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

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Background—Aortic insufficiency (AI) is increasingly recognized as a complication of continuous flow left ventricular assist device 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 patients with continuous flow left ventricular assist device at our institution. Patients with aortic valve (AV) surgery before left ventricular assist device 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 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. Nonopening 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 continuous flow left ventricular assist devices 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: aortic valve insufficiency • echocardiography • heart-assist devices

Aortic insufficiency (AI) may develop during continuous flow left ventricular assist device (CF-LVAD) support. It has been proposed that this is because of commissural fusion and deterioration of leaflet tissue, both possibly promoted by failure of the aortic valve (AV) to open during support.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.2,3 Less certainty exists with regard to the question of how many patients will develop clinically significant AI, that is, resulting in heart failure (HF), although the number of case reports describing severely leaking AVs leading to symptomatic HF is increasing.

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Because AI has been recognized as a potentially significant long-term complication of CF-LVAD support, some have proposed to facilitate AV opening actively by running the pump at lower speeds4; others have advocated surgically addressing AI at the time of LVAD implantation by approximating the nodules of Arantius with a stitch5 or closing the valve altogether.6 We first noticed that de novo development of AI was common in 2010 and, based on the belief that AI is progressive3,7 and can lead to clinical HF, we have since routinely placed approximation stitches as described by Park et al7 on valves with mild or more AI at the time of implantation. 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 and the results of our attempts to prevent AI. Finally, we review our experience and propose treatment algorithms for patients in whom clinically significant AI has occurred during support.

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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 AV surgery and manipulation of the AV at the time of device implantation. Patients who had a history of AV surgery (repair, replacement, and closure) before 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 MR 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 who (1) had an echocardiogram between postoperative days 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 to 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. 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 MR is mild or less, blood pressure is adequate (usually >70 mmHg), and the patient does not report symptoms.

Results
Overall, 232 patients (223 HeartMate [HM] II and 9 Heart-Ware) had undergone CF-LVAD implantation at the time of data collection and comprise the study population. Eight HM II patients who had previously undergone prosthetic AV replacement were excluded from analysis because their valves were patch-closed at the time of device implant. In the remaining 224 patients, mean duration of device support was 344±352 days (median, 245 days). Of the 224 patients described in our study, 28 patients had an unscheduled ramp study after discharge. These postdischarge ramp studies led to 19 instances of speed change. Because RPM may affect 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
Table 1. Demographics and Clinical Characteristics of Patients With Continuous Flow Left Ventricular Assist Device Without AV Manipulation Before Implantation (N=224)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58±14</td>
</tr>
<tr>
<td>Men</td>
<td>179 (79.9)</td>
</tr>
<tr>
<td>Ischemic CMP</td>
<td>104 (46.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>116 (51.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>75 (32.5)</td>
</tr>
<tr>
<td>COPD</td>
<td>16 (7.2)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>81 (38.3)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.96±0.26</td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>77 (34.4)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.50±0.58</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8±1.87</td>
</tr>
<tr>
<td>Bridge to transplant</td>
<td>162 (72.3)</td>
</tr>
<tr>
<td>Destination therapy</td>
<td>62 (27.7)</td>
</tr>
<tr>
<td>Pre-VAD IABP</td>
<td>66 (29.5)</td>
</tr>
<tr>
<td>Pre-VAD CentriMag</td>
<td>13 (5.8)</td>
</tr>
<tr>
<td>Pre-VAD ECMO</td>
<td>7 (3.1)</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or n (%). BSA indicates body surface area; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; and VAD, ventricular assist device.

Development of AI in Patients Without AI at Baseline and Without AV Surgery: De Novo AI

Before 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, whereas 62 had closed AVs. One of 29 patients 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 nonopeners at baseline TTE were significantly more likely to develop AI (hazard ratio, 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 before hospital discharge. Seventeen of 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, whereas 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 MR reduced from mild to none, blood pressure increased 1.2±2.6 mm Hg, 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 mm Hg, 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 nonopener group) developed greater than mild AI. Device thrombosis occurred in 2
openers and 1 nonopener (P=0.60). Given the discrepancy in AI prevalence between retrospective and prospective nonopeners (20/62 versus 1/18), we compared these 2 subgroups (Table 2). The retrospective cohort had a longer total follow-up time (420±438 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 and after 9 months (blood pressure values could not be obtained in patients implanted before 2010 because of a change in the electronic medical record). Given the complexities of blood pressure assessment in patients with LVAD, 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 because we recently demonstrated that in patients with LVAD this (rather than mean arterial pressure) is closest to Doppler pressure. We did not detect a difference in blood pressure in openers versus nonopeners at the time of the baseline echocardiogram used to assign opening status (91±5.6 versus 90.0±6.0 mm Hg; P=NS; Figure 5) or at 9 months (102±6.35 versus 94±8.98 mm Hg). Furthermore, we did not detect differences in blood pressure baseline (90±16.6 versus 86±10.6 mm Hg) or at 9 months (94±13.8 versus 100±16.4 mm Hg) between patients who did and did not develop AI.

Development of AI in Patients After Stitch Repair of the AV
AV repair was performed at the time of device implantation in 43 patients with CF-LVAD (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 to severe AI, and 1/43 (2.3%) developed severe AI.
It is somewhat controversial whether AV opening still occurs in patients with CF-LVAD who have undergone AV repair. On routine follow-up echocardiogram, 12/43 (27.9%) patients had evidence of regular AV opening (Movie I in the Data Supplement) and an additional 4/43 (9.3%) patients had evidence of intermittent AV opening after stitch repair. Of 43 patients, 2 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 to moderate AI after 364 days of support.

Management of Clinically Significant Postimplant AI
Of the 21 patients that developed at least moderate AI (18 de novo cases and 3 after AV stitch repair), 7 (33.3%) were transplanted without requiring urgent UNOS status upgrade, and 6 (28.6%) remain asymptomatic (2 with now mild to moderate AI) on device support at the end of data collection. The remaining 8 (38.1%) developed symptomatic HF 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 had significant symptomatic relief. Of these 4 patients, 1 has been transplanted, and the remaining 3 are destination therapy patients who are alive and asymptomatic 203±160 days after AV manipulation.

Relationship of AI Severity, Pump Speed, and Invasive Hemodynamics
AV surgery in HM II 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

<table>
<thead>
<tr>
<th>Table 2. Aortic Valve Nonopeners: Comparison of the Retrospective and Prospective De Novo Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective (n=29)</strong></td>
</tr>
<tr>
<td>Development of greater than mild AI</td>
</tr>
<tr>
<td>Total support time, d</td>
</tr>
<tr>
<td>LVEDD, cm</td>
</tr>
<tr>
<td>At least mild MR at baseline</td>
</tr>
</tbody>
</table>

Values are n (%), median (25%, 75%), and mean±SD. AI indicates aortic insufficiency; AV, aortic valve; LVEDD, left ventricular end diastolic diameter; and MR, mitral regurgitation.

*Log-rank test was used.
†Mann–Whitney test was used because the null hypothesis of normality was rejected via D’Agostino-Pearson.
‡ t Test was used because the null hypothesis of normality was accepted via D’Agostino-Pearson.
§ Two patients were excluded from MR analysis for poor visualization and prosthesis.
|| Fisher exact test was used because of small sample size.
Aortic Insufficiency in Patients With CF-LVAD

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Table 3. Acute Hemodynamics Study for Case 2

<table>
<thead>
<tr>
<th>Speed, RPM</th>
<th>AI</th>
<th>PAP (s/d/m)</th>
<th>PCWP (a/v/m)</th>
<th>RAP (a/v/m)</th>
<th>BP (Doppler)</th>
<th>HR</th>
<th>CO</th>
<th>MVO2, %</th>
<th>LVEDD, cm</th>
<th>LVESD, cm</th>
<th>MR</th>
<th>Pi</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>8000</td>
<td>Mild to moderate</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>8400</td>
<td>Mild to moderate</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>8800</td>
<td>Moderate</td>
<td>41/20/27</td>
<td>20/23/20</td>
<td>...</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>
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<tr>
<td>9200</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>
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<td>Mild</td>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>9600</td>
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<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>
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<td>Mild</td>
<td>4.7</td>
<td>6.5</td>
</tr>
<tr>
<td>10000</td>
<td>Moderate</td>
<td>37/17/24</td>
<td>11/21/13</td>
<td>15/29/18</td>
<td>100</td>
<td>58</td>
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<tr>
<td>10400</td>
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<td>30/16/21</td>
<td>13/14/11</td>
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<td>6.1</td>
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<td>10/12/10</td>
<td>20/21/17</td>
<td>100</td>
<td>60</td>
<td>6.7</td>
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<td>Trace</td>
<td>2.7</td>
<td>9.7</td>
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<td>Severe</td>
<td>36/13/22</td>
<td>8/12/7</td>
<td>16/21/16</td>
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<td>60</td>
<td>7.1</td>
<td>64.7</td>
<td>5.59</td>
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<td>2</td>
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<tr>
<td>12000</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>
<td>67.6</td>
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<td>4.48</td>
<td>None</td>
<td>1.9</td>
<td>12</td>
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</tbody>
</table>

Al indicates aortic insufficiency; BP, blood pressure; CO, cardiac output; HR, hazard ratio; 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; and RAP, right atrial pressure.

Figure 6. Time to intervention for symptomatic aortic insufficiency (AI): Kaplan–Meier analysis of freedom from symptomatic intervention after diagnosis of moderate or greater AI.

time point, reoperation with sternotomy will be performed in a patient who now overwhelmingly likely has acquired von Willebrand factor deficiency and the need for anticoagulation. Accordingly, we think 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 well living independently at home in New York Heart Association class II after LVAD implant as destination therapy. He presented with new dyspnea and moderate de novo AI 1 year after implantation. Physical examination revealed mild volume overload. A ramp study was performed, and his pump speed was increased from 8800 to 9200 RPM. The patient has done well clinically with higher speed (9200 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 after device implant. There was no evidence of device malfunction based on routine pump interrogation, and symptoms persisted after significant diuresis. Baseline speed was 8800 RPM. A Swan–Ganz catheter was placed, and a speed optimization ramp study from 8000 to 12000 RPM was performed under echocardiographic guidance with serial hemodynamics (Table 3). Although AI increased throughout the ramp, blood pressure increased, pulmonary capillary wedge pressure (PCWP) decreased, and cardiac output increased. Of note, right atrial pressure also decreased. The patient has done well on a higher pump speed (9600 RPM).

Case 3 is a 73-year-old destination therapy patient who presented with symptomatic HF and severe AI 128 days after implant. A Swan–Ganz catheter was placed, and a formal speed optimization ramp study from 8000 to 12000 RPM was performed under echocardiographic guidance with serial hemodynamics (Table 4). Initial symptomatic relief was achieved by increasing his pump speed to 10000 RPM, but symptoms recurred several days later and repeat Swan–Ganz catheterization revealed PCWP of 24 mmHg. The AV was closed percutaneously with immediate normalization of filling pressures, and maintenance speed was set at 9600 RPM.

Discussion

We present our experience with the prevalence and management of AI in patients after 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 2 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. On the basis of our findings, we found that moderate or worse AI is expected to develop in ~30% of patients on device support for 3 years or longer absent preventive measures.
2. Nonopening of the AV around the time of discharge from the initial implant stabilization is strongly associated with future development of AI.
Table 4. Acute Hemodynamics Study for Case 3

<table>
<thead>
<tr>
<th>Speed, rpm</th>
<th>AI</th>
<th>CVP, mm Hg</th>
<th>PAP, mm Hg</th>
<th>Mean PAP, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>MVO2, %</th>
<th>LVEDD, cm</th>
<th>PI</th>
<th>CO, L/min</th>
<th>CI, L/min per Square Meter</th>
</tr>
</thead>
<tbody>
<tr>
<td>8000</td>
<td>Moderate to severe</td>
<td>...</td>
<td>55/20</td>
<td>32</td>
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<td>41</td>
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<td>50/19</td>
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</tbody>
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AI indicates aortic insufficiency; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; LVEDD, left ventricular end diastolic diameter; MVO2, mixed venous oxygen saturation; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and PI, pulsatility index.

3. Only 1 of 35 patients with prospective speed optimization developed mild to 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 HF attributable to AI and requiring surgical intervention occurred in 7/21 patients who developed at least moderate AI.

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

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

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 al1 demonstrated near-identical prevalence of greater than mild de novo AI at 1 year and a trend toward progression of AI with increased duration of CF-LVAD support. A more recent study by Soleimani et al10 reported the occurrence of greater than mild de novo AI in 31.6% of patients at 1 year. Notably, neither Cowger et al1 nor Soleimani et al10 reported any cases of severe AI and 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 surgical intervention for severe AI in the literature is increasing.3 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 previous work given cohort size, time of observation, and resultant new insights on prevalence, possible prevention, and management of clinically significant AI.

Physiology and Relevance of AI in Patients With CF-LVAD

Although we are only beginning to understand the true effect 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 HF. 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.11,12 Despite the ensuing abnormally high LVAD flow rates, which may range from 7 to 10 L/min, true forward cardiac output is diminished, end-organ perfusion becomes inadequate, and symptoms of HF may occur.13 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.

Association of AV Opening and AI

AV opening is determined by the pressure differential across the valve, known as the transvalvular pressure. Normally, the AV opens when transvalvular pressure 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, whereas continuous delivery of blood flow to the aorta via the outflow graft increases pressure on the aortic aspect of the valve. Facing the negative transvalvular pressure generated by this scenario, the AV remains closed and the result is 2 pumps (the native left ventricle and the CF-LVAD) that effectively operate in series with one another.12 Alternatively, if pump speeds are reduced and sufficient myocardial contractility persists, the left ventricle can overcome aortic pressure load and the AV opens. In this latter scenario, the 2 pumps effectively operate both in series and in parallel and the AV opens intermittently or regularly.

Prevention of AI

It is now widely thought 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.3,14 In a study of explanted hearts in patients who had been supported by a HM II for a mean of 367 days, Mudd et al14 identified commissural fusion in 8 of 9 cases, and on retrospective review found a decreasing prevalence of AV 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 patients with CF-LVAD.3,15 Our study is
the first to identify AV nonopening at baseline, that is, 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 think that efforts to maintain AV opening as is recommended in current guidelines are warranted.4 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 (heartware assist device) and planned for MVAD and HM III.

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 1 of 18 patients whose AV remained closed after prospective speed optimization developed AI 342 days after 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 (ie, possibly less pressure on the aortic leaflets from the ventricular side). We compared LVEDD and degree of MR 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 MR 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 an association of blood pressure and the development of AI, but one must be careful not to overinterpret this finding because our current data set only uses blood pressure at 2 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. Irrespective, 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 HF or an elevated 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 congestive HF symptoms. In addition, it is likely that high pump speeds will eventually induce right ventricular failure. Therefore, we 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 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 after 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. Finally, it is possible that overall outcomes of percutaneous valve closure attempts reported to date, despite excellent immediate procedural success, are poor

Figure 7. Management of aortic insufficiency (AI): algorithm for AI management based on our observed outcomes and hemodynamics study. AV indicates aortic valve; CF-LVAD, continuous flow left ventricular assist device; DT, destination therapy; HF, heart failure; HTX, heart transplant; and MR, mitral regurgitation.
because procedures were performed as a last resort. We think that our current data may enhance awareness of and provide guidance for monitoring of AI and more timely intervention.

AV 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 with 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 AV commissures. We observed opening of the AV after chronic support in nearly half our patients at rest, indicating that AV opening is preserved. Further study is needed to determine whether the AV 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.

Although repair/closure of moderate or severely leaking valves is intuitive and supported by expert consensus, our data cannot be used as evidence that mildly leaking AVs 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 to 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 1-year point are near identical to those published by 2 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 (1 year) AI development should provide significant reassurance that our novel long-term observation of at least moderate AI in nearly one third at the 3-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. Therefore, it should 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 think that these cases are highly educational and instructive for those pursuing invasive assessment of hemodynamics.

Finally, 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 AV to open may cause aortic root thrombus and subsequent embolic complications, including device thrombosis in the event of retrograde flow though the AV because of AI. Regrettably, our data set does not give conclusive evidence 1 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 >5% to 10% in those patients who remain on support for >3 years unless strategies to prevent AI are developed. Our observations on possible avoidance of this scenario require large-scale validation, but at the least should stimulate further research to prevent AI through blood pressure management, pump management, or new pump technology, including intermittent low speed algorithms. With all its limitations, we do think our data put to rest the notion that AI is only a cosmetic complication of CF-LVAD therapy.

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Disclosures

Dr Jorde has received consulting fees of <5000 annually each from Thoratec, HeartWare, and Jarvik. Dr Naka has received consulting fees of <5000 from Thoratec. Dr Uriel has received consulting fees of <5000 from HeartWare. The other authors report no conflicts.

References

Mechanical circulatory support with continuous flow left ventricular assist devices (CF-LVADs) has dramatically improved survival in patients with advanced heart failure and long-term destination therapy with 2-year survival, currently approaching 70% is now the leading indication. Longer support times in this setting without the possibility of cardiac transplantation have shifted attention to serious adverse events of CF-LVAD support, namely bleeding, infection, device thrombosis, and more recently aortic insufficiency (AI). Because CF-LVADs drain blood from the left ventricular apex directly to the ascending or descending aorta, aortic valve opening may or may not occur depending on pump speed settings and native LV contractility.

In this article, we report our experience with AI in 232 consecutive patients with CF-LVAD at a single institution. We conclude that the development of new onset or worsening AI during CF-LVAD support is frequent, may lead to decompensated heart failure, and is possibly preventable. We review our clinical experience with surgical manipulation of the aortic valve at the time of LVAD implant and provide suggestions to attempt AI prevention during long-term support. Finally, we share our experience in the management of those patients in whom clinically significant AI has newly developed while supported with a CF-LVAD.
Prevalence, Significance, and Management of Aortic Insufficiency in Continuous Flow Left Ventricular Assist Device Recipients

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SUPPLEMENTAL MATERIAL

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