Concomitant mitral repair and continuous-flow left ventricular assist devices: Is it warranted?

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ABSTRACT

Background: Pre-existing mitral pathology is common in patients undergoing continuous-flow left ventricular assist device implantation. We sought to investigate whether concurrent mitral repair confers any advantage.

Methods: From March 2004 to October 2014, 374 patients received a continuous-flow left ventricular assist device. Of these, a total of 115 patients with pre-existing mitral regurgitation (MR) greater than moderate were identified and included in the analysis. Outcomes were compared between patients with concurrent mitral repair (n = 52 [45.2%]; Group A) and without repair (n = 63 [54.8%]; Group B).

Results: The mean age was 56.8 years and 25 (21.5%) were women. Patients in Group A were more likely to have undergone destination therapy (48.1% vs 11.1%; $P < .001$) and had a greater cardiopulmonary bypass time (125 vs 89 minutes; $P < .001$) than did patients in Group B. Longitudinal analysis using a generalized mixed-effects model demonstrated the odds of developing moderate or severe MR during device support were 86% lower for Group A patients ($P < .001$). Among those who were discharged alive, 9 (8.6%)—consisting of 1 (2.2%) in Group A and 8 (13.6%) in Group B ($P = .039$)—developed late right heart failure requiring a total of 13 readmissions (0.03 vs 0.15 readmissions per patient-year; $P = .011$). Multivariable competing risks regression revealed mitral repair to be a protective factor (hazard ratio, 0.16; 95% confidence interval, 0.03–0.94; $P = .042$) for late right heart failure occurrence.

Conclusions: Concurrent mitral repair appears to be efficacious in controlling MR after device implant. The fact that repaired patients developed late right heart failure less frequently than did patients without repair challenges the notion that concurrent mitral repair is unwarranted. (*J Thorac Cardiovasc Surg* 2017;154:1303–12)

Late right heart failure occurrence in patients with mitral repair versus without repair.

Central Message

Concurrent mitral repair appears to be efficacious in controlling mitral regurgitation after device implant with less frequent late right heart failure compared with patients without repair.

Perspective

Pre-existing mitral pathology is common in patients receiving a continuous-flow left ventricular assist device, whereas clinical implication of concurrent repair is unknown. Concurrent repair appears to be efficacious in controlling mitral regurgitation postimplant with less frequent late right heart failure compared with patients without repair, challenging the notion that concurrent repair is unwarranted.

See Editorial Commentary page 1313.

With the evolution of technology and patient management, continuous-flow left ventricular assist device (CF-LVAD) use has grown rapidly.¹ In this context, the

management of pre-existing valvular lesions has become a subject of interest. The management of native valve dysfunction in CF-LVAD recipients has been discussed mainly with regard to aortic and tricuspid valves.^{2–4} By contrast, pre-existing mitral pathology and its clinical influence has not been extensively investigated, despite being the most prevalent valvular pathology.⁵ The

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Abbreviations and Acronyms

BMI	= body mass index
CF-LVAD	= continuous-flow left ventricular assist device
CPB	= cardiopulmonary bypass
LV	= left ventricle
MR	= mitral regurgitation
RHF	= right heart failure
RV	= right ventricle
RVAD	= right ventricular assist device

mechanism of mitral regurgitation (MR) in most patients receiving device therapy is functional, resulting from tethering of the leaflets secondary to left ventricular (LV) dilatation and a change in geometry from an elliptical to spherical shape.^{2,6,7} With device decompression, LV dimensions decrease and allow mitral leaflets to coapt, making MR insignificant in most patients.⁸ Furthermore, the severity of pre-existing MR does not necessarily provide independent prognostic information.⁵ The current consensus statement does not recommend concomitant mitral interventions, regardless of severity, unless there is expectation of ventricular recovery.⁹ However, it is of critical importance to note that previous studies were lacking a surgical control group. Therefore, it remains unclear whether patients with pre-existing MR would benefit from repair at device insertion. We have reviewed our experience of CF-LVAD implantation with and without mitral repair to demonstrate the outcomes and ultimately elucidate its clinical implications.

METHODS

The Columbia University Institutional Review Board approved all aspects of the study.

Patients and Study Design

We retrospectively reviewed 374 consecutive patients who underwent CF-LVAD implantation between March 2004 and October 2014. Of these, 35 patients with previous mitral procedures and 1 with concomitant mitral replacement were excluded. A total of 115 patients with baseline pre-existing MR greater than moderate were identified and included in the analysis. Patients were grouped into Group A (52 [45.2%] with concomitant mitral repair) and Group B (63 [54.8%] without repair). Abstracted data included the following: patient demographic, clinical, and treatment variables, cardiopulmonary bypass (CPB) time, blood product use, dose of vasoactive drugs at device implantation, perioperative and follow-up echocardiographic variables, adverse events, and survival. Follow-up was completed as of July 1, 2015, with a completion rate of 98.3%. The types of CF-LVADs implanted comprise HeartMate II (Thoratec, Pleasanton, Calif) ($n = 86$; 74.8%), HeartWare HVAD (HeartWare Inc, Framingham, Mass) ($n = 21$; 18.3%), Ventrassist (Ventracor Ltd, Chatswood, New South Wales, Australia) ($n = 3$; 2.6%), DuraHeart (TerumoHeart, Ann Arbor, Mich) ($n = 2$; 1.7%), and DeBakey VAD (MicroMed Technology Inc, Houston, Tex) ($n = 3$; 2.6%).

Assessment of MR

Details of our protocol have been reported elsewhere.^{10,11} In brief, serial transthoracic echocardiography and intraoperative transesophageal echocardiography evaluations, reviewed by the same echocardiographers at our institution, were performed in all patients. The presence of MR was determined at baseline before device implant, and until time of last follow-up or censoring event as clinically indicated. Each valve was evaluated visually in the parasternal short- and long-axis views by transthoracic echocardiography and was graded as none, trace, mild, mild-moderate, moderate, moderate-severe, and severe on an interval scale based on the color flow jet according to the recommendations of the American Society of Echocardiography.¹² Regarding speed optimization, we followed the current recommendations¹³ to ensure middle interventricular septum position and intermittent aortic valve opening while attempting to maintain less-than-mild MR.

Right Heart Failure Definition and Management

Right heart failure (RHF) during index hospitalization was captured using the Interagency Registry for Mechanically Assisted Circulatory Support definition.¹⁴ Late RHF was defined as RHF requiring rehospitalization after indexed hospital discharge and medical/surgical treatments, including strengthening of diuretics, inotropic support, and right ventricular assist device (RVAD).^{15,16}

Patients who were hospitalized due to symptoms of heart failure routinely underwent interrogation of the device and hemolysis workup to rule out device failure and thrombosis, implantable cardioverter-defibrillator/pacemaker interrogation to identify presence of arrhythmia that may have exacerbated RHF, and echocardiography for optimization of pump speed. Initial medical management included intensification of diuretic therapy. Patients with severe RHF, as defined by the presence of end-organ dysfunction, underwent right heart catheterization, with inotropic therapy initiated if needed. In patients with medically refractory RHF, RVAD implantation was then considered.^{15,16}

Detection of late RHF was based on clinical findings, including edema, weight gain, ascites, and jugular venous distention. Heart failure related to device failure, such as device thrombosis, inflow and outflow obstruction, or drive-line fracture, was not considered late RHF.

Indications and Operative Technique of Mitral Repair

The indication for mitral repair is pre-existing MR greater than moderate. The decision to perform a repair was based on clinical characteristics in each patient, essentially bridge-to-transplant patients with anticipated prolonged device support (such as blood type O, large body size with body mass index [BMI] > 35) and patients with destination therapy intent at time of device insertion.

Tricuspid repair was performed for moderate or greater tricuspid regurgitation.⁴ Tricuspid ring annuloplasty was the first choice of procedure. In the case of severe leaflet tethering or destruction, tricuspid replacement was performed with a bioprosthetic valve.

Annuloplasty. This is our preferred approach for repair. After establishing CPB with standard aortobicaval cannulation, mitral repair was performed with a beating heart. A standard right-sided left atriotomy was made. A commercially available annuloplasty ring (Table 1) was implanted using interrupted 2-0 polyester sutures placed circumferentially around the annulus in mattress fashion (Figure E1, A). The annulus was usually undersized by 2 sizes. The atriotomy was then closed.

Edge-to-edge repair. Edge-to-edge repair (Alfieri stitch)¹⁷ was chosen when other concomitant valve repair/other procedures were performed or ring annuloplasty was not possible due to severe mitral annular calcification. For instance, when concomitant aortic valve repair was performed, CPB was established with the standard aortoatrial cannulation followed by aortic crossclamping and cardioplegia administration. A central

TABLE 1. Intraoperative data

Variable	(+) Repair (n = 52)	(-) Repair (n = 63)	P value
Implanted device			
HeartMate II*	39 (75.0)	47 (74.6)	.96
HeartWare†	13 (25.0)	8 (12.7)	.089
Ventrassist‡	0	3 (4.8)	
DuraHeart§	0	2 (3.2)	
DeBaKey VAD	0	3 (4.8)	
Other concomitant procedures			
Aortic valve repair	13 (28.9)	10 (16.9)	.15
Tricuspid repair	12 (23.1)	18 (28.6)	.50
TVR	3 (5.8)	1 (1.6)	.63
PFO closure	1 (1.9)	3 (4.8)	.63
CABG	1 (1.9)	0	.45
RVAD implantation	3 (5.8)	1 (1.6)	.33
CPB time, min	125.0 ± 35.1	89.4 ± 42.0	< .001
Isolated mitral repair vs no repair	117.6 ± 31.6 (n = 28)	65.9 ± 39.9 (n = 35)	< .001
Transfusions, units			
Packed red blood cell	2.1 ± 2.8	1.6 ± 2.4	.29
Fresh frozen plasma	3.4 ± 2.8	3.1 ± 3.2	.65
Platelet	10.5 ± 6.6	8.9 ± 7.1	.22
Vasoactive-inotropic score¶	20.5 ± 13.9	24.2 ± 14.4	.15
Ring annuloplasty (n = 34)		Edge-to-edge/others (n = 18)	
No. of patients			
Cosgrove-Edwards#	20 (58.8)	LV apex	8 (44.4)
SJM Saddle Ring**	7 (20.6)	Aortotomy	4 (22.2)
Profile 3D Ring††	4 (11.8)	Left atriotomy	4 (22.2)
GeoForm Ring#	3 (8.8)	Transseptal	2 (11.1)
CPB time, min			
All	134.5 ± 34.5	111.2 ± 30.8	.020
Isolated repair	120.8 ± 31.5	102.6 ± 31.1	.25

Values are presented as n (%) or mean ± standard error. VAD, Ventricular assist device; TVR, tricuspid valve replacement; PFO, patent foramen ovale; CABG, coronary artery bypass graft; RVAD, right ventricular assist device; CPB, cardiopulmonary bypass; LV, left ventricle; SJM, St Jude Medical. *Thoratec, Pleasanton, Calif. †HeartWare, Framingham, Mass. ‡Ventracor Ltd, Chatswood, Australia. §TerumoHeart, Ann Arbor, Mich. ||Statistically significant values ($P < .05$). ¶Vasoactive-inotropic score = dopamine dose ($\mu\text{g/kg/min}$) + dobutamine dose ($\mu\text{g/kg/min}$) + $100 \times$ epinephrine dose ($\mu\text{g/kg/min}$) + $10 \times$ milrinone dose ($\mu\text{g/kg/min}$) + $10,000 \times$ vasopressin dose (U/kg/min) + $100 \times$ norepinephrine dose ($\mu\text{g/kg/min}$).²¹ #Edwards Lifesciences, Irvine, Calif. **St Jude Medical, St Paul, Minn. ††Medtronic, Minneapolis, Minn.

edge-to-edge stitch (Alfieri stitch) using 2-0 polyester sutures with or without pledgets was placed approximately 10 mm away from the free edges of A2 and P2 through the transverse aortotomy (Figure E1, B). The aortic valve repair was then performed. The rest of the procedure was conducted in the usual fashion¹⁸ after aortotomy closure and unclamping. This repair was also performed through the LV apex after coring for the inflow cannula placement or transseptally when concomitant tricuspid procedure was performed.

Statistical Analysis

Continuous variables were expressed as mean ± 1 standard deviation. Categorical variables were presented as proportions and absolute numbers. Differences were detected using χ^2 or Fisher exact test for categorical and the Mann-Whitney U or Student t test for continuous variables. The survival was estimated using Kaplan-Meier method and compared with log-rank test. Patients were censored for transplant or device explant. Pre-implant clinical parameters were analyzed to determine contributing factors for late RHF using the competing risks regression methods of Fine and Gray¹⁹ to account for competing events, which were death and transplant. For multivariable analysis, variables with a P value $\leq .25$ on

univariable analysis were included into a final model. In addition, due to the small number of events, concomitant tricuspid repair and baseline pulmonary vascular resistance were also included as surrogates of baseline right ventricle (RV) function by clinical judgment. Results are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). For longitudinal data analysis, a mixed-effects logistic regression model with a logit link was employed to assess the association between treatment and MR severity.²⁰ The final models included fixed effects for treatment group, time (continuous scale), and a random effect to account for within-subject variation. To satisfy the linearity assumption, a log transformation was applied to the time variable. In addition, a time $\times$ group interaction was tested, but found to be statistically nonsignificant. All P values were results of 2-tailed tests. The statistical analysis was performed using SPSS 22.0 (IBM-SPSS Inc, Armonk, NY), Stata 14.2 (StataCorp, College Station, Tex), and SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Demographic Characteristics

Patient demographic characteristics are shown in Table 2. The mean age was 56.8 years and 25 (21.7%) were women.

TABLE 2. Predevice implantation clinical characteristics

Patient demographic characteristic	(+) Repair (n = 52)	(-) Repair (n = 63)	P value
Female gender	14 (26.9)	11 (17.5)	.21
Mean age, y	58.5 ± 13.9	55.5 ± 13.3	.24
Race or ethnicity			
Nonwhite	32 (61.5)	34 (54.0)	.41
Body mass index	26.3 ± 6.6	25.9 ± 5.1	.76
> 35	5 (9.6)	1 (1.6)	.054
Etiology			.59
Ischemic cardiomyopathy	18 (34.6)	18 (28.6)	
Dilated cardiomyopathy	32 (61.5)	40 (63.5)	
Others	2 (3.8)	5 (7.9)	
Device intent at insertion			< .001*
BTT	4 (7.7)	44 (69.8)	
DT	27 (51.9)	10 (15.9)	
Undetermined	21 (40.4)	9 (14.3)	
Device intent at most recent follow-up			< .001*
BTT	27 (51.9)	56 (88.9)	
DT	25 (48.1)	7 (11.1)	
Medical comorbidities			
Hypertension	24 (46.2)	32 (50.8)	.62
Dyslipidemia	19 (36.5)	19 (30.2)	.47
Coronary artery disease	20 (38.5)	23 (36.5)	.85
Diabetes	15 (28.8)	21 (33.3)	.61
Chronic obstructive pulmonary disease	3 (5.8)	5 (7.9)	.65
Prior cardiovascular accident	5 (9.6)	7 (11.1)	.79
Drug abuse	5 (9.6)	6 (9.5)	.99
Previous malignancy	5 (9.6)	4 (6.3)	.94
Smoking	20 (38.5)	19 (30.2)	.35
Previous cardiac surgery			
Coronary artery bypass graft	8 (15.4)	13 (20.6)	.47
Aortic valve	0	2 (3.2)	.50
Ventricular assist device/extracorporeal membrane oxygenation	2 (3.8)	4 (6.3)	.69
Automated implantable cardioverter-defibrillator	42 (80.8)	52 (82.5)	.81
Others	2 (3.8)	3 (4.8)	.80
Intra-aortic balloon pump	16 (30.8)	17 (27.0)	.66
Inotrope	44 (84.6)	54 (85.7)	.87
Vasopressor	7 (13.5)	3 (4.8)	.18
Mechanical ventilation	2 (3.8)	1 (1.6)	.59
Laboratory values			
Blood urea nitrogen, mg/dL	34.4 ± 19.6	38.0 ± 18.7	.32
Creatinine, mg/dL	1.36 ± 0.55	1.54 ± 0.51	.065
Albumin, g/dL	3.6 ± 0.6	3.7 ± 0.5	.48
Total bilirubin, mg/dL	1.6 ± 1.2	1.4 ± 1.0	.36
Direct bilirubin, mg/dL	0.7 ± 0.7	0.5 ± 0.5	.17
Aspartate aminotransferase, U/L	62.7 ± 169.9	34.1 ± 39.9	.24
Alanine aminotransferase, U/L	53.4 ± 135.5	56.7 ± 149.7	.90
Alkaline phosphatase, U/L	97.8 ± 59.1	98.5 ± 50.5	.90
Prothrombin time/international normalized ratio	1.44 ± 0.52	1.34 ± 0.35	.20
Hemodynamic parameters			
Systolic blood pressure, mm Hg	98.7 ± 10.1	102.1 ± 13.8	.18
Central venous pressure, mm Hg	10.8 ± 5.7	11.6 ± 5.4	.50
Mean pulmonary pressure, mm Hg	35.7 ± 10.8	37.0 ± 8.2	.48

(Continued)

TABLE 2. Continued

Patient demographic characteristic	(+) Repair (n = 52)	(-) Repair (n = 63)	P value
Wedge pressure, mm Hg	23.3 ± 8.1	25.9 ± 7.7	.11
Cardiac index, L/min/m ²	1.8 ± 0.6	1.5 ± 0.4	.13
Pulmonary vascular resistance, wood units	4.0 ± 2.2	3.9 ± 2.5	.95
INTERMACS profiles			.43
1-2	42 (80.8)	47 (74.6)	
HeartMate II† risk score	1.63 ± 1.02	1.54 ± 0.70	.55
Year of device implantation			< .001*
2004-2007	1 (1.9)	22 (34.9)	
2008-2011	28 (53.8)	32 (50.8)	
2012-2015	23 (44.2)	9 (14.3)	
Baseline echocardiographic characteristic			
Left ventricular ejection fraction	14.0 ± 5.7	16.2 ± 5.8	.054
Mitral regurgitation degree			.23
Moderate-severe	12 (23.0)	9 (14.3)	
Severe	40 (76.9)	54 (85.7)	
Tricuspid regurgitation ≥ moderate	23 (44.2)	35 (55.6)	.23
Moderate	8 (15.4)	18 (28.6)	
Moderate-severe	3 (5.8)	5 (7.9)	
Severe	12 (23.1)	12 (19.0)	
Aortic insufficiency > mild	5 (9.6)	3 (4.8)	.20
Left ventricular end-systolic diameter, mm	65.0 ± 11.6	68.9 ± 12.9	.25
Left ventricular end-diastolic diameter, mm	71.7 ± 11.7	74.4 ± 12.4	.24

Values are presented as n (%) or mean ± standard error. *BTT*, Bridge-to-transplant; *DT*, destination therapy; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support. *Statistically significant values ($P < .05$). †Thoratec, Pleasanton, Calif.

Patients in Group A were more likely to be planned for destination therapy than were patients in Group B. There were more patients with BMI > 35 in Group A, whereas the mean BMI is indifferent. Furthermore, concurrent mitral repair was more often performed in relatively recent patients, with the first in 2007 (there were no destination therapy patients before 2007 in the present study cohort). Otherwise, the groups both displayed similar clinical characteristics.

The baseline echocardiographic variables are further displayed in Table 2. The severity of MR was similar and moderate or greater tricuspid regurgitation was common in both groups.

Intraoperative Data

Table 1 illustrates the intraoperative data. Implanted device brand and the frequency of other concomitant procedures performed were similar. Subjects in Group A had a greater CPB time than did individuals in Group B. In contrast, the dose of vasoactive drugs, as represented by the vasoactive-inotropic score²¹ and blood product use, were comparable between groups.

Regarding the repair method, 34 (65.4%) received a ring annuloplasty, 15 (28.9%) received an edge-to-edge repair, and 2 (3.9%) received a repair with other

techniques. Annuloplasty rings used included the Cosgrove-Edwards Annuloplasty System (n = 20 [58.8%]) (Edwards Lifesciences, Irvine, Calif), SJM Rigid Saddle Ring (n = 7 [20.6%]) (St Jude Medical Inc, St Paul, Minn), GeoForm Ring (n = 3 [8.8%]) (Edwards Lifesciences), and Profile 3D Annuloplasty System (n = 4 [11.8%]) (Medtronic, Minneapolis, Minn). The median annuloplasty size was 28 mm (interquartile range, 26-32 mm). As for edge-to-edge repair, almost half were performed through the LV apex. The CPB time was significantly longer in patients with annuloplasty compared with others, but not with isolated ring annuloplasty versus isolated edge-to-edge repair (Table 1).

Adverse Events and Survival

Early postoperative outcomes and adverse events were summarized in Table E1. There was no difference regarding early postoperative complications between groups. Among discharged patients alive with either HeartMate II or HeartWare device, predischARGE pump speed in the repaired patients supported with HeartMate II was significantly lower than that of nonrepaired patients with HeartMate II, whereas no difference among patients with HeartWare between groups. Regarding overall adverse events, more frequent RHF, which is attributable to late RHF occurrence,

FIGURE 1. Nelson-Aalen cumulative hazard plot of postimplant adverse event in patients with mitral repair versus without repair. A, Right heart failure (during index hospitalization + late right heart failure). B, Late right heart failure. 95% CI, Confidence interval.

was observed in Group B (Figure 1, A and B), whereas RHF during the index hospitalization was comparable between groups (Table E1). Overall, 5 (9.6%) in Group A and 3 (4.8%) in Group B received an RVAD. There was no difference regarding the occurrence of other adverse events (Figure 1, A and B, Figure E2, A and B, Figure E3, A and B, and Figure E4).

The estimated on-device survival at 2 years was 79.9% (6.5%) and 68.8% (11.1%) ($P = .83$), and the overall survival at 2 years was 79.1% (6.0%) and 85.5% (4.5%) ($P = .40$) in Group A and B, respectively (Figure 2 and Figure E5).

Comparison of Postimplant MR Between Groups

Significant postimplant residual MR was defined as at least moderate MR despite medical therapy, device decompression, and pump speed optimization. A total of 429 post-implant echocardiographic studies were available. Table E2

FIGURE 2. Kaplan-Meier curve for on-device survival at 2 years; comparison of patients with mitral repair versus without repair. 95% CI, 95% Confidence interval.

demonstrates the number of echocardiographic studies remaining at each time point. Longitudinal changes in MR grades over time at time of/after index hospital discharge in each group are shown in Figure 3. At time of discharge, no patients in Group A had residual MR, whereas 20% in Group B ($P < .001$) did. Approximately 30% of patients in the nonrepair group demonstrated significant residual MR consistently across the follow-up periods up to 2 post-device years. MR appeared to be well controlled regardless of surgical technique (ring annuloplasty vs edge to edge). Furthermore, the longitudinal analysis using generalized mixed effects model showed the odds of developing a moderate/severe MR were 86% lower for patients who underwent repair versus those who did not ($P < .001$) (Table 3).

Contributing Factors for Late RHF and Posttransplant Survival

Among 105 patients (46 repaired and 59 nonrepaired) who were discharged alive, 9 (8.6%), consisting of 1 (2.2%) in Group A and 8 (13.6%) in Group B ($P = .039$), developed late RHF requiring a total of 13 readmissions (0.03 vs 0.15 readmissions per patient-year; $P = .011$). All patients received intensified diuretic therapy, 4 received inotropic therapy, and 1 (1 out of 8; 12.5%) in Group B required an RVAD implantation. Further subgroup comparison stratified by the presence of tricuspid repair was also performed. The incidence of late RHF in each group was 3.0% (mitral repair alone; $n = 33$), 0% (mitral + tricuspid repair; $n = 10$), 11.1% (tricuspid repair alone; $n = 18$), and 12.5% (no mitral or tricuspid repair; $n = 40$), respectively ($P = .34$).

Clinical parameters before/at device insertion were analyzed to identify contributing factors for late RHF occurrence. Multivariable competing risks regression analysis revealed that blood urea nitrogen was a contributing factor

FIGURE 3. Proportion of patients with moderate or greater mitral regurgitation (MR) postdevice implant at baseline pump speed at discharge, 6 months, 1 year, and 2 years or beyond.

(HR, 1.21 per 5-point increase; 95% CI, 1.03-1.42; $P = .022$), whereas mitral repair was a protective factor (HR, 0.15; 95% CI, 0.028-0.85; $P = .031$) (Table 4). A list of variables entered in the analysis is shown in Table E3.

Among those 9 patients who developed late RHF, 6 patients underwent bridge to transplant. The 2-year survival after transplant was 33.3% among these 6 patients. Two died of primary graft dysfunction/multiorgan failure and other two died of sepsis/multiorgan failure. In contrast, the 2-year survival among transplanted patients who did not experience late RHF was 93.3% (42 out of 45).

TABLE 3. Longitudinal analysis using generalized mixed effects model to assess the association between the treatment (mitral repair vs no repair) and mitral regurgitation moderate or greater following device insertion

Variable	Estimate $\pm$ standard error	Odds ratio (95% confidence interval)	P value
Repair vs nonrepair	-1.98 ± 0.39	0.14 (0.06-0.30)	$< .001^*$
Time †	0.05 ± 0.09	1.05 (0.88-1.25)	.599

*Statistically significant. † Time was fitted on the log scale.

DISCUSSION

The fact that late RHF was observed less frequently in the repaired patients, even compared with nonrepaired patients with baseline severe MR, clearly challenges the notion that concurrent mitral repair is unwarranted. We speculate that more controlled postimplant MR enables less challenging volume management postoperatively. Furthermore, having more controlled MR would be safer in cases of unexpected device failure (Video 1).

In contrast to the attention paid to aortic/tricuspid disease in patients with a CF-LVAD, mitral pathology has received less attention for surgical repair largely due to the reduction in left ventricular end-diastolic diameter and MR severity following device insertion.^{2,8,22} Furthermore, no previous studies have demonstrated uncorrected MR to be associated with worse survival. Stulak and colleagues²² reported on 491 patients among whom 189 had greater-than-moderate MR and 302 had moderate MR or less. There was more favorable survival in patients with severe preimplant MR, suggesting lack of value of surgical repair. However, neither surgical control nor postimplant MR data were provided in their study. Another study with a smaller cohort, again without a surgical control group, demonstrated

TABLE 4. Multivariable competing risks regression for contributors to late right heart failure among patients who were discharged from index hospitalization (n = 105). Competing events included death, transplant, and device removal

Variable	Hazard ratio (95% confidence interval)	P value
Mitral repair	0.15 (0.028-0.85)	.031*
Blood urea nitrogen†	1.21 (1.03-1.42)	.022*
Tricuspid repair	1.11 (0.25-5.02)	.89
Pulmonary vascular resistance	1.08 (0.79-1.50)	.63
Female	0.54 (0.061-4.74)	.58

*Statistically significant values ($P < .05$). †The hazard ratio for blood urea nitrogen is shown for 5-unit increment.

similar 1-year survival between patients with (n = 13) and without (n = 64) significant postdevice implant MR.² Despite lack of surgical control groups across all of these studies, there has been a general consensus that pre-existing MR does not require repair at device implantation, irrespective of its severity. Consequently, most centers presently avoid any procedures on regurgitant mitral valves. Meanwhile, there have been a few studies describing concurrent mitral repair from small cohorts of patients. Russo and colleagues²³ examined the outcomes of transapical edge-to-edge mitral repair on 19 patients who underwent CF-LVAD placement. Taghavi and colleagues²⁴ reported on 57 patients among whom 18 (32%) received a repair and 3 (5%) received a replacement. Although sample size and lack of clinical details limit interpretation of these study results, both demonstrated acceptable postoperative morbidity. Moreover, the latter showed greater postimplant decrease in pulmonary vascular resistance in the repair group.²⁴ More recently, Tanaka and colleagues²⁵ demonstrated that patients whose MR was corrected with valve repair or replacement had significantly better hemodynamic profiles postimplant compared with patients whose MR spontaneously resolved with CF-LVAD implantation alone.

VIDEO 1. Introduction and brief overview of the present study by one of authors. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30840-1/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30840-1/addons).

In addition, heart failure-related readmission rate was observed less frequently in the repaired group. Their results are partially in line with findings in the present study.

Although the severity of MR has been demonstrated to regress without repair, CF-LVAD unloading may not be sufficient to counteract functional MR in a subset of patients. Kitada and colleagues² reviewed 82 patients who underwent CF-LVAD insertion after excluding patients with organic lesions. More than 30% of patients continued to have significant MR despite device support. Although MR usually decreases with higher speeds, it appears that preoperative posterior displacement of mitral leaflets is associated with persistent MR. Their results are compatible with the present study, in which 20% to 35% of patients in the nonrepair group demonstrated persistent MR postimplant.

Pump speed is determined based on optimal LV unloading and severity of MR while avoiding complications related to high pump flow. The MR degree significantly varies with pump speed and hemodynamic parameters during echocardiography.¹¹ Furthermore, there is a trade-off relationship between pump speed and RV function. By increasing pump speed, which is used to reduce MR degree, RV function and aortic valve opening can be compromised. The degree of septal deviation may predict the development of RV failure during CF-LVAD support.^{26,27} With reduced LV pressures, bowing of the interventricular septum away from the RV into the decompressed LV can alter RV shape and size and reduce the efficiency of RV contraction.²⁵ The RV may be further challenged by the increased preload provided by the device effect on increased systemic blood flow, which is increased at higher pump-speed settings.²⁸ Again, pump speed has such dynamic characteristics determined by multiple factors. Optimal pump speed widely varies in each individual and therefore the mean pump speed as a group (repair or nonrepair) has little clinical relevance, although repaired patients with a HeartMate II device demonstrated lower mean pump speed in the present study. We suspect the relatively small sample size of the HeartWare cohort (11 patients in Group A and 7 patients in Group B) might be insufficient to detect significant differences in pump speed. We postulate mitral repair might have lowered pump speed, which would have been the amount of speed to be added to suppress MR degree. Uriel and colleagues¹¹ conducted a study to evaluate the utility of ramp tests for assessing ventricular decompression in HeartWare ventricular assist device patients.¹¹ The interaction of left ventricular end diastolic diameter with mitral repair suggests that ventricular geometry influences the device unloading properties. By decreasing the size of the mitral annulus, the mitral repair amplifies the effects of ventricular decompression. The authors suggested mitral repair might be indicated if lower speeds are necessary to preserve aortic valve integrity or maintain pulsatility within the peripheral circulation.

The optimal repair method remains unclear. In the present study, 2 techniques, consisting of annuloplasty and edge-to-edge repair, were performed. Although the technical feasibility and durability of each technique appeared acceptable, no conclusion could be drawn from the data regarding the choice of repair technique. The criticism edge-to-edge repair alone without annuloplasty is suboptimal durability¹⁷ in non-CF-LVAD settings. On the contrary, there is a paucity of data specifically related to patients supported by CF-LVAD. In addition, in cases of severe annular calcification annular manipulation should be avoided. Our data confirmed the midterm durability of concurrent edge-to-edge repair in patients who underwent CF-LVAD insertion. Although an advantage of these repair techniques includes procedural simplicity, concurrent mitral repair is not without risk. In fact, CPB time was significantly greater in the repair cohort. However, bleeding, blood product use, and vasoactive-inotropic score were similar. Additionally, on-device and overall survival were comparable between groups.

Study Limitations

First, our investigation is limited by the retrospective nature. Second, the serial follow-up echocardiographic studies, which can be often influenced by hemodynamic parameters, were performed in a variety of clinical settings such as in the intensive care unit and outpatient clinic. Third, the decision for repair was made by surgeons based on various clinical characteristics and repair technique in each patient was not selected randomly, introducing further selection bias into the results and making our conclusion not convincing. Furthermore, there were no data correlating repaired/nonrepaired patients with functional capacity testing or hemodynamic parameters due to lack of a postimplant cardiac catheterization. Fourth, many underwent concomitant aortic/tricuspid valve repairs in addition to mitral repair. Lastly, mitral repair was more frequently performed in relatively recent patients simply because there were few destination therapy patients before 2007 in the present study population. Although these potential confounders, including year of device implantation and other valve repairs, were all entered into the multivariable analysis and demonstrated no association with late RHF. Clinical effect by these factors to the outcomes could not be completely eliminated.

CONCLUSIONS

Concurrent mitral repair, irrespective of technique, appears to be durable in controlling MR postdevice implant. Although this study has a number of limitations, the fact that mitral repair was associated with less frequent

occurrence of late RHF, which appears to be a significant factor for worse posttransplant survival,¹⁵ is particularly noteworthy, cautioning against the concept that concurrent mitral repair is unnecessary. Considering our observation, further studies are truly needed to validate our results and clarify the unanswered questions in this society.

Conflict of Interest Statement

Y.N. has been a consultant for the Thoratec Corporation. All other authors have nothing to disclose with regard to commercial support.

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Key Words: mitral valve repair, continuous-flow left ventricular assist device, right heart failure

FIGURE E1. Mitral valves from explanted hearts of patients who received a concomitant mitral repair. A, Cosgrove-Edwards annuloplasty ring (Edwards Lifesciences, Irvine, Calif) (arrow). B, Edge-to-edge repair (arrow).

FIGURE E2. Nelson-Aalen cumulative hazard plot of postimplant adverse event in patients with mitral repair versus without repair. A, Bleeding. B, Cerebrovascular accident. 95% CI, 95% Confidence interval.

FIGURE E3. Nelson-Aalen cumulative hazard plot of postimplant adverse event in patients with mitral repair versus without repair. A, Device-related infection. B, Device-nonrelated infection. 95% CI, 95% Confidence interval.

FIGURE E4. Nelson-Aalen cumulative hazard plot of postimplant ventricular arrhythmia occurrence in patients with mitral repair versus without repair. 95% CI, 95% Confidence interval.

FIGURE E5. Kaplan-Meier curve for overall survival at 2 years. 95% CI, 95% Confidence interval.

TABLE E1. Early and late postimplantation follow-up data

Variable	(+) Repair (n = 52)	(-) Repair (n = 63)	P value
30-d mortality	2 (3.8)	0	.20
In-hospital mortality	6 (11.5)	2 (3.2)	.14
Intensive care unit stay			
Days	12.6 ± 17.4	9.6 ± 5.4	.24
Median (interquartile range)	7.0 (5.0-11.0)	7.0 (5.0-11.5)	
Hospital stay			
Days	41.3 ± 54.0	34.2 ± 34.7	.39
Median (interquartile range)	28.5 (21.0-42.5)	26.0 (20.0-38.0)	
PredischARGE pump speed, RPM (n = 98)			
HeartMate II (n = 80)*,†	8931 ± 460 (n = 35)	9200 ± 451 (n = 45)	.010
HeartWare (n = 18)‡	2522 ± 92 (n = 11)	2594 ± 133 (n = 7)	.19
Transplanted*	17 (32.7)	43 (68.3)	< .001
Postoperative complications			
Acute kidney injury	11 (21.2)	8 (12.7)	.22
CVVHD	5 (9.6)	2 (3.2)	.15
Bleeding requiring re-exploration	13 (25.0)	10 (15.9)	.22
CVA	4 (7.7)	2 (3.2)	.41
Urinary tract infection	10 (19.2)	7 (11.1)	.22
Sepsis	8 (15.4)	4 (6.3)	.12
Atrial fibrillation/flutter	15 (28.8)	17 (27.0)	.82
VT/VF	17 (32.7)	15 (23.8)	.29
RHF	8 (15.4)	12 (19.0)	.61

Values are presented as n (%) unless otherwise noted. CVVHD, Continuous venovenous hemodialysis; CVA, cerebrovascular accident; VT, ventricular tachycardia; VF, ventricular fibrillation; RHF, right heart failure. *Statistically significant values ($P < .05$). †Thoratec Corporation, Pleasanton, Calif. ‡HeartWare, Framingham, Mass.

TABLE E2. The number of patients and corresponding echocardiographic studies remaining at each time point

Study variable	Time, y							
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
(-) Repair								
No. of patients	63	35	21	16	11	10	8	5
No. of studies	225	78	47	29	20	15	12	10
(+) Repair								
No. of patients	52	43	30	20	15	12	7	4
No. of studies	204	86	49	32	21	10	3	0

TABLE E3. List of variables entered into the Cox regression analysis

Year (2004-2007, 2008-2011, 2012-2015)	Gender
Age	Race/ethnicity
Hypertension	Dyslipidemia
Chronic kidney disease	COPD
Smoking	Diabetes
Carotid disease	Peripheral arterial disease
Hemodialysis	Height
Weight	BMI
Previous sternotomy	IABP
BSA	Prior stroke
Etiology of heart failure (ischemic, dilated cardiomyopathy, others)	AICD
Left ventricular ejection fraction	Moderate to severe LVH
Baseline left ventricular end-diastolic diameter	Baseline left ventricular end-systolic diameter
Vasoactive-inotropic score	INTERMACS 1/2
Supported with ECMO at time of CF-LVAD implantation	Supported with short-term VAD at time of CF-LVAD implantation
Uncorrected tricuspid regurgitation	Uncorrected mitral regurgitation
Concomitant right ventricular assist device implantation	Concomitant aortic valve closure
Concomitant aortic valve repair	Concomitant aortic valve replacement
Concomitant mitral repair	Concomitant tricuspid repair
Concomitant tricuspid replacement	Cardiopulmonary bypass time
Device intent (BTT, DT)	Packed red blood cell transfusion
Platelet transfusion	Fresh frozen plasma transfusion
Baseline sodium	Baseline creatinine
Baseline BUN	Baseline ALT
Baseline AST	Baseline ALP
Baseline bilirubin	Baseline INR
Baseline albumin	Systolic blood pressure
Diastolic blood pressure	Mean pulmonary artery pressure
Pulmonary vascular resistance	Transpulmonary gradient
Systolic blood pressure	Device brand (HeartMate II*, HeartWare VAD System†, others)
Mean arterial blood pressure	Central venous pressure
Pulmonary artery wedge pressure	Cardiac output, L/min
HeartMate II* risk score	

COPD, Chronic obstructive pulmonary disease; *BMI*, body mass index; *IABP*, intra-aortic balloon pump; *BSA*, body surface area; *AICD*, automated implantable cardioverter-defibrillator; *LVH*, left ventricular hypertrophy; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support; *ECMO*, extracorporeal membrane oxygenation; *CF-LVAD*, continuous-flow left ventricular assist device; *VAD*, ventricular assist device; *BTT*, bridge-to-transplant; *DT*, destination therapy; *BUN*, blood urea nitrogen; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *ALP*, alkaline phosphatase; *INR*, international normalized ratio. *Thoratec Corporation, Pleasanton, Calif. †HeartWare, Framingham, Mass.