	42 (30.7%)	<.001
3	46 (41.8%)	24 (37.5%)	7 (43.8%)	99 (60.7%)	53 (38.7%)	.001
4	12 (10.9%)	2 (3.1%)	2 (12.5%)	28 (17.2%)	16 (11.7%)	.064

All nominal data expressed as presented as n and percentage of total population and compared with Pearson χ^2 or Fisher exact test. Continuous data expressed as mean ± standard deviation with comparisons calculated with one-way analysis of variance. *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support.

entire study population (n = 490), there was a trend toward severe MR being predictive for RVF ($P = .229$) and RVAD implantation ($P = .228$), although this was not statistically significant. In group 3, characterized by severe AI, none of the patients experienced RVF despite a 62.5% incidence of preoperative moderate-severe RVD and significantly longer duration of cardiopulmonary bypass and period of cold ischemia (ie, aortic crossclamp).

Analyzing our entire patient population (n = 490) using binary logistic regression, in patients with mild or less TR (n = 271), neither preoperative MR grade ($P = .653$) nor preoperative AI grade ($P = .999$) predicted postoperative RVF. Although the presence of preoperative moderate-severe RVD predicted postoperative RVF (OR 2.17, $P < .001$), the additional presence of severe TR (OR 3.22, $P = .026$) was associated with almost twice the likelihood of developing postoperative RVF compared with patients with moderate or less TR (OR 1.78, $P = .009$). Of the patients with mild or less RVD, only 5.5% (13/235) had severe TR. Conversely, in patients with moderate-severe RVD, 21.2% (54/255) had severe TR. Of the patients with mild or less RVD, 4.3% had RVF and of the patients with moderate-severe RVD 11% had RVF. In patients with severe TR (n = 67), the incidence of RVF in those who did and did not undergo TV repair was 16.4% (9/55) and 33.3% (4/12), respectively ($P = .178$).

DISCUSSION

In this study, the nonhypothesis-driven statistical classification of preoperative echocardiographic findings using cluster analysis has revealed novel insights into the determinants of postoperative complications including RVF. Interestingly, the incidence of postoperative RVF (20.3%) and RVAD use (17.2%) was by far the greatest in group 2, as characterized by biventricular failure and severe regurgitation of both the mitral and tricuspid valves. This group had the greatest portion of patients with bridge to transplant indication (78%, $P = .002$). Conversely in group 1, even in the presence of severe MR, the absence of significant severe TR, suggestive of lack of chronic annular remodeling due to RVD, is associated with a low incidence of RVF and RVAD use at 5.5% and 4.5%, respectively.

It is possible that increased PVR from persistent MR after LVAD implant accompanied by remodeling and enlargement of the tricuspid annulus from long-standing RVD leads to predictably poor RV function after LVAD implant. Morgan and colleagues[15] previously reported that LVAD implantation decreased MR severity from moderate-severe in 76% preoperatively to 8% at 6 months postoperatively. Although recent publications have improved our understanding of mitral valve pathology in the setting of LVAD implantation, there remains no consensus indication for repair of moderate-severe MR.[16] Computer modeling

TABLE 4. Preoperative hemodynamics parameters

Cluster	1 (n = 110)	2 (n = 64)	3 (n = 16)	4 (n = 163)	5 (n = 137)	*P* value
Cardiac output, L/min	4.31 ± 1.22	4.27 ± 1.16	4.07 ± 0.73	4.77 ± 1.25	4.62 ± 1.36	.006
Cardiac index, L/min/m^2	2.20 ± 0.55	2.19 ± 0.56	1.99 ± 0.36	2.34 ± 0.55	2.30 ± 0.65	.065
PCWP, mm Hg	20.29 ± 6.65	20.52 ± 6.79	20.53 ± 9.01	19.06 ± 6.59	20.64 ± 7.20	.309
PVR, wood units	3.09 ± 1.64	2.79 ± 1.46	2.74 ± 0.84	2.63 ± 1.33	2.79 ± 1.52	.275
Transpulmonary gradient, mm Hg	12.27 ± 5.11	11.01 ± 4.55	11.10 ± 3.91	11.77 ± 5.06	11.78 ± 4.52	.549
Systemic vascular resistance, dysnes/s/cm^5	1338.41 ± 453.46	1257.50 ± 388.36	1357.50 ± 330.83	1220.26 ± 373.79	1245.33 ± 445.76	.178
Central venous pressure, mm Hg	8.40 ± 4.45	11.09 ± 5.34	8.40 ± 5.33	7.91 ± 4.59	9.69 ± 5.35	<.001
RVSWI, gm/m/m^2/beat	606.06 ± 255.33	489.32 ± 227.98	551.16 ± 247.55	673.32 ± 271.64	562.81 ± 241.09	<.001
Central venous pressure/PCWP ratio	0.43 ± 0.21	0.56 ± 0.27	0.42 ± 0.21	0.41 ± 0.22	0.47 ± 0.25	<.001
SVO_2, %	55.13 ± 9.28	53.61 ± 9.78	54.36 ± 7.25	57.49 ± 8.12	54.89 ± 8.58	.023
White blood count, × $10^3/\mu L$	8.94 ± 3.36	8.67 ± 3.04	7.96 ± 1.66	8.21 ± 2.53	9.86 ± 4.43	.019
Sodium, mEq/L	133.56 ± 4.35	132.36 ± 4.85	134.31 ± 4.13	134.56 ± 4.96	134.25 ± 4.01	.035
Bicarbonate, mEq/L	27.99 ± 3.80	27.30 ± 4.26	27.50 ± 5.19	27.83 ± 3.81	28.56 ± 3.90	.255
Blood urea nitrogen, mg/dL	29.01 ± 12.13	31.48 ± 18.31	31.56 ± 15.33	30.49 ± 14.19	32.85 ± 16.06	.364
Creatinine, mg/dL	1.28 ± 0.37	1.32 ± 0.53	1.48 ± 0.48	1.36 ± 0.60	1.30 ± 0.46	.485
Alkaline phosphatase, IU/L	99.13 ± 45.19	108.33 ± 44.42	94.81 ± 35.34	94.13 ± 44.58	107.85 ± 56.57	.010
Total bilirubin, mg/dL	1.23 ± 0.70	1.50 ± 1.02	1.19 ± 0.61	0.93 ± 0.55	1.33 ± 1.09	<.001
Brain natriuretic peptide, pg/mL	1002.60 ± 988.17	1156.60 ± 1047.45	1026.53 ± 839.00	604.12 ± 699.57	1134.87 ± 1214.68	<.001

Continuous data expressed as mean ± standard deviation with comparisons calculated with one-way analysis of variance. *PCWP*, Pulmonary capillary wedge pressure; *PVR*, pulmonary vascular resistance; *RVSWI*, right ventricular stroke work index; *SVO_2*, mixed venous oxygen saturation.

demonstrated that at LVAD speeds that allow AV opening, moderate-severe MR can cause a significant increase in left atrial and pulmonary artery pressures.[17] It is worth noting that mitral valve repair may lead to greater reductions in PVR and increase the likelihood of bridge to transplantation. This may also lower the incidence of heart failure related readmissions.[18]

A recent study by Robertson and colleagues[19] demonstrated a decreased rate of readmission and an improved quality of life in patients who had mitral valve intervention at the time of LVAD implantation. Although our results demonstrated a trend ($P = .2$) toward severe MR being predictive for postoperative RVF and RVAD in the immediate postoperative period, this may hold greater implications for long-term outcomes. A larger study with greater power may clarify this issue. Furthermore, it may be post-LVAD implant MR severity, not preoperative MR severity, that impacts RV function in addition to native RV function and contributions by other valvular pathologies.

Group 3 was characterized by severe AI and had a 62.5% incidence of moderate-severe RVD as well as 38.9% with severe MR. Although many studies have focused on new-onset AI after prolonged cfLVAD support,[20] the implications of preoperative AI are less well understood. Our data show that preoperative RVD in this setting rarely translates into severe RVD after LVAD implant, as illustrated by a 0% incidence of RVF and RVAD when not accompanied by moderate-severe TR. It is also likely that mechanical circulatory support was contraindicated in the presence of severe AI and lead to this group undergoing early cfLVAD implantation. Our results show that end-stage heart failure in this group is relatively well compensated and the right ventricle responds well to a decrease in LVEDP after AV surgery and LVAD implantation. Interestingly, this group had the oldest age ($P = .010$), the largest portion of these patients who received cardiac resynchronization therapy (78.6%, $P = .008$), and the lowest proportion of patients classified as INTERMACS 1 at the time of LVAD implantation (6.3%, $P = .010$).

In group 4, which had isolated LV dysfunction in the presence of predominantly mild or less RVD and without valvular disease, the proportion presenting in INTERMACS 1 was relatively low at 8.6% and brain natriuretic peptide was the lowest at 604.1 ± 699.6 ($P < .001$). Preserved RV function can be seen with the lowest central venous pressure (7.9 ± 4.6, $P < .001$) and greatest RVSWI 673.3 ± 271.6 ($P < .001$). Postoperative RVF was also relatively low at 4.3%. Therefore, in the absence of valvular pathology and relatively preserved RV function preoperatively, the incidence of RVF will be predictably low post-LVAD.

Group 5 was characterized by 93.4% moderate-severe RVD but a lack of valvular pathology. A significant

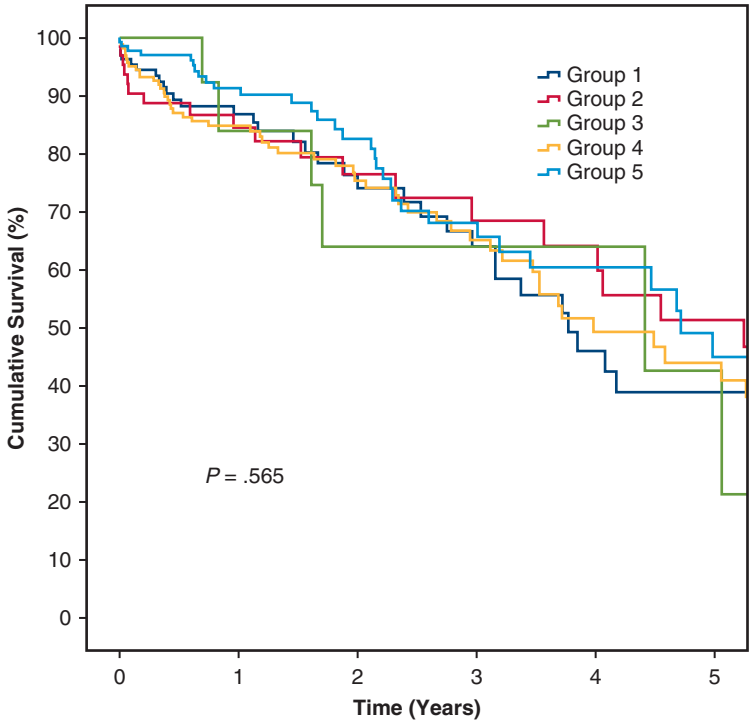
TABLE 5. Postoperative outcomes

Cluster	1 (n = 110)	2 (n = 64)	3 (n = 16)	4 (n = 163)	5 (n = 137)	*P* value
Total intensive care unit LOS, d, median	7.0 (IQR 5.0)	8.0 (IQR 12.0)	7.0 (IQR 10.0)	7.0 (IQR 6.0)	7.0 (IQR 6.0)	.702
Total LOS, d, median	20.5 (IQR 13.0)	25.0 (IQR 13.0)	19.5 (IQR 19.0)	21.0 (IQR 13.0)	21.0 (IQR 14.0)	.556
Total days of readmission, median	23.0 (IQR 44.0)	20.5 (IQR 60.0)	47.5 (IQR 83.0)	26.0 (IQR 79.0)	20.0 (IQR 52.0)	.268
Number of readmissions, median	3.0 (IQR 4.0)	3.0 (IQR 5.0)	6 (IQR 8.0)	3.0 (IQR 9.0)	2.0 (IQR 5.0)	.197
RV failure	6 (5.5%)	13 (20.3%)	0 (0%)	7 (4.3%)	12 (8.8%)	.001
RVAD	5 (4.5%)	11 (17.2%)	0 (0%)	5 (3.1%)	9 (6.6%)	.001
Concurrent LVAD/RVAD	5 (100.0%)	10 (90.9%)	0 (0%)	3 (60.0%)	9 (100.0%)	.087
Delayed unplanned RVAD	0 (0.0%)	1 (9.1%)	0 (0%)	2 (40.0%)	0 (0.0%)	.087
RVAD duration, d, median	45.5 (IQR 118)	13.0 (IQR 52.0)	0 (0%)	17.0 (IQR 90.0)	17.0 (IQR 19.0)	.426
RVAD duration, d, median	57.75 ± 62.73	34.0 ± 46.17	43.0 ± 46.17	43.0 ± 68.22	19.29 ± 13.61	.622
Nitric oxide use	108 (98.2%)	63 (98.4%)	16 (100%)	159 (97.5%)	136 (99.3%)	.796
Nitric oxide duration, d, median	2.0 (IQR 1.0)	3.0 (IQR 1.0)	2.0 (IQR 1.0)	2.0 (IQR 1.0)	2.0 (IQR 2.0)	.001
Delayed sternal closure	42 (38.2%)	39 (60.9%)	9 (56.3%)	54 (33.1%)	50 (36.5%)	.002
Chest open days, mean	1.43 ± 0.83	1.56 ± 0.91	1.11 ± 0.33	1.37 ± 0.65	1.30 ± 0.61	.358
Device infection	25 (22.7%)	22 (34.4%)	5 (31.3%)	42 (25.8%)	27 (19.7%)	.218
Device exchange infection	6 (5.5%)	8 (12.5%)	0 (0%)	9 (5.5%)	5 (3.6%)	.107
Late AV intervention	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)	4 (2.9%)	.304
All stroke	27 (24.5%)	12 (18.8%)	3 (18.8%)	39 (23.9%)	22 (16.1%)	.415
Hemorrhagic stroke	13 (11.8%)	6 (9.4%)	2 (12.5%)	21 (12.9%)	10 (7.3%)	.591
Embolic stroke	14 (12.7%)	6 (9.4%)	1 (6.3%)	18 (11.0%)	12 (8.8%)	.831
Hemolysis	25 (22.7%)	14 (21.9%)	4 (25.0%)	39 (23.9%)	33 (24.1%)	.996
Postoperative dialysis	4 (3.6%)	6 (9.4%)	1 (6.3%)	7 (4.3%)	5 (3.6%)	.422
Postoperative permanent dialysis	3 (2.7%)	4 (6.3%)	0 (0%)	1 (0.6%)	1 (0.7%)	.041
Reoperation for bleeding	11 (10.0%)	7 (10.9%)	3 (18.8%)	14 (8.6%)	11 (8.0%)	.607
Operative mortality (30-d or in-hospital)	5 (4.5%)	6 (9.4%)	0 (0%)	8 (4.9%)	5 (3.6%)	.397
cfLVAD death (cumulative)	32 (29.1%)	21 (32.8%)	4 (25.0%)	53 (32.5%)	33 (24.1%)	.535
Heart transplant	46 (41.8%)	25 (39.1%)	6 (37.5%)	50 (30.7%)	47 (34.3%)	.400

All nominal data expressed as presented as n and percentage of total population and compared with Pearson χ^2 or Fisher exact test. Continuous data expressed as mean ± standard deviation with comparisons calculated with one-way analysis of variance. Median test was used to analyze total days of readmission, RVAD duration, nitric oxide duration, and chest open days. *LOS*, Length of stay; *IQR*, interquartile range; *RV*, right ventricle; *RVAD*, right ventricular assist device; *LVAD*, left ventricular assist device; *AV*, aortic valve; *cfLVAD*, continuous-flow left ventricular assist device.

proportion in this group needed temporary circulatory support preoperatively (14.6%). This group had a postoperative RVF rate of 8.8%, but was much lower compared with group 2 (20.3%, $P = .021$). In the absence of MR and TR, the incidence of RVF remains relatively low even in the presence of biventricular failure. This finding reinforces the important role of TR and RV remodeling in the prediction of postoperative RVF during LVAD implant.

The presence of both severe TR and RVD is highly predictive of RVF with an OR of 3.22 ($P = .026$). Moderate-severe RVD alone with moderate or less TR is a much weaker RVF predictor with an OR 1.78 ($P = .009$). This association is further strengthened if the patient echo profile conforms to cluster number 2 with biventricular failure and severe MR. An interpretation of these findings is that if severe TR persists after diuresis and medical optimization, then the TR is likely reflective of chronic tricuspid annular remodeling by enlargement due to long standing RVD rather than acute volume overload. Indeed, TR in patients with heart failure was previously demonstrated to be associated with tricuspid annular dilatation and RV enlargement with apical leaflet displacement, which is associated with RVF after LVAD implantation.[21,22] Piacentino and colleagues[21] found that at late follow-up after LVAD implant (mean 156 ± 272 days), the incidence of moderate-severe TR deceased from 49% to 32%, consistent with slow and incomplete RV remodeling. Although a survival benefit for TV repair during LVAD implantation was demonstrated by some investigators,[23] others did not demonstrate a positive impact on survival.[24]



Patients at Risk

Group 1	110	65	34	23	14	9
Group 2	64	38	24	17	15	12
Group 3	16	9	6	6	4	2
Group 4	163	99	61	37	20	14
Group 5	137	83	48	30	18	12

A

Follow Up Years	1	2	3	4	5
Group 1	87.8 (79.4; 92.9)	77.0 (65.1; 85.3)	64.7 (50.0; 76.0)	46.6 (30.7; 61.1)	39.4 (23.7; 54.8)
Group 2	85.9 (73.5; 92.7)	77.7 (62.6; 87.3)	69.5 (51.4; 82.0)	65.2 (46.1; 78.9)	52.1 (32.3; 68.7)
Group 3	82.5 (46.1; 95.3)	72.2 (35.7; 90.2)	72.2 (35.7; 90.2)	72.2 (35.7; 90.2)	48.1 (8.6; 80.4)
Group 4	86.6 (79.9; 91.2)	76.2 (67.4; 83.0)	63.2 (52.2; 72.4)	48.6 (35.9; 60.2)	43.1 (29.8; 55.6)
Group 5	91.2 (84.2; 95.2)	82.3 (72.0; 89.0)	71.2 (58.6; 80.6)	61.2 (46.9; 72.8)	46.6 (30.1; 61.4)

B

FIGURE 1. Kaplan–Meier survival plot for cluster categories. A, There was no difference in combined left ventricular assist device survival and survival to heart transplantation between the 5 cluster groups. Comparable survival outcomes can be achieved despite varying degrees of preoperative valvular pathology and ventricular dysfunction. B, Survival proportion (%) with 95% confidence intervals for each group at 1, 2, 3, 4, and 5 years' follow-up is presented. For the study population the 1-, 3-, and 5-year survival was 87.1%, 66.2%, and 44.4%, respectively.

Whether severe TR is simply a marker of significant underlying RVD versus having an independent role in worsening forward right-sided cardiac output remains unclear. Furthermore, TR can mask underlying RVD, leading to worsened apparently RV function after re-establishing TV competence.[25] We did identify a small population of patients with mild or less RVD but severe TR (n = 13). It is possible that underlying RV myocardial contractility in this group was overestimated on echo due to the presence of severe TR and decompression into a low pressure central venous system. Our present study suggests that multivalvular interactions may be important to predict RVF. TV repair in severe TR may not effectively improve RV performance if significant MR remains after LVAD implantation. Residual severe MR will negatively impact RV performance by increasing pulmonary artery pressures and resistance.

An improved ability to identify patients at risk for RVF will facilitate early or simultaneous use of RVAD with cfLVAD implantation. This is important, given the improved 180 days survival for patients who received an

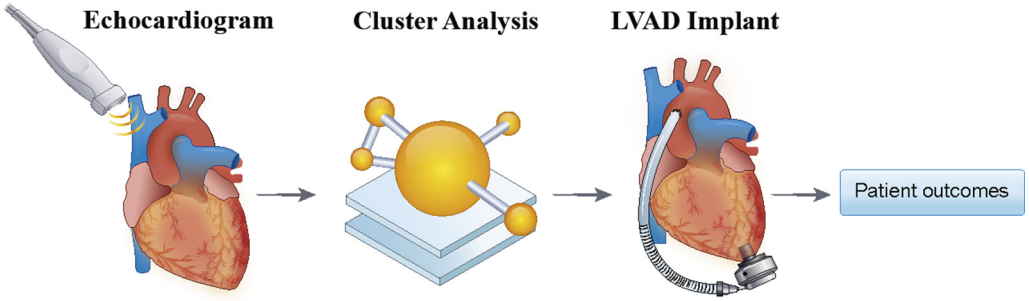


FIGURE 2. Cluster analysis of preoperative echocardiographic findings and association with outcomes after LVAD implantation. Shown is a graphical depiction of the study design using cluster analysis to categorize preoperative echocardiographic findings. The segregated groups have implications for postoperative course after LVAD implantation. *LVAD*, Left ventricular assist device.

RVAD within 24 hours of LVAD surgery rather than adopting a strategy of watchful waiting.[3] Kapelios and colleagues[26] also describes a syndrome of late-onset RVF during LVAD support where RVF can manifest several months to years from device implantation with adverse prognostic implications in terms of mortality and survival to heart transplantation. However, as our LVAD survival and survival to heart transplantation data show, comparable long-term outcomes can be achieved using modern mechanical circulatory support strategies.

Presently, our practice is that severe degrees of TR was nearly all uniformly treated with TV repair. The decision for TV repair has been influenced by surgeon preference, and treatment of lesser degrees of TR has been evolving over time. MR was almost always not repaired even under circumstances of severe MR. Severe AI is uniformly addressed intraoperatively although treatment of AI has also been evolving to address lesser degrees of AI at the time of LVAD implant, which is also influenced by surgeon preference.

This study is limited by the retrospective single-center design with inherent biases. Ventricular contractility is load-dependent and may vary between echocardiographic assessment at different times. RVF was not defined by a quantitative parameter of RV contractility, which leads to a degree of subjectivity. Detailed echocardiographic data regarding RV function (eg, tricuspid annular plane systolic excursion, RV dimension, RV ejection fraction) were not available. Concomitant valvular procedures may have influenced outcomes. Although we did not find a statistically significant impact on RVF by TV repair in the setting of severe TR ($P = .178$), our study may not be sufficiently powered to demonstrate an effect and TR severity may be dynamic. The lack of difference in survival can be explained by the fact the group 2 received further post-implant treatments for RVF (eg, pulmonary vasodilators, RVAD) that lead to improved hemodynamics sufficiently for bridge to transplantation or destination therapy. Our study did not capture outpatients who return with mild RVF symptoms, thus underestimating the burden of late RVF. RVF post-cfLVAD can also be precipitated by other causes, including acute postoperative pulmonary hypertension (eg, hypoxia) or impairment of RV function from inadequate myocardial preservation.[27] Because of the limited patient population, we were not able to include cfLVAD device type in our analyses.

CONCLUSIONS

Our study uses an unsupervised nonhypothesis-driven statistical clustering methodology that reveals a grouping of echocardiographic findings that predict postoperative outcomes after cfLVAD implant (Figure 2). Moderate-severe RVD, severe TR, as well as severe MR portend a high risk of RVF. In particular, severe TR is an important marker for postoperative RVF. Despite the diverse cardiac morphologies and dysfunction leading to LVAD implant, comparable LVAD survival and bridge to transplant can be achieved.

Conflict of Interest Statement

Dr Keith Aaronson has received grants from Medtronic, and Abbott as well as received personal fees from Medtronic, Procyrion, and NuPulseCV. Other authors have nothing to disclose with regard to commercial support.

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Key Words: cluster analysis, left ventricular assist device, mitral regurgitation, tricuspid regurgitation, right ventricular failure, echocardiography

TABLE E1. Demographics of patient population

	N = 490
Age, y	55.16 ± 13.1
Male	284 (78.4%)
Height, cm	174.46 ± 9.85
Weight, kg	85.55 ± 21.63
Body mass index	28.13 ± 6.95
Hypertension	234 (47.8%)
Diabetes	167 (34.1%)
Stroke or transient ischemic attack	60 (12.2%)
Carotid disease	35 (7.1%)
Hyperlipidemia	294 (60.0%)
Atrial fibrillation	109 (22.2%)
Dialysis	1 (0.2%)
INTERMACS	
1	72 (14.7%)
2	129 (26.3%)
3	229 (46.7%)
4	60 (12.2%)

All nominal data expressed as presented as n and percentage of total population and continuous data expressed as mean ± standard deviation. *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support.

TABLE E2. Hemodynamics and preoperative echocardiographic findings in the patient population

	N = 490
Cardiac output, L/min	4.54 ± 1.27
Cardiac index, L/min/m^2	2.27 ± 0.58
PCWP, mm Hg	20.02 ± 6.89
PVR, wood units	2.80 ± 1.47
Transpulmonary gradient, mm Hg	11.76 ± 4.83
Systemic vascular resistance, dysnes/s/cm^5	1262.88 ± 415.23
Central venous pressure, mm Hg	8.95 ± 5.01
RVSWI, g/m/m^2/beat	599.25 ± 259.96
Central venous pressure/PCWP ratio	0.45 ± 0.23
SVO_2, %	55.63 ± 8.80
White blood count, × $10^3/\mu L$	8.89 ± 3.44
Sodium, mEq/L	133.95 ± 4.57
Bicarbonate, mEq/L	27.99 ± 3.95
Blood urea nitrogen, mg/dL	30.99 ± 14.95
Creatinine, mg/dL	1.33 ± 0.51
Alkaline phosphatase, IU/L	100.98 ± 48.32
Total bilirubin, mg/dL	1.19 ± 0.85
Brain natriuretic peptide, pg/mL	930.16 ± 1005.92
Lactic acid, mg/dL	1.32 ± 2.34
LVEF, %	15.36 ± 5.72
Moderate-severe RVF	255 (52.0%)
Severe AI	16 (3.3%)
Severe MR	163 (33.3%)
Severe TR	67 (13.7%)
Heart rate	88.42 ± 17.76

All nominal data expressed as presented as n and percentage of total population and continuous data expressed as mean ± standard deviation. *PCWP*, Pulmonary capillary wedge pressure; *PVR*, pulmonary vascular resistance; *RVSWI*, right ventricular stroke work index; *SVO_2*, mixed venous oxygen saturation; *LVEF*, left ventricular ejection fraction; *RVF*, right ventricular failure; *AI*, aortic insufficiency; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation.