Concomitant aortic valve repair with continuous-flow left ventricular assist devices: Results and implications

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ABSTRACT

Objectives: Aortic insufficiency (AI) after continuous-flow left ventricular assist device implantation can affect patient outcomes. Central aortic valve closure (CAVC) is a strategy commonly practiced; however, its efficacy has not been extensively investigated.

Methods: From March 2004 to May 2014, a total of 340 patients received a continuous-flow left ventricular assist device (89; 26.2%) as destination therapy (DT). Outcomes were compared between patients with CAVC (n = 57 [16.8%]; group A) versus without repair (n = 283 [83.2%]; group B).

Results: Patients in group A were older, were more likely to be having DT, had a greater cardiopulmonary bypass and aortic crossclamp time, and more often received intraoperative transfusions than did patients in group B. Twenty-three (40.4%) patients in group A had significant pre-existing AI, defined as >mild AI, whereas none did in group B. Kaplan-Meier analysis revealed that freedom from significant AI was 66.7% and 59.9% at 2 years ($P = .77$) in groups A and B, respectively. In the DT cohort, freedom from significant AI was 78.1% and 41.8% at 2 years ($P = .077$). A generalized mixed-effects model demonstrated a 57% and 69% decrease in the odds of significant AI progression among repaired patients in the entire and DT cohort, respectively, after adjusting for time effect and degree of baseline pre-existing AI.

Conclusions: Despite pre-existing AI, the prevalence of significant AI in patients with CAVC was comparable to the AI in those without pre-existing AI/CAVC. The efficacy of this technique was more evident in DT patients. Thus, CAVC may be an effective and durable strategy, especially in patients who require lengthy device support. (J Thorac Cardiovasc Surg 2016;151:201-10)

Freedom from significant aortic insufficiency: patients with, versus without, repair, for (A) entire cohort and (B) destination therapy subgroup.

Central Message

Concomitant aortic valve repair may be an effective strategy in addressing pre-existing aortic insufficiency for device-supported patients.

Perspective

The present study is the largest series describing concomitant aortic valve repair in patients undergoing continuous-flow left ventricular assist device placement. Concomitant central aortic valve closure may be an effective and durable strategy in addressing pre-existing aortic insufficiency for device-supported patients, especially those expected to require multiyear device support, such as those in destination therapy.

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See Editorials page 10 and 13.

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Continuous-flow left ventricular assist devices (CF-LVADs) have been used increasingly as either bridge-to-transplant or destination therapy (DT). Because the CF-LVADs offer more durability and are associated with fewer adverse events, thereby providing patients with improved functional capacity and quality of life, compared with the

Abbreviations and Acronyms

AI	= aortic insufficiency
AV	= aortic valve
CAVC	= central aortic valve closure
CF-LVAD	= continuous-flow left ventricular assist device
DT	= destination therapy
INTERMACS	= Interagency Registry for Mechanically Assisted Circulatory Support

earlier-generation pulsatile LVADs, they have rapidly become integral to the treatment of patients who have advanced heart failure.¹⁻³ The recipients of CF-LVADs are more likely than recipients of pulsatile LVADs to develop worsening aortic insufficiency (AI).⁴ Therefore, progressive AI, either de novo or developing from pre-existing AI, and its impact on clinical outcomes, has received increasing attention.^{5,6} With an increasing number of patients being supported with longer-term usage of CF-LVADs, investigation of the optimal management of AI progression has become compelling.

Patients with pre-existing AI have undergone aortic valve (AV) surgery concomitantly with or after undergoing implantation, including AV closure, AV repair with varied techniques,^{7,8} AV replacement with a bioprosthesis,⁹ and more recently, percutaneous device closure.¹⁰ However, data are scarce regarding the applicability, efficacy, and durability of each strategy, mainly because of the small sample size and limited follow-up periods. Central aortic valve closure (CAVC), first described by Park and colleagues,¹¹ has been a commonly practiced strategy to eliminate central regurgitation while allowing opening of the AV through the lateral aspect of the valve leaflets.¹² Previous studies describing this technique were performed on short- and/or mid-term data only, from small patient cohorts.^{12,13} Therefore, the optimal management approach for pre-existing AI remains to be determined. We have reviewed our experience with CF-LVAD implantation, with and without concomitant CAVC, to assess its clinical efficacy, which is defined as a reduction of native AI to trace or none at the time of repair, and a decreased prevalence of greater-than-mild AI during CF-LVAD support.

METHODS**Patients and Study Design**

The Columbia University Institutional Review Board approved all aspects of the present study, and individual patient consent was waived. We retrospectively reviewed 360 patients who underwent CF-LVAD implantation between March 2004 and May 2014. Of these, 4 patients who underwent concomitant AV replacement were excluded: 3 with concomitant AV closure with a Dacron or bovine pericardial patch; 1 with concomitant AV repair using a different technique; and 9 who had previously undergone AV procedures (8 replacements; 1 repair). Additionally, 3 individuals were

excluded who received the Jarvik 2000 (Jarvik Heart, New York, NY) via left thoracotomy. A total of 340 patients were included in this analysis (Figure E1). Subjects were grouped into group A (n = 57 [16.8%] with concomitant CAVC) and group B (283 [83.2%] without CAVC).

Abstracted data included the following: patient demographics, clinical and treatment variables, cardiopulmonary bypass and aortic crossclamp time, blood product use, dosage of vasoactive drugs at the time of device implantation, perioperative and follow-up echocardiographic variables, freedom from AI occurrence, number of adverse events, and survival in each group. Follow-up was complete as of October 1, 2014. The completion rate was 96.5%.

Devices Implanted

The types of CF-LVADs implanted are as follows: the HeartMate II (Thoratec Corporation, Pleasanton, Calif) (n = 281; 82.6%); the HeartWare Ventricular Assist System (HeartWare International, Inc, Framingham, Mass) (n = 36; 10.6%); the VentrAssist (Ventracor Ltd, Chatswood, New South Wales, Australia) (n = 9; 2.6%); the DuraHeart (Terumo Heart, Inc, Ann Arbor, Mich) (n = 8; 2.4%); and the MicroMed DeBakey (MicroMed Technology, Inc, Houston, Tex) (n = 6; 1.8%).

Assessment and Follow-Up of Aortic Insufficiency

Details of our protocol for echocardiographic evaluation have been reported elsewhere.¹⁴ In brief, serial transthoracic echocardiography and intraoperative transesophageal echocardiography evaluations were performed in all patients. The presence of AI was determined at baseline, prior to device implantation, and until the time of the last follow-up or censoring event, as clinically indicated, usually at 30 days, 3 months, 6 months, and annually thereafter. Aortic insufficiency was evaluated visually in the parasternal short- and long-axis views by transthoracic echocardiography and graded on an interval scale, based on AI jet width, according to the recommendations of the American Society of Echocardiography, as 1 of the following: none, trace, mild, mild to moderate, moderate, moderate to severe, or severe.¹⁵

Indications and Operative Technique of Central Aortic Valve Closure

All patients with pre-existing AI graded as >mild, or DT patients with mild AI, received a concurrent CAVC. In addition, 2 DT patients with trace AI underwent repair at the discretion of the surgeon. Cardiopulmonary bypass was established with the standard aorto-atrial cannulation, unless bicaval cannulation was needed for other procedures. The patient was cooled to 32°C, the aorta was crossclamped, and cardioplegia was administered through the aortic root. A transverse aortotomy was made to approach the AV. The repair was performed by approximating the center of the leaflets with a 4-0 pledgeted polypropylene suture. Typically, the pledget was made of CorMatrix ECM (CorMatrix Cardiovascular, Inc, Atlanta, Ga) or woven polyester from the outflow graft of the device. After completion of the CAVC and aortotomy closure, the aortic crossclamp was removed. The rest of the procedure was conducted in the usual fashion with a beating heart.¹⁶

Statistical Analysis

Continuous variables were expressed as mean $\pm$ 1 SD. Categorical variables were presented as proportions and absolute numbers. Differences were detected using χ^2 analysis or the Fisher exact test for categorical variables, and the Mann-Whitney *U* or Student *t* test for continuous variables. The cumulative probability of on-device survival and significant AI (defined as >mild) were each estimated using the Kaplan-Meier method, and compared with those from the log-rank test. Patients were censored for transplantation and device explantation for myocardial recovery for the former; for the latter, they were censored for transplantation, death, and device explantation. The time spent on device support was calculated from the date of the first device implantation.

For longitudinal data analysis, a mixed-effects logistic regression model with a logit link was employed to assess the association between CAVC and AI progression. This type of model is useful for incomplete longitudinal dichotomous outcomes, for which data are assumed to be missing at random.¹⁷ The final models included fixed effects for treatment group, time (continuous scale), and baseline AI degree (ordinal scale), as well as 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 and found to be statistically nonsignificant. Preimplantation clinical parameters were analyzed to determine predictors for post-device implantation AI progression, using Cox proportional hazards models. For multivariable analysis, variables with a P value $\leq .25$ on univariable analysis were included in a final model.

Results are presented as hazard ratios, with corresponding 95% confidence intervals. All P values were results of 2-tailed tests. The statistical analysis was performed using SPSS version 22.0 (SPSS, Inc, Chicago, Ill) and SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Baseline Characteristics

Patient demographic and clinical variables are shown in Table 1. The mean age was 56.6 years; 66 (19.4%) were women, and 89 (26.2%) received a device as DT. The mean follow-up period and device support duration were 2.3 ± 2.0 years, and 423.6 ± 453.2 days, respectively. Patients in group A were older (65.1 vs 54.9; $P < .001$), were more likely to be DT (47.4 vs 21.9%; $P < .001$), and had a higher blood urea nitrogen level (41.9 ± 21.6 vs 33.7 ± 19.7 ; $P = .005$) and a higher HeartMateII risk score¹⁸ (2.09 vs 1.50; $P < .001$) than did patients in group B. Otherwise, the groups displayed similar clinical characteristics.

The baseline echocardiographic variables are further displayed in Table 2. Twenty-three (40.4%) patients in group A had significant pre-existing AI, defined as $>$ mild AI, comprising 9 (15.8%) mild to moderate, 11 (19.3%) moderate, 1 (1.8%) moderate to severe, and 2 (3.5%) severe; none of the patients in group B were in this category ($P < .001$). Moderate or greater mitral, and/or tricuspid, regurgitation were common. The aortic root diameter was larger in group A.

Intraoperative Data

The intraoperative data show that subjects in group A had a greater cardiopulmonary bypass time (112.3 ± 44.2 vs 90.7 ± 48.1 minutes; $P < .001$) and aortic crossclamp time (23.3 ± 9.9 vs 1.6 ± 8.1 minutes; $P = .002$), and more often received transfusions than did those in group B (Table 3). In addition, the dosage of vasoactive drugs, as represented by the vasoactive-inotropic score,¹⁹ was higher in the former group. In addition, patients in group A received a concomitant mitral repair more often than did those in group B.

Adverse Events and Survival

Early postoperative outcomes and overall adverse event results showed that non-device-related infections were more frequent in group A (Tables 4 and 5). No difference was found regarding the occurrence of other adverse events. The estimated on-device survival in groups A and B, respectively, were $84.6\% \pm 5.1\%$ and $83.4\% \pm 2.6\%$ at 1 year ($P = .98$), and $65.2\% \pm 9.4\%$ and $77.8\% \pm 3.4\%$ at 2 years ($P = .41$) (Figure E2 and Table E2). A total of 157 (46.2%) patients were bridged to transplantation with a mean support duration of 322 days. At the latest follow-up, 131 (38.5%) patients were alive after the transplant; 115 (33.8%) remained on device support; and 90 (26.5%) had died. In addition, no difference was observed for posttransplantation survival at 3 years (84.2% vs 86.2% , $P = .81$) among those bridged to transplant.

Post-Device Implantation Aortic Insufficiency Progression

For the entire cohort, freedom from significant AI was $66.7\% \pm 8.9\%$ and $59.9\% \pm 5.1\%$ at 2 years ($P = .77$), in groups A and B, respectively (Figure 1, A); for the DT cohort, the percentages were $78.1\% \pm 8.7\%$ and $41.8\% \pm 8.3\%$ ($P = .077$) (Figure 1, B). No subjects in group A developed significant AI beyond 1 year after device placement. In group B, 41.7% had significant AI, in the period between 1 and 2 years after device implantation. Furthermore, the results of an additional mixed-effects model, used to address longitudinal data, are summarized in Table 6.

Both time and baseline AI degree had a significant association with AI progression. For every unit increase in baseline AI degree, the odds of developing a significant AI were 34% higher (odds ratio = 1.34, with 95% confidence interval 1.06-1.70). After adjustment for time and baseline AI degree, the decrease in the odds that a patient in group A would develop a significant AI decreased by 57% (odds ratio = 0.43, with 95% confidence interval 0.20-0.93; $P = .032$) (Table 6). The results were similar for the DT cohort, with a 69% decrease in the odds of significant AI progression (odds ratio = 0.31, with 95% confidence interval 0.12-0.79; $P = .015$) (Table 6).

Another subgroup analysis concerning AI progression among patients with mild pre-existing AI was performed. A total of 44 patients (32 in group A and 12 in group B) had mild AI at baseline. The comparison between groups revealed no difference with respect to progression to $\geq$ moderate AI (4 of 32 [12.5%] in group A vs 1 of 12 (8.3%) in group B; $P = .70$) over a median device support period of 207 days (interquartile range: 88 to 511 days).

TABLE 1. Patient demographics and clinical characteristics before device implantation

Variable	All	With repair	Without repair	P value
Number of patients	340	57 (16.8)	283 (83.2)	
Gender, female	66 (19.4)	6 (10.5)	60 (21.2)	.063
Age (y)	56.6 ± 13.9	65.1 ± 8.3	54.9 ± 14.1	<.001*
Aged ≥65 y	114 (33.5)	31 (54.4)	83 (29.3)	<.001*
Race/ethnicity, nonwhite	188 (55.3)	30 (52.6)	158 (55.8)	.66
Body mass index (kg/m ²)	26.3 ± 5.7	25.9 ± 5.5	26.4 ± 5.7	.53
Etiology				.26
Ischemic cardiomyopathy	148 (43.5)	30 (52.6)	118 (41.7)	
Dilated cardiomyopathy	171 (50.3)	23 (40.4)	148 (52.3)	
Other	21 (6.4)	4 (7.0)	17 (6.0)	
Device intent				<.001*
Bridge-to-transplant	251 (73.8)	30 (52.6)	221 (78.1)	
Destination therapy	89 (26.2)	27 (47.4)	62 (21.9)	
Medical comorbidities				
Hypertension	168 (49.4)	32 (56.1)	136 (48.1)	.27
Dyslipidemia	124 (36.5)	26 (45.6)	98 (34.6)	.12
Coronary artery disease	149 (43.8)	28 (49.1)	121 (42.8)	.38
Diabetes	116 (34.1)	18 (31.6)	98 (34.6)	.66
COPD	33 (9.7)	10 (17.5)	23 (8.1)	.028*
Prior CVA	41 (12.1)	9 (15.8)	32 (11.3)	.34
Previous malignancy	37 (10.9)	7 (12.2)	30 (10.6)	.71
Drug abuse	18 (5.3)	5 (8.8)	13 (4.6)	.20
Smoking	113 (33.3)	23 (40.4)	90 (31.8)	.21
Previous cardiac surgery				
CABG	70 (20.6)	17 (29.8)	53 (18.7)	.059
Mitral	24 (7.1)	9 (15.8)	15 (5.3)	.005*
Tricuspid	5 (1.5)	1 (1.8)	4 (1.4)	.85
VAD/ECMO	35 (10.3)	6 (14.0)	29 (10.2)	.95
AICD	270 (79.4)	42 (73.7)	228 (80.6)	.24
Other	11 (3.2)	1 (1.8)	10 (3.5)	.49
IABP	88 (25.9)	17 (29.8)	71 (25.1)	.46
Inotrope	271 (79.7)	39 (68.4)	232 (82.0)	.02*
Vasopressor	32 (9.4)	5 (8.8)	27 (9.5)	.86
Mechanical ventilation	16 (4.7)	5 (8.8)	11 (3.9)	.11
Laboratory values				
BUN (mg/dL)	35.1 ± 20.3	41.9 ± 21.6	33.7 ± 19.7	.005*
Creatinine (mg/dL)	1.51 ± 0.77	1.60 ± 0.65	1.49 ± 0.79	.35
Total protein (g/dL)	6.5 ± 1.2	6.4 ± 0.8	6.5 ± 1.3	.79
Albumin (g/dL)	3.6 ± 0.5	3.5 ± 0.6	3.6 ± 0.5	.14
Total bilirubin (mg/dL)	1.5 ± 1.1	1.4 ± 1.1	1.5 ± 1.1	.59
Direct bilirubin (mg/dL)	0.5 ± 0.6	0.5 ± 0.5	0.5 ± 0.6	.99
AST (U/L)	45.7 ± 92.1	64.9 ± 169.8	41.8 ± 66.0	.32
ALT (U/L)	57.4 ± 153.0	53.0 ± 130.9	58.3 ± 157.3	.81
ALP (U/L)	98.1 ± 52.1	99.7 ± 48.1	97.7 ± 52.9	.80
PT/INR	1.36 ± 0.40	1.46 ± 0.54	1.34 ± 0.36	.14
Hemodynamic parameters				
Systolic blood pressure (mm Hg)	102.0 ± 13.4	101.0 ± 11.1	102.2 ± 13.7	.59
Central venous pressure (mm Hg)	11.0 ± 5.5	9.7 ± 4.5	11.2 ± 5.6	.068
Mean pulmonary pressure (mm Hg)	34.8 ± 9.5	35.6 ± 9.4	34.6 ± 9.5	.49
Wedge pressure (mm Hg)	23.7 ± 7.9	24.5 ± 7.5	23.6 ± 8.0	.50
Cardiac index (L/min/m ²)	1.7 ± 0.5	1.7 ± 0.4	1.7 ± 0.5	.55
PVR (Wood units)	3.9 ± 2.7	3.8 ± 2.0	4.0 ± 2.8	.68
INTERMACS profiles				.26
1-2	253 (74.4)	39 (68.4)	214 (75.6)	
3-4	87 (25.6)	18 (31.6)	69 (24.4)	

(Continued)

TABLE 1. Continued

Variable	All	With repair	Without repair	P value
HeartMate II risk score	1.61 ± 0.92	2.09 ± 0.80	1.50 ± 0.93	<.001*
HeartMate II risk score profiles				<.001*
High	44 (12.9)	14 (24.6)	30 (10.6)	
Medium	122 (35.9)	27 (47.4)	95 (33.6)	
Low	174 (51.2)	16 (28.1)	158 (55.8)	

Values are n (%), or mean ± SD, unless otherwise indicated. COPD, Chronic obstructive pulmonary disorder; CVA, cerebrovascular accident; CABG, coronary artery bypass grafting; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation; AICD, automated implantable cardioverter-defibrillator; IABP, intra-aortic balloon pump; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; INR, International Normalized Ratio; PVR, pulmonary vascular resistance; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support. * $P < .05$.

During the follow-up period, 5 (8.8%) patients in group A, and 27 (9.5%) in group B, developed ≥moderate AI. Of these, 1 (20.0%) in group A, and 10 (37.0%) in group B required surgical interventions to address clinically significant, severe AI refractory to medical management (Table 7). One (1.7%) in group A, and 3 (1.1%) in group B, developed heart failure that required an urgent United Network for Organ Sharing status upgrade and resultant transplantation. Five (1.8%) underwent CAVC, and 2 (0.8%) had AV closure and replacement, respectively. One patient (0.4%) underwent percutaneous AV closure with an AMPLATZER (St Jude Medical, Inc, Minnetonka, Minn) and required AV replacement after the initial treatment failure. The 5 patients who additionally received CAVC remain well, and free of AI progression, with a mean follow-up period of 501 days, except for a patient who died from sepsis on the 21st postoperative day.

TABLE 2. Baseline echocardiographic characteristics before device implantation

Variable	All	With repair	Without repair	P value
LVEF	15.2 ± 6.2	18.5 ± 8.6	14.5 ± 5.4	.004*
Degree of AI				<.001*
None	166 (48.8)	0	156 (58.7)	
Trace	107 (31.5)	2 (3.5)	105 (37.1)	
Mild	44 (12.9)	32 (56.1)	12 (4.2)	
Mild to moderate	9 (2.6)	9 (15.8)	0	
Moderate	11 (3.2)	11 (19.3)	0	
Moderate to severe	1 (0.3)	1 (1.8)	0	
Severe	2 (0.6)	2 (3.5)	0	
AI > mild	23 (6.8)	23 (40.4)	0	<.001*
MR ≥ moderate	191 (56.2)	37 (64.9)	154 (54.4)	.15
TR ≥ moderate	96 (28.2)	20 (38.5)	76 (26.9)	.21
LVESD (mm)	63.0 ± 12.0	59.4 ± 10.2	63.7 ± 12.3	.10
LVEDD (mm)	69.2 ± 11.3	69.0 ± 11.0	69.3 ± 11.4	.85
Root diameter (cm)	3.21 ± 0.45	3.40 ± 0.41	3.16 ± 0.43	.002*

Values are n (%), or mean ± SD, unless otherwise indicated. LVEF, Left ventricular ejection fraction; AI, aortic insufficiency; MR, mitral regurgitation; TR, tricuspid regurgitation; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter. * $P < .05$.

Predictors for Aortic Insufficiency Progression

The clinical parameters before device implantation were analyzed to identify predictors for significant AI progression in each group. Among patients without

TABLE 3. Intraoperative data

Variable	All	With repair	Without repair	P value
Implanted device				.045*
HeartMate II	281 (82.6)	55 (96.5)	226 (79.9)	
HeartWare	36 (10.6)	1 (1.8)	35 (12.4)	
Ventassist	9 (2.6)	0	9 (3.2)	
DuraHeart	8 (2.4)	1 (1.8)	7 (2.5)	
DeBakey VAD	6 (1.8)	0	6 (2.1)	
CPB time (min)	94.4 ± 48.1	112.3 ± 44.2	90.7 ± 48.1	.002*
Crossclamp time (min)	5.2 ± 11.7	23.3 ± 9.9	1.6 ± 8.1	<.001*
Transfusions (units)				
Packed red blood cell	1.6 ± 2.5	2.5 ± 2.8	1.4 ± 2.4	.009*
Fresh frozen plasma	2.9 ± 2.7	3.8 ± 2.9	2.7 ± 2.6	.006*
Platelet	9.4 ± 7.4	11.1 ± 6.5	9.0 ± 7.5	.051*
Vasoactive-inotropic score†	22.9 ± 22.1	26.5 ± 13.3	22.1 ± 13.7	.044*
Concomitant procedures				
Mitral repair	53 (15.6)	14 (24.6)	39 (13.8)	.041*
Ring annuloplasty	45 (12.9)	12 (21.1)	33 (11.7)	.056*
Alfieri stitch	8 (2.4)	2 (3.5)	6 (2.1)	.57
Mitral replacement	1 (0.3)	0	1 (0.4)	.83
Tricuspid repair	64 (18.8)	9 (15.8)	55 (19.4)	.57
Tricuspid replacement	11 (3.2)	3 (5.3)	8 (2.8)	.42
RVAD implantation	15 (4.4)	2 (3.5)	13 (4.6)	.72
Centrimag	13 (4.0)	2 (3.6)	11 (4.0)	.89
HeartWare	2 (0.6)	0	2 (0.7)	.69
Device removal	32 (9.8)	7 (12.7)	25 (9.1)	.42
Centrimag	27 (8.3)	6 (10.9)	21 (7.7)	.43
ECMO	3 (0.9)	1 (1.8)	2 (0.7)	.44
Impella	2 (0.6)	0	2 (0.7)	.69
Other	29 (8.5)	4 (7.3)	25 (8.8)	.65

Values are n (%), or mean ± SD, unless otherwise indicated. Centrimag is from Thoratec Corporation (Pleasanton, Calif); Impella is from ABIOMED, Inc (Danvers, Mass). VAD, Ventricular assist device; CPB, cardiopulmonary bypass; RVAD, right ventricular assist device; ECMO, extracorporeal membrane oxygenation. * $P < .05$. †Vasoactive-inotropic score (with doses in $\mu\text{g/kg/min}$, unless otherwise indicated) = dopamine dose + dobutamine dose + $100 \times$ epinephrine dose + $10 \times$ milrinone dose + $10,000 \times$ vasopressin dose (U/kg/min) + $100 \times$ norepinephrine dose.¹⁹

TABLE 4. Early and late postimplantation follow-up data on early mortality and adverse events

Variable	All	With repair	Without repair	P value
30-d mortality	16 (4.7)	2 (3.5)	14 (4.9)	.64
In-hospital mortality	30 (8.8)	7 (12.3)	23 (8.1)	.31
ICU stay (d)	10.4 ± 10.6	11.1 ± 11.7	10.2 ± 10.4	.59
Hospital stay (d)	45.7 ± 36.3	46.6 ± 19.7	45.6 ± 38.3	.91
Early postdevice/predischarge AI				<.001*
None	135 (39.7)	39 (68.4)	96 (33.9)	
Trace	152 (44.7)	16 (28.1)	136 (48.1)	
Mild	36 (10.6)	1 (1.8)	35 (12.4)	
Mild to moderate	6 (1.8)	1 (1.8)	5 (1.8)	
Moderate	1 (0.3)	0	1 (0.4)	
N/A	10 (2.9)	0	10 (3.5)	
Postoperative complications				
Acute kidney injury	56 (16.5)	10 (17.5)	46 (16.3)	.72
CVVHD	34 (10.0)	7 (12.3)	27 (9.5)	.81
Bleeding requiring re-exploration	56 (16.5)	8 (14.0)	48 (17.0)	.59
CVA	23 (6.8)	4 (7.0)	19 (6.7)	.93
Urinary tract infection	39 (11.5)	6 (10.5)	33 (11.7)	.81
Sepsis	27 (7.9)	4 (7.0)	23 (8.1)	.78
Atrial fibrillation/flutter	79 (23.2)	10 (17.6)	69 (24.4)	.27
VT/VF	80 (23.5)	14 (24.6)	66 (23.3)	.84

Values are n (%), or mean ± SD, unless otherwise indicated. ICU, Intensive care unit; AI, aortic insufficiency; N/A, not available; CVVHD, continuous veno-venous hemodialysis; CVA, cerebrovascular accident; VT, ventricular tachycardia; VF, ventricular fibrillation. * $P < .05$.

CAVC, factors that were multivariably significant were female gender and older age (hazard ratio, with 95% confidence interval: 2.80, 1.45-5.41; $P = .002$; and 1.54, 1.22-1.93, respectively; $P < .001$) (Table E1). Conversely, no association was found between preimplantation clinical variables and AI progression among patients who had

CAVC. All 6 female patients in group A were free from significant AI progression.

DISCUSSION

We have demonstrated our outcomes of concurrent CAVC from a 10-year series of CF-LVAD experience. Our patient population has a high proportion of bridge-to-transplant patients among transplant recipients, with our current rate approaching 80%. Significant waiting times, with the resultant prolonged device support duration, are becoming more common, applying currently to a majority of patients. Given these circumstances, we have been aggressive about performing concomitant CAVC.

The primary findings of interest in this study were: (1) the survival between groups after device implantation was similar; (2) despite significant pre-existing AI, the prevalence of significant AI after device implantation, in patients who received CAVC, was comparable to that in those without pre-existing AI or repair; (3) the efficacy and durability of repair seem more evident among DT patients; (4) repaired patients in the entire cohort and the DT cohort demonstrated a 57% and 69% decrease in the odds of significant AI progression, respectively, after adjusting for time effect and pre-existing AI degree.

With the improved durability of CF-LVAD, and the undersupply of donor hearts, attention has been focused on AI progression as a potential obstacle to device support, especially for those who require an extended waiting time for transplantation, or for DT patients.⁶ The mechanism involved in AI progression is likely multifactorial and may be related to failure of the AV opening and prolonged coaptation time, in addition to exposure of valvular tissue to persistently elevated retrograde pressure, resulting in structural changes such as commissural fusion of AV leaflets.^{4,6,20,21} Consequently, development of AI

TABLE 5. Early and late postimplantation follow-up data, for all adverse events

Adverse event	With repair patients		Without repair patients		P value
	(n = 57)	Events rate*	(n = 283)	Events rate†	
Bleeding	25 (43.9)	45 (0.65)	89 (31.4)	157 (0.47)	.12
CVA	8 (14.0)	10 (0.14)	43 (15.2)	46 (0.14)	.88
Infection					
Device-related	6 (10.5)	18 (0.26)	32 (11.3)	70 (0.21)	.45
Non-device-related	16 (28.1)	23 (0.33)	36 (12.7)	42 (0.12)	.001‡
Device malfunction	3 (5.3)	5 (0.072)	49 (17.3)	58 (0.17)	.065
Ventricular arrhythmias	5 (8.8)	24 (0.35)	28 (10.4)	106 (0.31)	.72
Pump thrombosis	3 (5.3)	4 (0.058)	26 (9.2)	33 (0.098)	.33
Pump replacement	3 (5.3)	3 (0.043)	24 (8.5)	30 (0.089)	.24
Due to thrombus	3 (5.3)	3 (0.043)	10 (3.5)	14 (0.042)	.95
Heart failure	17 (29.8)	23 (0.33)	76 (27.6)	102 (0.30)	.73
Right heart failure	16 (28.1)	22 (0.32)	64 (25.1)	90 (0.27)	.53
RVAD	6 (10.5)	6 (0.086)	24 (8.5)	24 (0.071)	.68

Values are n (%), unless otherwise indicated. CVA, Cerebrovascular accident; RVAD, right ventricular assist device. *Events per 69.5 patient-years. †Events per 337.7 patient-years. ‡ $P < .05$.

FIGURE 1. Freedom from >mild AI at 2 years after device implantation: comparison between patients with, versus without, aortic valve repair. A, Entire cohort; (B) Destination therapy subgroup. AI, Aortic insufficiency.

compromises device flow and can lead to ineffective device output and end-organ malperfusion because of the recycling of regurgitant blood.⁵ Several recent studies have suggested that greater aortic root diameter, higher pump speeds, older age, being female, and greater body surface area are potential risk factors associated with AI progression.^{5,6,20,22}

In contrast, our results demonstrated that female gender and older age are significant predictors of AI progression. Greater baseline aortic root diameter and body surface area were not predictive, although the former was significantly larger among those who had undergone AV repair; the latter was univariably significant (Tables 2 and E1). Although this hypothesis may be controversial, one possibility is that female and elderly patients are more susceptible to an increased growth rate or geometric changes of the aortic root, owing to CF-LVAD outflow, as both factors have been shown to be risk factors for thoracic aortic aneurysmal disease.^{23,24}

By contrast, identification of clinical predictors for CAVC failure and resultant AI progression was difficult in such a small group (n = 57). However, 6 of 57 (10.5%)

patients in group A were women, and none of them developed significant AI during the follow-up period. Given the increased risk of significant AI, concurrent surgical correction may be particularly warranted in female and elderly patients.

Studies of the natural history of AI during device support have indicated that AI progression has a small clinical effect without any notable influence on survival.^{4,25} In fact, none of the CF-LVAD studies report an increase in mortality due to AI progression,²⁵ because these patients can be surgically salvaged at the expense of added significant morbidity, as shown in our study (Table 7). Clinically relevant AI that is refractory to medical management occurred in 10 group B patients (3.5%), which is 30% of those who developed ≥moderate AI in our series. Atkins and colleagues²⁶ reported reoperation using several techniques overall, on a total of 6 patients, for severe AI after implantation of an LVAD. The incidence of reoperation in their cohort was 2.7%, which was comparable to that in our series. Aortic insufficiency progression is not a “benign” complication of device support.

The question of what constitutes optimal surgical management of native AI is controversial. Moreover, the degree of AI that warrants concurrent surgical correction remains unclear.²² The recent guidelines²⁷ recommend surgical intervention for >mild AI, although this approach is based on past observations made on a limited number of patients who received varied AV procedures with relatively short-term device support. As for the efficacy and the durability of the CAVC technique, anecdotal experiences have been reported in a few studies. McKellar and colleagues¹³ reported on 18 patients who received concomitant CAVC, with a mean period of 441 days with excellent outcomes, although detailed follow-up data were not provided in their study. Schechter and colleagues¹² described the same technique with promising mid-term

TABLE 6. Longitudinal analysis using generalized mixed-effects model to assess the association between the treatment (repair vs no repair) and significant AI development during device support

Variable	Estimate (SE)	OR (95% CI)	P value
Entire cohort			
Repair vs no repair	−0.84 (0.39)	0.43 (0.20-0.93)	.032
Time*	0.63 (0.07)	1.88 (1.64-2.16)	<.001
Baseline AI degree†	0.29 (0.11)	1.34 (1.06-1.70)	.014
Destination therapy cohort			
Repair vs no repair	−1.18 (0.47)	0.31 (0.12-0.79)	.015
Time*	0.58 (0.09)	1.79 (1.48-2.18)	<.001
Baseline AI degree†	0.32 (0.14)	1.39 (1.04-1.85)	.026

All *P* < .05. SE, Standard error; OR, odds ratio; CI, confidence interval; AI, aortic insufficiency. *Time was fitted on the log scale. †Baseline AI was fitted using the original ordinal scale.

TABLE 7. Early and late postimplantation follow-up data on surgical interventions performed for clinically significant AI

Variable	All	With repair	Without repair	P value
Moderate or severe AI, n (%)	32 (9.1)	5 (8.8)	27 (9.5)	.86
Aortic valve non-opener, n (%)	28 (87.5)	3 (60.0)	25 (92.6)	.11
No. of patients who received surgical reintervention, n (%)	11 (3.2)	1 (1.8)	10 (3.5)	.49
No. of surgical reinterventions performed	12	1	11	
Aortic valve repair	5	0	5	
Aortic valve replacement	1	0	1	
Aortic valve closure	1	0	1	
AMPLATZER occluder	1	0	1	
Heart transplant	4	1	3	
Time to the surgical interventions undertaken (d)	367 ± 397 (range: 21-1205)	205	418 ± 425	.65

AI, Aortic insufficiency.

outcomes on 19 patients, of which 6 were not performed concomitantly.

More recently, Robertson and colleagues²⁸ described various concomitant AV procedures, including 95 patients who had undergone AV repair. These data were collected from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) dataset, although the type of repair was uncertain in 15.8% of cases. Moderate or greater AI after device implantation was observed in 18% of repaired patients by 6 to 12 months, which is a higher failure rate, compared with the studies mentioned earlier that have reported 0% to 10.5% recurrence rates of significant AI at a mean follow-up time of >1 year.^{12,13} However, use of a large registry limited access to potentially relevant clinical detail.

In contrast, the present study has a large sample size, with patients who have native AI treated consistently with the same technique. We excluded patients who had previously undergone AV surgery or received other AV procedures, to maintain the uniformity of the CAVC cohort. The prevalence of significant AI among those with CAVC was comparable to that among those without pre-existing AI or repair, despite the fact that many CAVC patients had significant pre-existing AI, which in some was even of >moderate degree.

Further, longitudinal data analysis showed that CAVC is protective against AI progression after adjustment for varying device-support duration and baseline AI degree in each individual (Table 6). Additional CVACs were performed in 5 patients who developed a clinically significant de novo AI, refractory to medical management. Except for 1 patient who died from sepsis, the patients have been free of significant AI at latest follow-up, suggesting that CAVC can be utilized as a salvage procedure for clinically significant de novo AI.

The efficacy and durability of CAVC for addressing pre-device AI and preventing de novo AI were more clearly illustrated among DT patients (Figure 1, B; Table 6). The risk of AI development is cumulative over time.^{6,29} We postulate that this observed tendency among DT patients

might be derived mainly from the fact that DT patients are on device support for a much longer period than are bridge-to-transplant candidates (725 vs 322 days). Most previous reports are based on trials for bridge-to-transplant patients, and few reported a follow-up time of >1 year on device support. Unlike bridge-to-transplant patients, most of whom bridged to transplant within 1 year, the DT cohort had fewer censoring events.

Another explanation of this superior efficacy includes the fact that the DT patients were a much older subgroup, with a mean age of 67 years (vs 53 years among the bridge-to-transplant patients). As described, age was a significant predictor for significant AI progression among patients without CAVC, with a hazard ratio of 1.54 per 10-year increment (Table E1). Considering the linear pattern of AI progression, more DT patients who have not undergone repair surgery may develop significant AI and require reoperation. Surgical reintervention in DT patients is not a trivial undertaking. Our results from this subgroup analysis indicate that the DT population in particular is the largest group who may potentially benefit from this technique.

Although 1 of advantages of this technique is its procedural simplicity, CAVC is not without risk. The cardiopulmonary bypass time in group A was significantly greater, with more-frequent usage of blood products and vasoactive drugs than for patients without repair. Nevertheless, our study did not show any survival difference between groups, despite the significant difference in these baseline and perioperative risk profiles. Furthermore, device exchange for pump thrombosis in the presence of CAVC was feasible and safe.

Finally, this repair technique may be applied to even those patients who have ≥moderate AI. Thirteen of 14 patients (93%) with pre-existing ≥moderate AI have been free from recurrent AI at latest follow-up. By contrast, applicability of the technique to mild AI remains unclear. However, based on our findings, consideration of CAVC as a prophylactic repair in DT, elderly, and female patients may be appropriate, even if they have mild-degree native AI.

Limitations

Our investigation is limited by its retrospective nature. Although this is the largest series describing the CAVC technique in the literature, the sample size still limits the statistical interpretation of the results. The serial follow-up echocardiographic studies, which often can be affected by hemodynamics, were performed in a variety of clinical settings, such as the intensive care unit and outpatient clinic. Additionally, the present data do not permit the comparison of CAVC with other surgical strategies, which remains an area for future investigation.

In conclusion, use of the CAVC technique at the time of CF-LVAD implantation is simple, effective, and durable in preventing AI progression, with a follow-up period that extends to 2 years after device implantation. In addition, clinically significant de novo AI that is refractory to medical management can be salvaged with this repair technique. This study provided data to support the practice of giving consideration to concurrent CAVC in DT or bridge-to-transplant patients who may need prolonged CF-LVAD support.

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: mechanical circulatory assistance, transplantation—heart, valve disease, aortic valve, repair

Discussion

Dr R. Davis (*Durham, NC*). Congratulations on an excellent presentation. It is interesting that one quarter of the patients are failing at 1 year, and in the overall cohort, it is approximately one third that fail at a later time point, and there seems to be a difference between your DT group and your overall group with respect to these failures. I will first just ask: What do you think that difference is? Why do you think your overall group did worse than the DT subgroup?

Dr S. Fukuhara. First, as I briefly mentioned, the DT cohort patients obviously stayed on device support much longer than those in the bridge-to-transplant cohort. Second, they have many fewer censoring events because they do not get transplanted. Another thing is that—but I did not include the data on these slides—1 of the predictors for AI progression, based on our analysis, was older age. The DT patients were older than the bridge-to-transplant patients. That was probably another reason that the repair was protective in the DT cohort.

Dr Davis. I would think that would be just the opposite—that the longer the on-device duration, the greater the likelihood of AI. Did some of those that you were planning on being DT receive transplantation because of the degree of AI?

Dr Fukuhara. Your question is about someone in the DT cohort who got a heart transplant?

Dr Davis. Well, you said in the overall cohort it was approximately one third of the patients who actually have a failure or a progression of AI in the overall cohort, but when you break out just your DT patients, it was approximately 20% to 22%. So that finding goes somewhat against the idea that longer duration would be more likely to be associated with AI, because theoretically your bridge-to-transplant group should have had shorter on-device times.

Dr Fukuhara. I see. As I showed in the Kaplan-Meier curve, patients who did not get a concurrent repair in the DT cohort obviously had progressed to de novo AI; on

the other hand, patients who got repaired basically stayed at the same degree of AI, despite the presence of a significantly worse degree of baseline AI. That is what we observed based on our analysis.

Dr Davis. What I really want to get at is: What are the predictors that indicate a patient is going to progress with AI? In your article, you really did not find anything within the group in which you did the repairs. But you were just using echo assessments of your aortic valve size and aortic size. I do not know if you actually looked at more CTs, or what would be more-sensitive impressions of the aortic size and the aortic valve as potential predictors of development of AI.

The other question is: What were you doing, both in terms of the flow rates and pump speed, as well as drug therapy for AI protection? Was there a difference between the groups that might explain that?

Dr Y. Naka (*New York, NY*). I can answer your question. In terms of the etiology—or how we can predict either AI or the kind of patient who will develop more AI—some studies from our group suggest that if we maintain normal aortic valve function, such as open and closed, with enough volume inside the left ventricle, we might prevent AI progression, because other studies show that AI is associated with aortic valve fusion peripherally, in the central opening of the aortic valve.

Another issue is the DT. Very few patients develop clinically meaningful AI, which required some aortic valve intervention or going to transplant based on transplant eligibility, but fewer patients in the AI repair group went to urgent transplant or something similar to it.

Dr Davis. So what are you doing—are you trying now to have lower flow and more ejection?

Dr Naka. Well, yes. So we tend to decrease the flow compared with our historical early experience. We used to use a HeartMate II, in particular, that went up to >9000 rpm. Now, our de novo HeartMate II goes up to >8600 to 9000 rpm.

FIGURE E1. Cohort derivation diagram.

FIGURE E2. Kaplan-Meier survival curve for on-device survival at 2 years after device implantation, for patients with, versus without, aortic valve repair.

TABLE E1. Predictors for progression of significant AI among patients without aortic valve repair

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
BSA	0.30 (0.10-0.88)	.028	1.01 (0.30-3.40)	.99
Gender, female	2.11 (1.22-3.64)	.007	2.80 (1.45-5.41)	.002*
Age†	1.44 (1.18-1.77)	<.001	1.54 (1.22-1.93)	<.001*
Baseline AI				
None	Reference		Reference	
Trace	1.01 (0.58-1.76)	.97	1.12 (0.64-1.97)	.69
Mild	2.09 (0.64-6.85)	.22	2.04 (0.60-6.86)	.25

HR, Hazard ratio; CI, confidence interval; BSA, body surface area; AI, aortic insufficiency. * $P < .05$. †The HR for age is shown for a 10-year increment.

TABLE E3. Each time point for Kaplan-Meier survival curve, for freedom from >mild AI at 2 years after device implantation

Time (d)	With repair	Without repair
	Freedom from significant AI (95% CI)	Freedom from significant AI (95% CI)
Entire cohort		
200	88.5 (83.6-93.4)	87.9 (85.7-90.1)
400	76.2 (69.1-83.4)	76.2 (72.8-79.6)
600	66.8 (57.9-75.7)	70.1 (66.0-74.2)
730	66.8 (57.9-75.7)	60.6 (55.5-65.7)
Destination therapy subgroup		
200	82.7 (74.8-90.6)	85.3 (80.5-90.1)
400	78.1 (69.4-86.8)	69.3 (62.5-76.1)
600	78.1 (69.4-86.8)	57.9 (50.2-65.6)
730	78.1 (69.4-86.8)	42.0 (33.7-50.3)

See Figure 1, A and B. AI, Aortic insufficiency; CI, confidence interval.

TABLE E2. Kaplan-Meier curve time points, for on-device survival at 2 years after device implantation

Time (d)	With repair	Without repair
	Survival (95% CI)	Survival (95% CI)
200	87.1 (82.5-91.7)	87.8 (85.8-90.2)
400	84.7 (79.6-89.8)	83.1 (80.5-85.7)
600	70.7 (62.2-79.2)	80.0 (76.9-83.1)
730	65.7 (56.4-75.0)	78.6 (75.3-81.9)

See Figure E2 for survival curve. CI, Confidence interval.