Prevalence, Significance, and Management of Aortic Insufficiency in Continuous Flow Left Ventricular Assist Device Recipients

Jorde et al: Aortic Insufficiency in CF-LVAD Patients

Ulrich P. Jorde, MD; Nir Uriel, MD; Nadav Nahumi, BA; David Bejar, MD;
Jose Gonzalez-Costello, MD; Sunu S. Thomas, MD; Jason Han, BA; Kerry A. Morrison, BA;
Sophie Jones, MD; Susheel Kodali, MD; Rebecca T. Hahn, MD; Sofia Shames, MD;
Melana Yuzefpolskaya, MD; Paolo Colombo, MD; Hiroo Takayama, MD;
Yoshifumi Naka MD, PhD

Divisions of Cardiology and Cardiothoracic Surgery. New York Presbyterian Hospital / Columbia University Medical Center, New York

Correspondence to
Ulrich P. Jorde, MD
Medical Director, MCSD programs.
New York Presbyterian Hospital / Columbia University Medical Center
622 West 168th Street, PH9-977
New York, NY 10032
Phone: 212-305-0167
Fax: 212-305-7139
E-mail: upj1@columbia.edu

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Abstract

Background—Aortic insufficiency (AI) is increasingly recognized as a complication of continuous flow left ventricular assist device (CF-LVAD) support; however, its long term prevalence, clinical significance, and efficacy of potential interventions are not well known.

Methods and Results—We studied the prevalence and management of AI in 232 CF-LVAD patients at our institution. Patients with aortic valve (AV) surgery prior to LVAD implantation were excluded from analysis. To examine the prevalence of “de novo” AI, patients without preoperative AI were divided into a retrospective and a prospective cohort based on whether or not a dedicated speed optimization study had been performed at the time of discharge. Forty-three patients underwent AV repair at the time of implant and 3 subsequently developed greater than mild AI. In patients without surgical AV manipulation and no AI at the time of implant, Kaplan-Meier analysis revealed that freedom from greater than mild de novo AI at 1 year was 77.6±4.2%, and that at least moderate AI is expected to develop in 37.6±13.3% after 3 years. Non-opening of the AV was strongly associated with de novo AI development in patients without prospective discharge speed optimization. Seven of 21 patients with at least moderate AI developed symptomatic heart failure requiring surgical intervention.

Conclusions—AI is common in patients with CF-LVADs and may lead to clinical decompensation requiring surgical correction. The prevalence of AI is substantially less in patients whose AV opens, and optimized loading conditions may reduce AI prevalence in those patients in whom AV opening cannot be achieved.

Key Words: left ventricular assist device, aortic insufficiency, echocardiography
Aortic insufficiency (AI) may develop during continuous flow left ventricular assist device (CF-LVAD) support. It has been proposed that this is due to commissural fusion and deterioration of leaflet tissue, both possibly promoted by failure of the aortic valve to open during support\textsuperscript{1}. Moreover, it has been demonstrated that mild to moderate pancyclic AI is a frequent phenomenon after chronic support, even in those patients who had no AI at the time of LVAD implant\textsuperscript{2,3}. Less certainty exists with regard to the question of how many patients will develop clinically significant AI, i.e. resulting in heart failure, although the number of case reports describing severely leaking aortic valves (AV) leading to symptomatic heart failure is increasing.

Since AI has been recognized as a potentially significant long term complication of CF-LVAD support, some have proposed to actively facilitate AV opening by running the pump at lower speeds\textsuperscript{4}; others have advocated surgically addressing AI at the time of LVAD implantation by approximating the nodules of Arantius with a stitch\textsuperscript{5} or closing the valve altogether\textsuperscript{6}. We first noticed that \textit{de novo} development of AI was common in 2010 and, based on the belief that AI is progressive\textsuperscript{3,7} and can lead to clinical heart failure, we have since routinely placed approximation stitches as described by Park et al. on valves with mild or more AI at the time of implantation\textsuperscript{5}. In addition, we have aimed to facilitate AV opening by performing a speed ramp study at the time of discharge in newly implanted patients since 2011. Here we report our experience with the natural history of AI in patients without prospective AI management as well as the results of our attempts to prevent AI. Lastly, we review our experience and propose treatment algorithms for patients in whom clinically significant AI has occurred during support.
Methods

Medical records and transthoracic echocardiogram (TTE) reports of all patients who have undergone CF-LVAD implantation in our institution since April 2004 were reviewed through February 2013. Operating room reports were examined for history of aortic valve surgery as well as manipulation of the aortic valve at the time of device implantation. Patients who had a history of AV surgery (repair, replacement, closure) prior to device implantation were excluded from analysis.

The remaining patients were assigned to either the retrospective or the prospective cohort to assess for the development of de novo AI. Those who had a dedicated speed optimization study to ensure middle interventricular septum position and intermittent AV opening while maintaining no more than mild mitral regurgitation (MR) were assigned to the prospective cohort. Details of this speed optimization ramp have been previously described, but it should be emphasized that we only lower speed for the expressed purpose of facilitating AV opening if mitral regurgitation is mild or less, blood pressure is adequate (usually > 70 mmHg), and the patient does not report symptoms.

The retrospective cohort was comprised of all patients that 1) had an echocardiogram between postoperative day 30 and 180 that was interpretable for AV opening status and did not reveal more than trace AI and 2) did not have AV repair at the time of implant. The latter patients were analyzed separately.
The presence of AI was determined at baseline and until time of last follow-up or censoring event. AI was evaluated visually in the parasternal short- and long-axis views and was graded as none, trace, mild, mild-moderate, moderate, moderate to severe, severe on an interval scale based on AI jet width.

To examine the association of “baseline” AV opening and the development of de novo AI, we used the final setting of the speed optimization echo performed at time of discharge in the prospective cohort and the first TTE performed outside of the operative period (i.e. after 30 but no more than 180 days after implantation) in the retrospective cohort. To explore the association of blood pressure and AV opening / AI development, we retrieved blood pressures obtained at or near the baseline echocardiogram as well as 9 months after implant. Blood pressure was assessed by Doppler ultrasound (Lumeon Doppler System, Houston, TX), or Terumo Elemano BP (Somerset, NJ) monitor.

Although prior studies on AI prevalence in CF-LVADs have generally reported “greater than mild AI”\(^2\), AI associated with heart failure in our experience is usually moderate–to-severe or worse. Accordingly, we have used the latter two categories and a middle category of “at least moderate” AI throughout our manuscript and graphic representations. Figure 1 shows the cohort derivation.

This study was approved by the Institutional Review Board of Columbia University Medical Center, New York Presbyterian Hospital.
Statistical Methods

Data was collected using Excel software (2007 Microsoft Corp., Redmond, Washington). All data was analyzed using MedCalc version 12.2.1.0 (Mariakerke, Belgium). Categorical variables were summarized by frequencies and percentages, and were analyzed using Fisher’s Exact test. Normality was assessed using the D’Agostino-Pearson test for Normal distribution. Student’s \( t \)-test for independent samples was used to determine differences in means of normally distributed data. Difference in variance was assessed using F-test. Mann-Whitney’s rank sum test was used to determine differences in independent, non-normal distributions. Log Rank testing was used to compare Kaplan Meier freedom of event data. In the freedom from de novo AI analysis, censoring events were defined as ramp tests other than the prospective discharge ramp resulting in a speed change, cardiac transplantation, device exchange, surgical AV intervention or death. Each patient was analyzed separately and given equal weight in analysis.

Results

Overall, 232 patients (223 HM II, 9 HeartWare) had undergone CF-LVAD implantation at the time of data collection and comprise the study population. Eight HMII patients who had previously undergone prosthetic AV replacement were excluded from analysis as their valves were patch-closed at the time of device implant. In the remaining 224 patients mean duration of device support was \( 344\pm352 \) days (median 245 days). Of the 224 patients described in our study, 28 patients had an unscheduled ramp study after discharge. These post discharge ramp studies led to 19 instances of speed change. Since RPM may impact AI severity, these 19 patients have been censored at time of speed change ramp study. Other baseline demographics and clinical characteristics are shown in Table 1.
Development of AI – all patients

Kaplan-Meier analysis revealed that freedom from greater than mild AI at 1 year was 79.1±3.7%, and that at least moderate AI is expected to develop in 29.9±9.3% of patients who remain on pump support for 3 years (Figure 2). Mean time to greater than mild AI development was 229±186 days (median 169 days).

Development of AI in patients without AI at baseline and without AV surgery: De novo AI

Prior to device implantation, no or trace AI was present in 174/224 (77.7%); these patients were included in the “de novo” cohort. Kaplan-Meier analysis revealed that freedom from greater than mild “de novo” AI at 1 year was 77.6±4.2%, and that at least moderate AI is expected to develop in 37.6±13.3% of patients who remain on pump support for 3 years (Figure 3). Mean time to greater than mild AI development was 236±193 days (median 175 days).

Baseline AV opening as a risk factor for de novo AI: Retrospective cohort

We examined AV opening as a risk factor for AI development by looking at patients’ AV opening status at the first available TTE outside of the operative period. Of the 139 patients in the retrospective cohort at risk for de novo AI, 48 patients were excluded from analysis for the following reasons: 40 patients did not have a TTE in the previously defined baseline range, 6 patients had poorly visualized AV that could not be assessed for opening, and 2 patients already had AI at first recorded TTE.

Of the 91 included patients, 29 had at least intermittent AV opening, while 62 had closed AVs.
1/29 whose AV opened at least intermittently and 20/62 AV whose AV remained closed developed greater than mild AI. Log rank comparison of Kaplan Meier survival curves revealed that AV non-openers at baseline TTE were significantly more likely to develop AI (HR 11.2, p=0.003) (Figure 4).

Prospective attempts to maintain AV opening and de novo AI development

A total of 35 patients without AV surgery and without AI at baseline had a speed optimization study prior to hospital discharge. 17/35 (48.6%) patients had at least intermittent AV opening and 18/35 (51.4%) patients had no AV opening at their optimized speed.

Of the 35 patients, 17 (48.6%) did not have their speed changed as a consequence of the optimization ramp, while 9 (25.7%) had their speed increased (mean 444±240 RPM, median 400 RPM), and 9 (25.7%) had their speed decreased (mean -422±120 RPM, median -400 RPM). Of the 9 that increased speed, 1 patient had mitral regurgitation (MR) reduced from mild to none, blood pressure increased 1.2±2.6 mmHg, and the average change in left ventricular end diastolic diameter (LVEDD) was -0.35±0.41 cm. Of the 9 that decreased speed, none had a change in MR, blood pressure decreased 2±3.0 mmHg, and average change in LVEDD was 0.22±0.18 cm.

During a mean follow-up time of 241±153 days (median 201 days), only 1 patient (in the AV non-opener group) developed greater than mild AI. Device thrombosis occurred in two openers and one non-opener (p=0.60). Given the discrepancy in AI prevalence between retrospective and prospective non-openers (20/62 versus 1/18) we compared these two subgroups (Table 2). The retrospective cohort had a longer total follow up time (420 ± 438 days versus 252±164 days,
p=0.41), same size LVEDD (5.78 ± 1.56 versus 5.91 ± 1.36, p=0.75), and more MR at baseline (p=0.053) than the prospective cohort.

**Association of AV opening, blood pressure, and AI**

Blood pressure data could be retrieved in a subset of 85 patients at risk for de-novo AI near the baseline echocardiogram as well as after 9 months (Blood pressure values could not be obtained implanted in patients implanted before 2010 due to a change in the electronic medical record). Given the complexities of blood pressure assessment in LVAD patients, we chose Doppler pressure for analysis. In those patients who did not have a Doppler pressure, we used systolic blood pressure obtained with the Terumo cuff as we recently demonstrated that in LVAD patients this (rather than MAP) is closest to Doppler pressure*. We did not detect a difference in blood pressure in openers versus non-openers at the time of the baseline echocardiogram used to assign opening status (91 +/- 5.6 versus 90.00 +/- 6.0 mmHg p NS; Figure 5) or at 9 months (102 +/- 6.35 vs. 94 +/- 8.98 mmHg ). Furthermore, we did not detect differences in blood pressure baseline (90 +/- 16.6 vs 86 +/- 10.6 mmHg) or at 9 months (94 +/- 13.8 vs. 100 +/- 16.4 mmHg) between patients who did and did not develop AI.

**Development of AI in patients following stitch repair of the AV**

AV repair was performed at the time of device implantation in 43 CF-LVAD patients (26/43 (60.5%) for mild AI, 5/43(11.6%) for mild-moderate AI, 11/43 (25.6%) for moderate AI, and 1/43(2.3%) for severe AI). During a mean follow up time of 324±292 days (median 209 days), 1/43 (2.3%) developed moderate AI, 1/43 (2.3%) developed moderate-severe AI, and 1/43 (2.3%) developed severe AI.
It is somewhat controversial whether AV opening still occurs in CF-LVAD patients who have undergone AV repair. On routine follow-up echocardiogram, 12/43 (27.9%) patients had evidence of regular AV opening (Video 1) and an additional 4/43 (9.3%) patients had evidence of intermittent AV opening after stitch repair. 2/43 patients had a device thrombosis, 0.05 events per year).

**Prevalence of worsening AI in patients with mild AI at time of implant and no stitch repair of the AV**

In our study, a subset of 7 patients had mild AI at baseline that was not addressed surgically at the time of device implantation. In the cohort’s mean follow-up time of 595±849 days (median 155 days), 1/7 (14.3%) of these patients developed mild-moderate AI after 364 days of support.

**Management of clinically significant post implant AI**

Of the 21 patients that developed at least moderate AI (18 de novo cases, 3 following AV stitch repair), 7 (33.3%) were transplanted without requiring urgent UNOS status upgrade, and 6 (28.6%) remain asymptomatic (two with now mild to moderate AI) on device support at the end of data collection. The remaining 8 (38.1%) developed symptomatic heart failure and required urgent management as follows: 3 patients were upgraded to UNOS 1A status and transplanted; 1 patient’s device speed was increased 400 RPM; 1 patient’s AV was surgically closed; 2 patients underwent surgical AV repair; and 1 patient underwent percutaneous AV closure with an Amplatzer device. Figure 6 illustrates the time course from the initial diagnosis of at least moderate AI to intervention for symptom management. All 4 patients who underwent AV repair/replacement experienced significant symptomatic relief. Of these 4 patients, 1 patient has
been transplanted, and the remaining 3 are destination therapy patients who are alive and asymptomatic 203±160 days following AV manipulation.

Relationship of AI severity, pump speed, and invasive hemodynamics

Aortic valve surgery in HMII recipients is not a trivial undertaking. If performed at the time of initial LVAD implant, addition of aortotomy and full cross clamp will prolong bypass time and may worsen associated coagulopathy. If performed at a later time point reoperation with sternotomy will be performed in a patient who now overwhelmingly likely has acquired von Willebrand factor deficiency as well as the need for anticoagulation. Accordingly, we believe it is useful to include details on our stepwise approach to symptomatic AI in 3 of the 8 cases noted above:

Case 1 is a 78-year-old man who had done quite well living independently at home in NYHA class II following LVAD implant as destination therapy. He presented with new dyspnea and moderate de novo AI one year after implantation. Physical examination revealed mild volume overload. A ramp study was performed and his pump speed was increased from 8,800 to 9,200 RPM. The patient has done well clinically with higher speed (9,200 RPM), although AI on follow up echo 4 months later was moderate to severe.

Case 2 is a 56-year-old bridge to transplant candidate with blood type 0. This patient presented with progressive dyspnea on exertion, clinical biventricular failure, and moderate AI 4.7 months following device implant. There was no evidence of device malfunction based on routine pump interrogation and symptoms persisted after significant diuresis. Baseline speed was 8,800 RPM.
A Swan-Ganz catheter was placed, and a speed optimization ramp study from 8,000 to 12,000 RPM was performed under echocardiographic guidance with serial hemodynamics (Table 3). Although AI increased throughout the ramp, blood pressure increased, pulmonary capillary wedge pressure decreased, and cardiac output increased. Of note, right atrial pressure also decreased. The patient has done well on a higher pump speed (9,600 RPM).

Case 3 is a 73-year-old destination therapy patient who presented with symptomatic HF and severe AI 128 days following implant. A Swan-Ganz catheter was placed and a formal speed optimization ramp study from 8,000 to 12,000 RPM was performed under echocardiographic guidance with serial hemodynamics (Table 4). Initial symptomatic relief was achieved by increasing his pump speed to 10,000 RPM, but symptoms recurred several days later and repeat SG catheterization revealed PCWP of 24 mmHg. The AV was closed percutaneously with immediate normalization of filling pressures and maintenance speed was set at 9,600 RPM.

**Discussion**

We present our experience with the prevalence and management of aortic insufficiency in patients following CF-LVAD implantation. Our study is the largest of its kind to date, the first to identify AV opening status shortly after implant as a risk factor for the development of AI, and the first to report on prospective management of AV opening. Albeit anecdotal and in only two cases, serial invasive hemodynamic and echocardiographic assessments have not previously been reported in patients with CF-LVADs and AI. On this background, our principal findings are as follows:
1. The risk of AI development is cumulative over time. Based on our findings, moderate or worse AI is expected to develop in approximately 30% of patients on device support for 3 years or longer absent preventive measures.

2. Non-opening of the aortic valve around the time of discharge from the initial implant stabilization is strongly associated with future development of AI.

3. Only one of 35 patients with prospective speed optimization developed mild-moderate AI during a mean follow up of 241±153 days (median 201 days) despite the fact that half of those patients did not open the AV at the optimized speed.

4. Symptomatic heart failure attributable to AI and requiring surgical intervention occurred in 7/21 patients who developed at least moderate AI.

5. CHF symptoms can be alleviated and hemodynamics can be improved by increasing the pump speed and despite simultaneously worsening AI.

6. Following stitch repair of the aortic valve in those patients who already have AI at the time of LVAD implant, prevalence of AI is comparable to those without AI at implant.

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**AI as a complication of CF-LVAD support**

AI is increasingly recognized as a major complication of CF-LVAD support. We previously reported a 25% 1 year prevalence of greater than mild AI in 73 HM II patients. Similarly, in a
cohort of 53 HM II patients, Cowger et al demonstrated near identical prevalence of greater than mild de novo AI at 1 year and a trend towards progression of AI with increased duration of CF-LVAD support. A more recent study by Soleimani et al reported the occurrence of greater than mild de novo AI in 31.6% of patients at 1 year. Notably, neither Cowger et al nor Soleimani et al reported any cases of severe AI and/or the need of surgical correction in their HM II cohorts after mean total support times of 239 and 336.5 days, respectively, although the number of case reports describing percutaneous and/or surgical intervention for severe AI in the literature is increasing. Our findings in the current study are not only concordant with the reported findings on lower grade AI, but also constitute a significant extension of prior work given cohort size, time of observation, and resultant new insights on prevalence, possible prevention as well as management of clinically significant AI.

The physiology and relevance of AI in CF-LVAD patients

While we are only beginning to understand the true impact of AI on clinical outcomes in patients maintained on CF-LVAD support, it is clear that valvular incompetence decreases pump efficiency and can lead to worsening heart failure. The immediate consequence of any degree AI is the creation of a redundant circulatory loop whereby retrograde blood flow is returned to the left ventricle via the incompetent valve. Despite the ensuing abnormally high LVAD flow rates, which may range from 7 to 10 L/minute, true “forward” cardiac output is diminished, end-organ perfusion becomes inadequate, and symptoms of heart failure may occur. Because of the tendency for AI severity to worsen over time, and the increasing number of patients who require support as long-term destination therapy, it is likely that more cases of clinically significant AI will come to attention.
The association of AV opening and AI

AV opening is determined by the pressure differential across the valve, known as the transvalvular pressure (TVP). Normally, the AV opens when TVP is zero as the pressure on the ventricular aspect of the valve increases to match aortic root pressure. Conversely, the AV closes when the pressure load on the aortic aspect of the valve supersedes left ventricular pressure. In the setting of high CF-LVAD pump speeds, effective left ventricular decompression leads to low left ventricular pressures, while continuous delivery of blood flow to the aorta via the outflow graft increases pressure on the aortic aspect of the valve. Facing the negative TVP generated by this scenario, the AV remains closed and the result is two pumps (the native left ventricle and the CF-LVAD) that effectively operate in series with one another. Alternatively, if pump speeds are reduced and sufficient myocardial contractility persists, the left ventricle can overcome aortic pressure load and the aortic valve opens. In this latter scenario, the two pumps effectively operate both in series and in parallel and the AV opens intermittently or regularly.

Prevention of AI

It is now widely believed that failure of the AV to open and ensuing prolonged coaptation time in addition to exposure of valvular tissue to persistently elevated retrograde pressure results in commissural fusion of AV leaflets. In a study of explanted hearts in patients who had been supported by a HM II for a mean of 367 days, Mudd et al identified commissural fusion in 8 of 9 cases, and on retrospective review found a decreasing prevalence of aortic valve opening and an associated increasing prevalence of AI over time. Since then, multiple groups have reported an association with decreased AV opening and AI in CF-LVAD patients. Our study is the first to identify AV non-opening at baseline, i.e. on the initial echocardiogram outside of the
operative period, as a risk factor prior for the development of AI. The current data therefore provide the hitherto strongest and possibly definitive evidence that establishing AV opening early on in the stable support phase protects against the development of AI. Thus, in conjunction with a hypothetical benefit of preserving pulsatile circulation, we believe that efforts to maintain AV opening as is recommended in current guidelines are warranted. Our data further provide strong support for trends in current technology improvements incorporating intermittent low speed phases to allow AV opening as used in the Jarvik 2000 and the European version of HVAD, and planned for MVAD and HeartMate 3.

The results of prospective speed optimization to maintain AV opening have not previously been reported and we describe our experience in 35 patients. As expected, AI was not observed in 17 patients who had at least intermittent AV opening at the time of discharge. To our surprise, however, only one of 18 patients whose AV remained closed after prospective speed optimization developed AI 342 days post implantation. This finding would indicate that AV opening is only a major driver of the development of AI in hearts where loading conditions are poorly optimized. Alternatively, and given the shorter duration of follow-up in the prospective group, it is conceivable that the onset of AI is delayed with optimized left ventricular loading conditions; i.e. possibly less pressure on the aortic leaflets from the ventricular side. We compared LVEDD and degree of mitral regurgitation in patients with closed AVs in our retrospective cohort to those in the prospective cohort. Although we did not detect a difference in LVEDD, subjects in whom the AV remained closed after speed optimization had much less mitral regurgitation indicating successful optimization of loading conditions. We did not see an association of blood pressure and AV opening at the time of our baseline assessment and/or an
association of blood pressure and the development of AI, but one must be careful not to over interpret this finding as our current data set only utilizes blood pressure at two time points and is limited by its cross sectional nature. Clearly, longer follow-up in a larger cohort with meticulous blood pressure measurements is needed to examine this issue further – such studies are currently underway at our institution. Irrespectively, loading conditions should be optimized during CF-LVAD support and intermittent opening of the AV should be pursued.

Management of clinically significant AI

As illustrated by our overall results and hemodynamic studies, even severe AI does not necessarily equate clinical heart failure or an elevated pulmonary capillary wedge pressure (PCWP). Specifically, during hemodynamic ramp studies, PCWP decreased while AI increased as a function of increased pump speed.

Despite our anecdotal experience, it is conceivable that increasing pump speed in a patient with moderate or severe AI may not have the observed effect, but rather increase left ventricular end diastolic and PCWP pressure and possibly worsen CHF symptoms. In addition, it is quite likely that very high pump speeds will eventually induce right ventricular failure. We therefore believe that symptomatic patients with AI who fail to improve after echocardiographic optimization with focus on MR reduction and septal positioning should undergo hemodynamic studies (Figure 7).

Although valve closure and/or replacement may be inevitable, these procedures should only be performed if noninvasive management has proven futile; a recent case series reported 60% 30-day mortality following percutaneous valve closure. In this context, it is of note that none of
the case reports on AV closure for severe AI published to date provides hemodynamic testing with different pump speeds. Lastly, it is quite possible that overall outcomes of percutaneous valve closure attempts reported to date - despite excellent immediate procedural success - are poor because procedures were performed as a last resort. We believe our current data may enhance awareness of and provide guidance for monitoring of AI and more timely intervention.

Aortic valve repair / closure at the time of device implant

We report good results using the “Park stitch” at the time of implant with prevalence and severity of AI comparable to those observed in patients without AI at the time of implant. It is sometimes controversially discussed whether AV repair with the Park stitch may indeed constitute AV closure. In fact, a modification of the Park stitch has been introduced that calls for complete oversewing of the aortic valve commissures.17 We observed opening of the aortic valve after chronic support in nearly half our patients at rest indicating that AV opening is preserved. Further study is needed to determine whether the aortic valve in the remaining patients opens in demand situations such as exercise and whether opening with a Park stitch would be adequate to allow enough blood flow to maintain end organ function during complete device failure.

While repair/closure of moderate or severely leaking valves is intuitive and supported by expert consensus18, our data cannot be used as evidence that mildly leaking aortic valves should be addressed at the time of implant. In contrast, our data on the time course of AI development support NOT addressing a mildly leaky AV if cardiac transplantation is expected to occur within the next 6-12 months. With more experience and a growing burden of AI induced HF in patients
supported for years, a more aggressive approach might be reasonable in destination therapy recipients.

**Limitations**

The principal limitation of our study is that this is a single center observation; however, our data on the prevalence of mild-to-moderate AI up to the one-year point are near identical to those published by two other centers. Although some of our data are obtained retrospectively and with the additional caveat of difficulty in grading AI, this concordance with the published literature on early (one year) AI development should provide significant reassurance that our novel long-term observation of at least moderate AI in nearly 1/3rd at the three year time point is not an institutional idiosyncrasy. Similarly, our data are in line with the growing body of severe AI case reports. Unfortunately, we do not have prospectively collected and comprehensive blood pressure data and echocardiograms were not performed at strictly prespecified time intervals. It should therefore be noted that absent prospective studies with serial echocardiographic and blood pressure assessments, our findings constitute an association of baseline AV opening and long term AI development rather than a clear cause and effect phenomenon. Similarly, we provide only anecdotal data on invasive hemodynamic assessment with a simultaneous speed ramp; we do believe these cases are highly educational and instructive for those pursuing invasive assessment of hemodynamics.

Lastly, it is often discussed and somewhat intuitive that lower speeds may promote device thrombosis, although this has never been proven. It is equally intuitive (and equally unproven) that failure of the aortic valve to open may cause aortic root thrombus and subsequent embolic complications including device thrombosis in the event of retrograde flow though the aortic
valve because of AI. Regrettably, our data set does not give conclusive evidence one way or the other in this regard.

Conclusions

In summary, our data demonstrate that AI is a common and likely progressive complication of CF-LVAD therapy as currently practiced. With more patients implanted as destination therapy and longer successful support times, we estimate that AI requiring intervention (surgical or percutaneous) may occur with a prevalence of at least 5-10% in those patients who remain on support for more than three years unless strategies to prevent AI are developed. Our observations on possible avoidance of this scenario require large scale validation, but at the very least should stimulate further research to prevent AI either through blood pressure management, pump management, or new pump technology including intermittent low speed algorithms. With all its limitations, we do believe our data put to rest the notion that AI is only a cosmetic complication of CF-LVAD therapy.

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Disclosures

Dr. Ulrich Jorde has received consulting fees of less than $ 5000 annually each from Thoratec, HeartWare, and Jarvik. Dr. Yoshifumi Naka has received consulting fees of less than $ 5000 from Thoratec. Dr. Nir Uriel has received consulting fees of less than $ 5000 from HeartWare.
References


Table 1. Demographics and Clinical Characteristics of CF-LVAD Patients Without AV Manipulation Prior to Implantation (N=224)

<table>
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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Male (n, %)</td>
<td>179 (79.9)</td>
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<tr>
<td>Ischemic CMP (n, %)</td>
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<tr>
<td>Hypertension (n, %)</td>
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<tr>
<td>Diabetes (n, %)</td>
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<td>COPD (n, %)</td>
<td>16 (7.2)</td>
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<td>History of Smoking (n, %)</td>
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<tr>
<td>BSA, m² (mean ± SD)</td>
<td>1.96 ± 0.26</td>
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<tr>
<td>Prior Cardiac Surgery (n, %)</td>
<td>77 (34.4)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
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<td>Hemoglobin (g/dL)</td>
<td>11.8 ± 1.87</td>
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<td>Bridge to Transplant (n, %)</td>
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<tr>
<td>Pre-VAD ECMO</td>
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Data are expressed as mean ± standard deviation or n (%). BSA = body surface area; CMP = cardiomyopathy; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; VAD = ventricular assist device.
Table 2. Aortic Valve Non-openers – comparison of the retrospective and prospective de novo cohorts

<table>
<thead>
<tr>
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<th>Prospective (n=29)</th>
<th>Retrospective (n=62)</th>
<th>Significance</th>
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<tr>
<td>Development of Greater than Mild AI</td>
<td>1 (5.6%)</td>
<td>20 (31.3%)</td>
<td>Hazard Ratio: 11.2 [4.6, 27.4] * (p=0.003^*)</td>
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<td>Total Support Time, Days</td>
<td>205 (128, 324)</td>
<td>265 (121, 507)</td>
<td>(p=0.41^†)</td>
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<td>LVEDD, cm</td>
<td>5.91 ± 1.36</td>
<td>5.78 ± 1.56</td>
<td>(p=0.75^‡)</td>
</tr>
<tr>
<td>At Least Mild MR at Baseline</td>
<td>3 (16.7%)</td>
<td>27 (43.5%)</td>
<td>(p=0.053^§)</td>
</tr>
</tbody>
</table>

Values are n (%), median (25%, 75%), and mean ± standard deviation

*Log rank test was used.

†Mann-Whitney test was used since the null hypothesis of normality was rejected via D’Agostino-Pearson.

‡T-Test was used since the null hypothesis of normality was accepted via D’Agostino-Pearson.

§2 patients were excluded from MR analysis for poor visualization and prosthesis.
Fisher’s exact test was used due to small sample size.

AI = aortic insufficiency; AV = aortic valve; LVEDD = left ventricular end diastolic diameter; MR = mitral regurgitation.
Table 3. Acute hemodynamics Study for Case #2

<table>
<thead>
<tr>
<th>Speed</th>
<th>AI</th>
<th>PAP</th>
<th>PCWP</th>
<th>RAP</th>
<th>BP</th>
<th>HR</th>
<th>CO</th>
<th>MVO2</th>
<th>LVEDD</th>
<th>LVESD</th>
<th>MR</th>
<th>PI</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM</td>
<td></td>
<td>(s/d/m)</td>
<td>(a/v/m)</td>
<td>(a/v/m)</td>
<td>(doppler)</td>
<td>(%)</td>
<td>(cm)</td>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8,000</td>
<td>Mild-</td>
<td>43/21/31</td>
<td>27/28/25</td>
<td>27/29/24</td>
<td>70</td>
<td>59</td>
<td>4.8</td>
<td>47.7</td>
<td>6.28</td>
<td>5.65</td>
<td>Mild</td>
<td>5</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8,400</td>
<td>Mild-</td>
<td>41/20/27</td>
<td>20/23/20</td>
<td>90</td>
<td>59</td>
<td>4.6</td>
<td>47.8</td>
<td>6.91</td>
<td>6.31</td>
<td>Mild</td>
<td>5.9</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8,800</td>
<td>Moderate</td>
<td>33/14/22</td>
<td>20/24/17</td>
<td>22/29/20</td>
<td>96</td>
<td>60</td>
<td>4.7</td>
<td>47.8</td>
<td>6.2</td>
<td>6.05</td>
<td>Mild</td>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>9,200</td>
<td>Moderate</td>
<td>36/16/23</td>
<td>17/20/14</td>
<td>20/27/19</td>
<td>92</td>
<td>60</td>
<td>5.3</td>
<td>53.2</td>
<td>5.79</td>
<td>5.55</td>
<td>Mild</td>
<td>4.7</td>
<td>6.5</td>
</tr>
<tr>
<td>9,600</td>
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<td>11/17/24</td>
<td>11/21/13</td>
<td>15/29/18</td>
<td>100</td>
<td>58</td>
<td>5.4</td>
<td>56.6</td>
<td>5.81</td>
<td>5.24</td>
<td>Mild</td>
<td>4</td>
<td>7.3</td>
</tr>
<tr>
<td>10,000</td>
<td>Moderate</td>
<td>30/19/21</td>
<td>14/14/14</td>
<td>17/31/19</td>
<td>100</td>
<td>60</td>
<td>5.9</td>
<td>58.6</td>
<td>5.7</td>
<td>5.13</td>
<td>Mild</td>
<td>3.8</td>
<td>8</td>
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<tr>
<td>10,400</td>
<td>Moderate-</td>
<td>35/14/23</td>
<td>12/17/12</td>
<td>23/25/18</td>
<td>100</td>
<td>59</td>
<td>6.1</td>
<td>60.3</td>
<td>5.6</td>
<td>5.43</td>
<td>Trace</td>
<td>3.4</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10,800</td>
<td>Moderate-</td>
<td>31/17/23</td>
<td>10/12/10</td>
<td>20/21/17</td>
<td>100</td>
<td>60</td>
<td>6.7</td>
<td>63.2</td>
<td>5.7</td>
<td>5.16</td>
<td>Trace</td>
<td>2.7</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11,200</td>
<td>Severe</td>
<td>36/13/22</td>
<td>8/12/7</td>
<td>16/21/16</td>
<td>104</td>
<td>60</td>
<td>7.1</td>
<td>64.7</td>
<td>5.59</td>
<td>5.19</td>
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<td>10.5</td>
</tr>
<tr>
<td>11,600</td>
<td>Severe</td>
<td>27/13/18</td>
<td>8/10/7</td>
<td>16/20/16</td>
<td>100</td>
<td>60</td>
<td>7.8</td>
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<td>4.48</td>
<td>None</td>
<td>1.9</td>
<td>12</td>
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</table>

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Table 4. Acute hemodynamics Study for Case #3

<table>
<thead>
<tr>
<th>Speed rpm</th>
<th>AI</th>
<th>CVP</th>
<th>PAP</th>
<th>mean PAP</th>
<th>PCWP</th>
<th>MVO2 %</th>
<th>LVEDD cm</th>
<th>PI</th>
<th>CO L/min</th>
<th>CI L/min/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>8000</td>
<td>moderate -</td>
<td>55/20</td>
<td>32</td>
<td>22</td>
<td>41</td>
<td>6.4</td>
<td>7</td>
<td>3.08</td>
<td>1.57</td>
<td></td>
</tr>
<tr>
<td>9000</td>
<td>moderate -</td>
<td>50/19</td>
<td>29</td>
<td>20</td>
<td>48</td>
<td>6.2</td>
<td>7</td>
<td>3.5</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td>10000</td>
<td>moderate -</td>
<td>4</td>
<td>53/18</td>
<td>30</td>
<td>49</td>
<td>6.3</td>
<td>7</td>
<td>3.57</td>
<td>1.82</td>
<td></td>
</tr>
<tr>
<td>11000</td>
<td>severe</td>
<td>51/19</td>
<td>30</td>
<td>16</td>
<td>52</td>
<td>6.3</td>
<td>7</td>
<td>3.79</td>
<td>1.93</td>
<td></td>
</tr>
<tr>
<td>12000</td>
<td>severe</td>
<td>47/18</td>
<td>28</td>
<td>15</td>
<td>54</td>
<td>6</td>
<td>7.1</td>
<td>3.96</td>
<td>2.02</td>
<td></td>
</tr>
<tr>
<td>13000</td>
<td>severe</td>
<td>44/17</td>
<td>26</td>
<td>13</td>
<td>56</td>
<td>6.1</td>
<td>5.5</td>
<td>4.33</td>
<td>2.21</td>
<td></td>
</tr>
<tr>
<td>14000</td>
<td>severe</td>
<td>47/15</td>
<td>26</td>
<td>12</td>
<td>60</td>
<td>6.1</td>
<td>4.1</td>
<td>4.55</td>
<td>2.32</td>
<td></td>
</tr>
</tbody>
</table>

AI = aortic insufficiency; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; MR = mitral regurgitation; MVO2 = mixed venous oxygen saturation; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PI = pulsatility index; RAP = right atrial pressure.
Figure Legends

Figure 1. Cohort derivation – A visual representation of cohort breakdown.

Figure 2. Freedom from Developing Aortic Insufficiency in All CF-LVAD Patients - Freedom from aortic insufficiency was assessed for all patients receiving CF-LVAD our institution at three different severity cutoffs.

Figure 3. Freedom from de novo Aortic Insufficiency Development in CF-LVAD Patients - Patients who did not have AV surgery at time of implantation and no aortic insufficiency at baseline were considered at risk for “de novo” development of aortic insufficiency. Freedom from aortic insufficiency was assessed in this cohort at three different severity cutoffs.

Figure 4. Non-Opening Aortic Valve at stable baseline as a risk factor for de novo aortic insufficiency: Retrospective cohort - Patients with aortic valve opening in their first echocardiogram outside of the operative period were much less likely to develop greater than mild aortic insufficiency.

Figure 5. Blood pressure comparison at baseline – Non-openers versus openers.

Figure 6. Time to intervention for symptomatic AI – Kaplan Meier analysis of freedom from symptomatic intervention following diagnosis of moderate or greater AI.
Figure 7. Management of Aortic Insufficiency - Algorithm for aortic insufficiency management based on our observed outcomes and hemodynamics study.
Patients with continuous-flow LVAD support (n=232)

- No aortic valve surgery (n=181)
  - Less than mild aortic insufficiency at baseline – “de novo” cohort (n=174)
    - Speed optimization before discharge (n=35)
    - No speed optimization before discharge (n=139)

- Aortic valve surgery at time of implantation (n=43)
  - Mild aortic insufficiency at baseline (n=7)

- Aortic valve surgery prior to device implantation (n=8)
Freedom from Worsening or New Aortic Insufficiency (N=224)

Cumulative Probability (%) Free of AI

Months from Implantation

Number at risk
Group: Greater than Mild
224 173 122 90 57 41 25 22 16 14 12 7 6
Group: At Least Moderate
224 175 132 99 64 47 29 26 21 18 15 9 8
Group: Moderate-Severe or Severe
224 178 133 101 69 52 34 31 25 22 19 12 10
Freedom from Developing Aortic Insufficiency De Novo (N=174)

Cumulative Probability (%) Free of AI De Novo

Degree of Aortic Insufficiency
- Greater than Mild
- At Least Moderate
- Moderate-Severe or Severe

Number at risk
Group: Greater than Mild
174 134 96 71 44 32 19 16 11 10 8 4 4
Group: At Least Moderate
174 137 104 78 49 37 22 19 15 13 10 5 5
Group: Moderate-Severe or Severe
174 138 105 80 53 41 26 23 18 16 13 9 7
AV Opening As a Risk Factor for Greater than Mild AI

Log Rank p = 0.003
HR = 11.2 [4.6, 27.4]

Cumulative Probability (%) Free of Greater Than Mild AI

AV Opening at 1st Echo 30 Days Post Op:
- Closed
- Intermittent and Open

Number at risk
Group: Closed
62 37 25 17 13 10 6 5 5 5 3 3 2
Group: Intermittent and Open
29 21 16 8 8 4 3 3 3 3 3 1 0 0
Management of Aortic Insufficiency

Pre CF-LVAD Implantation:
Does the patient currently have AI?

- Mild AI
  Consider repair if DT or HTX not expected within 12 months

- Greater than Mild AI
  Repair or replace AV

- Symptomatic AI
  Increase speed irrespective of AI severity

Post CF-LVAD Implantation:
Optimize speed to eliminate more than mild MR and position septum at midline. If both achieved, reduce speed to allow intermittent AV opening.

- Asymptomatic AI
  Optimize speed to maintain intermittent AV opening and monitor patient’s AI status

- No Improvement
  Perform hemodynamic studies and consider repairing, replacement, or closing of AV.

- Improvement
  Monitor patient’s AI status closely for HF development
Prevalence, Significance, and Management of Aortic Insufficiency in Continuous Flow Left Ventricular Assist Device Recipients
Ulrich P. Jorde, Nir Uriel, Nadav Nahumi, David Bejar, Jose Gonzalez-Costello, Sunu S. Thomas, Jason Han, Kerry A. Morrison, Sophie Jones, Susheel Kodali, Rebecca T. Hahn, Sofia Shames, Melana Yuzefpolskaya, Paolo Colombo, Hiroo Takayama and Yoshifumi Naka

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SUPPLEMENTAL MATERIAL

Video 1: Consistent Aortic Valve Opening in CF-LVAD Patient after Stitch Repair of Aortic Valve.