Valvular Heart Disease in Patients Supported With Left Ventricular Assist Devices

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Heart failure (HF) has become increasingly prevalent with the progressive development of HF risk factors in our aging population. Although valvular heart disease (VHD) is not similarly considered as a public health concern (overall United States prevalence of 2.5%), many patients with advanced systolic HF have concurrent VHD. Because of the limited number of suitable donor organs for cardiac transplantation, advanced HF patients who have refractory or end-stage HF are often treated with left ventricular assist devices (LVADs). The impact of concomitant valvular lesions in those undergoing LVAD implantation has not been fully characterized and the management of these lesions is a subject of intense interest, particularly for patients for whom subsequent heart transplantation is not a viable option.

First-generation LVADs exhibited a pulsatile-flow mechanism, using positive displacement to move blood to the periphery. These regular intervals help mimic the systole-diastole phases of native cardiac physiology, which differs substantially from the mechanism of newer continuous-flow devices in which a nonpulsatile stream of blood provides systemic circulation. Second- and third-generation continuous-flow LVADs provide smaller size and enhanced durability, allowing for long-term support with improved quality of life. However, there are unique implications of contemporary LVAD support on cardiac circulation and valvular mechanics. Chronic unloading of the left ventricle (LV) via continuous, nonpulsatile flow alters blood flow dynamics through the left-sided cardiac chambers, with implications for the aortic valve (AV). Alteration of cardiac mechanics through continuous-flow can also impact the unsupported right ventricle (RV), leading to tricuspid regurgitation (TR). In this review, we aim to provide a background on the most common aortic, tricuspid, and mitral valve pathologies in patients supported with LVADs and highlight the outcomes and management of patients with VHD who undergo LVAD insertion.

AV Pathology
AV pathology is uncommon in advanced HF patients before LVAD implantation. Pal et al report in a single-center study (n=281) that only 4% of patients with advanced HF had moderate-to-severe aortic insufficiency (AI) at the time of referral for heart transplantation or LVAD. However, many studies have described progression of AI after continuous-flow LVAD support.

Aortic Blood Flow Dynamics
Continuous-flow LVADs draw blood from the LV and direct flow into the ascending aorta, thus increasing cardiac output and aortic root pressure while simultaneously decreasing LV pressure (Figure 1). This creates a continuous transvalvular pressure (aortic pressure–LV pressure) gradient across the AV (Figure 2). The AV opens when transvalvular pressure is less than zero and remains closed when greater than zero. Because many LVAD devices are set to near full support where the LV is fully decompressed, the transvalvular pressure is greater than zero, and the AV remains closed throughout the cardiac cycle (ie, LVAD provides flow in series). In contrast, when the transvalvular pressure is periodically allowed to decrease, blood is ejected through the AV and the heart operates in parallel with the LVAD, with circulation supported via both native LV function and the LVAD (partial support).

LVAD-Induced Commissural Fusion
Based on the physiology described above, continuous-flow LVADs may lead to fusion or deterioration of the AV (Figure 1). Fusion develops when fibrous tissue deposits along the commissures of the leaflets, resulting in leaflet adherence that reduces the opening area of the valve. The closed state maximally stretches the leaflets, preventing nutrient flow and stimulating collagen production and remodeling. Closed valves can also degenerate from disuse, especially in the setting of trauma from high-velocity supravalvular blood flow. Finally, a closed AV coupled with limited antegrade flow allows for stasis of blood on the ventricular surface of the valve favors thrombus formation and organization, which further contributes to leaflet fusion.

This leads to retraction of the leaflet tips and generation of a central orifice that becomes fixed in the absence of intermittent AV opening. The transvalvular pressure generated from LVAD support can then result in regurgitant flow from the aorta to the LV through the central orifice and development of AI.

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Preexisting Aortic Insufficiency

Initiation of LVAD support may exacerbate preexisting AI via the mechanisms highlighted above.9,12 An incompetent AV can lead to a closed loop with blood flowing from the LV through the LVAD into the aorta and back into the LV down a continuous pressure gradient. This recirculating blood volume may result in recurrence of HF symptoms because of increased LV pressure and volume as well as worsening AI.6 Importantly, although LVAD implantation is associated with an increased rate of development and progression of AI,8,9,13 no increase in mortality has been observed in patients who develop moderate-to-severe AI.13

Given the potential for AI to progress after LVAD insertion, many surgeons will correct moderate or greater degrees of AI at the time of implantation. Replacement with a bioprosthetic valve was previously the optimal method for AI correction but has fallen out of favor given the need for greater duration of cardiopulmonary bypass, potential for thromboembolic complications,14 and reports of bioprosthetic AV fusion and stenosis.12,15 Additionally, concomitant aortic procedures are associated with increased operative risk and an ≈5-fold increase in 30-day mortality.7 Use of a mechanical prosthesis is not recommended because of presumed high risk of thrombus formation and the potential for subsequent embolization.16

LV outflow tract closure is a definitive strategy for treating preexisting AI while circumventing challenges associated with an AV prosthesis, and multiple methods have been described.14,17–19 The Park stitch is a simple coaptation stitch placed at the central portion of the 3 aortic cusps. Bryant et al14 sutured the commissures either centrally with a single buttressed stitch or along the full length of noncoaptation. Adamson et al18 describe an alternative method using felt strips along each leaflet that are anchored to the aortic wall. Suture repair of the AV is simple, requires a shorter period of cardioplegic arrest, and may be associated with reduced thrombosis and embolism compared with AV replacement. However, potential complications include AI recurrence, sutures tearing or eroding through the AV, and lack of ability to maintain hemodynamic stability with pump failure. Moreover, this method complicates the process of weaning from LVAD support should the LV recover function.20

De Novo Aortic Insufficiency Post-LVAD Implantation

Multiple studies have found that de novo development of AI is common and can occur after a relatively short period of LVAD support.8 Rajagopal et al13 described that AI development was more pronounced in recipients of continuous-flow LVADs compared with pulsatile-flow LVADs but found no association between preoperative AI grade and development of moderate or greater postoperative AI. In other studies, progression of AI was correlated with female sex, smaller body surface area,
HeartMate II support, increasing aortic sinus diameter, and an AV that remained predominantly closed. For patients who develop de novo AI, medical therapy includes vasodilators to lower systemic afterload and diuretics to lower ventricular preload. In cases where refractory HF symptoms or cardiogenic shock develop, inotropic support may be required until a surgical intervention can be implemented. There have been several reports of minimally invasive and percutaneous strategies for treatment of patients with previously implanted LVADs experiencing HF secondary to progressive AI. Santini et al described transcatheter aortic valve implantation with CoreValve (Medtronic, Minneapolis, WI) as a life-saving intervention in a patient who developed de novo AI after LVAD insertion. D’Ancona et al described successful transcatheter aortic valve implantation with a SAPIEN valve (Edwards Lifesciences, Irvine, CA) through a transapical approach in a patient who had an otherwise normal AV with absence of aortic calcifications. However, neither the SAPIEN nor CoreValve device has been Food and Drug Administration approved for this particular use. Parikh et al described percutaneous transcatheter AV closure in 5 patients using the Amplatzer device (AGA Medical, Plymouth, MN), which improved cardiac hemodynamics. We have yet to understand the long-term outcomes of these innovative techniques, particularly any susceptibility to development of AI similar to native valves. However, these reports provide promising evidence for novel techniques in the treatment of AI in patients with LVADs.

Aortic Stenosis
Because the LVAD is not dependent on flow through the AV when functioning in series, preexisting aortic stenosis (AS) does not adversely affect the normal functioning of an LVAD. On the rare occasion that the LVAD could be explanted, AV replacement may be considered to permit successful weaning of LVAD support.

Current Approach and Future Direction
Recent recommendations from the International Society of Heart Lung Transplantation suggest that moderate or greater AI be considered for surgical correction at the time of LVAD implantation (Table 1). We favor suture closure of the AV leaflets as the treatment of choice given its low risk of complications and durable results. Transcatheter aortic valve implantation and percutaneous transcatheter AV closure could become reasonable options in the future with modifications in the design of the prosthesis or implantation technique. Preexisting AS is not a significant concern unless partial or parallel support is being implemented to maintain native pulsatility. Finally, given the mechanism of AV commissural fusion, we think that achieving a range of optimal pump speed that allows for adequate AV opening is another method of prevention against de novo pathology.

Tricuspid Valve Pathology
Patients with advanced HF frequently progress to develop symptoms of biventricular failure with associated dilation of both the LV and RV. Dilation of the RV leads to secondary tricuspid annular dilation, apical leaflet displacement, and restriction with resultant incomplete coaptation. Between 30% and 64% of patients with advanced HF will have associated TR, which further contributes to RV failure through the development of right-sided volume overload and reduced RV ejection. Because development of worsening RV failure after LVAD implantation is associated with reduced survival, tricuspid valve (TV) pathology is a major concern at the time of surgery.

Effect of LVAD Implantation on Tricuspid Regurgitation
LVAD therapy favorably reduces LV end-diastolic pressure and pulmonary venous pressures. Reduced pulmonary pressures can decrease RV afterload and help normalize right-sided hemodynamics with resolution of TR. Furthermore, LVAD therapy significantly reduces central venous pressure and RV end-diastolic dimensions, thus improving RV function and contractility. However, in the immediate postoperative period, flow can be limited across the pulmonary vasculature, thus delaying reduction of RV afterload. Furthermore, patients often undergo volume resuscitation in the perioperative period, which exacerbates RV dilation and TR. Finally, unloading of the LV by the LVAD results in a leftward shift of the interventricular septum that can restrict the TV leaflets, thereby worsening TR (Figure 3). Holman et al found that TR acutely worsened, and that RV enlargement persisted 30 days postimplant, presumably because of the mechanisms noted above. In contrast, Piacentino et al found that at late follow-up (mean 156±272 days), TR decreased significantly (32% with moderate-severe TR versus 49% preoperatively), suggesting that RV remodeling is an incomplete and slow process.

Concomitant Tricuspid Valve Repair With LVAD Implantation
Because RV failure can lead to prolonged hospitalizations and increased mortality, there is interest in concomitant tricuspid valve repair (TVR) during LVAD implantation in select patients. Potential benefits of TVR include reduced right atrial pressure and reduced sequelae of venous congestion, leading to improvement in renal and hepatic function. Downsides might include longer operative time, increased bleeding risks, and potential for development of tricuspid stenosis. Furthermore, there are no studies examining the impact of concomitant TVR on long-term outcomes, such as survival free of transplant, quality of life, and readmission rates. Several single-center studies have examined the short-term impact of this procedure for moderate-to-severe TR. However, to our knowledge, there have been no such multicenter studies.

Saeed et al reported on 42 patients with moderate-to-severe TR undergoing LVAD implantation, with 8 patients receiving concomitant TVR. TVR prolonged the operative time and showed similar outcomes to LVAD implantation alone, including incidence of RV failure, end-organ function, and survival. This absence of benefit led the authors to suggest that TVR may not be necessary at the time of LVAD implantation. Similarly, Krishan et al reported on 51 LVAD patients (37 concomitant TVR, 14 control) and found no difference in outcomes including postoperative hemodynamics, rates
of bleeding, duration of mechanical ventilation and inotropic support, and hospital mortality. However, given the lack of obvious increase in perioperative risk, they advocated for a liberal approach, supporting the use of TVR at LVAD implantation.

Piacentino et al.31 performed 2 studies on concomitant TVR.31,32 The first involved 115 patients with moderate-to-severe TR, 34 of whom underwent concomitant TVR. A related report looked at 200 consecutive patients with continuous-flow LVAD, 61 of whom had moderate-to-severe TR (33 underwent concomitant TVR).32 Concomitant TVR reduced postprocedure RV failure and postoperative TR compared with LVAD alone. Additionally, there was a trend toward improved survival and early clinical outcomes, including decreased postoperative inotrope use and decreased incidence of renal dysfunction.

Current Approach and Future Direction
These single-center studies are provocative but do not provide definitive guidelines about perioperative risk of concomitant TVR. However, with some evidence showing improved early clinical outcomes with TV intervention, it is reasonable to suggest that concomitant TVR provides salient benefits in patients with moderate-to-severe TR receiving long-term LVAD support.16 Whether this intervention is repair versus replacement will also need to be evaluated given comparable outcomes in the Mayo experience.33 Alternatively, in the event that the LVAD is used as partial support, lower speeds might limit net flow across the pulmonary vasculature, thus delaying reduction of RV afterload and contributing to RV failure. This may be less clinically relevant given the ability of LVAD therapy to lower pulmonary pressures,34 thereby generating a pressure gradient favoring antegrade flow across the pulmonic valve. Therefore, pulmonic valve pathology may have minimal untoward consequences and is unlikely to be a frequent site of intervention. However, intrinsic pulmonary arterial hypertension, disease secondary to long-standing valvular disease, or previous chronic pulmonary emboli may not always respond to reduction of left-sided filling pressures with LVAD therapy.

Pulmonic Valve Pathology

Pulmonic Regurgitation and Stenosis
There are no studies comprehensively investigating the incidence and clinical impact of pulmonic stenosis or regurgitation in patients supported with LVADs. In theory, either lesion might limit net flow across the pulmonary vasculature, thus delaying reduction of RV afterload and contributing to RV failure. This may be less clinically relevant given the ability of LVAD therapy to lower pulmonary pressures,34 thereby generating a pressure gradient favoring antegrade flow across the pulmonic valve. Therefore, pulmonic valve pathology may have minimal untoward consequences and is unlikely to be a frequent site of intervention. However, intrinsic pulmonary arterial hypertension, disease secondary to long-standing valvular disease, or previous chronic pulmonary emboli may not always respond to reduction of left-sided filling pressures with LVAD therapy.

Mitral Valve Pathology
There is a paucity of information about mitral valve pathology in patients supported with LVADs, and surgical correction of mitral valve disease (particularly for mitral regurgitation, MR) has not been used frequently in patients with LVAD.35 Nonetheless, hemodynamically significant mitral valve disease is common among patients with advanced HF and remains the most prevalent VHD in the United States.36

Table 1. Options in the Management of Preoperative or Progressive Aortic Insufficiency in Patients With LVAD Support

<table>
<thead>
<tr>
<th>Management</th>
<th>Pros</th>
<th>Cons</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical valve (ie, vasodilators, diuretics)</td>
<td>Lower systemic afterload and ventricular preload</td>
<td>High risk of thrombus formation</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Bioprosthetic valve</td>
<td>Left ventricle can eject through artificial valve if device fails</td>
<td>Potential for subsequent embolization</td>
<td></td>
</tr>
<tr>
<td>TAVI (not FDA approved for AI)</td>
<td>Immediate symptom relief</td>
<td>Provides temporary relief and symptom management</td>
<td></td>
</tr>
<tr>
<td>Percutaneous transcatheter AV closure</td>
<td>Effective; reduces pulmonary capillary wedge pressure</td>
<td>Time-consuming operation</td>
<td></td>
</tr>
<tr>
<td>LV outflow tract closure</td>
<td>Safe, well tolerated</td>
<td>Paravalvular regurgitation</td>
<td></td>
</tr>
<tr>
<td>Felt strips anchored to aortic wall</td>
<td>Simple, quick</td>
<td>Device failure may lead to hemodynamic instability</td>
<td></td>
</tr>
<tr>
<td>Suture closure of AV commissures</td>
<td>≥1 yr durability in case reports</td>
<td>Device failure may lead to hemodynamic instability</td>
<td></td>
</tr>
</tbody>
</table>

Al indicates aortic insufficiency; AV, aortic valve; FDA, Food and Drug Administration; LV, left ventricle; LVAD, left ventricular assist device; and TAVI, transcatheter aortic valve implantation.
Most MR associated with cardiomyopathy is functional and results from LV dilation. With LVAD decompression, LV dimensions decrease and allow the mitral leaflets to coapt, making MR insignificant during device support. Morgan et al found that continuous-flow LVAD implantation significantly decreased the severity of MR (moderate-severe) from 76.0% preoperatively to 8.0% at 1 and 6 months postoperatively. However, there is still potential risk for residual MR when device support cannot be optimized to provide low left-sided filling pressures, such as when there is suction of the interventricular septum over the inflow cannula at higher speeds or the need for intermittent AV opening.

Some have described the use of an edge-to-edge technique in the treatment of moderate-to-severe MR, which fixes the anterior leaflet to the posterior leaflet at a central location and may be effective for a central regurgitant jet. It is important to note that exposure of the valve via the left atrium usually requires cardioplegic arrest and possibly increased operative risk. Further investigation is necessary to define the correlation between MR and AI in the setting of varying pump speeds, especially given the implications for AV opening and AI progression (Figure 4). Mitral valve repair might be indicated if lower speeds are necessary to preserve AV integrity or maintain pulsatility within the peripheral circulation.

### Current Approach
MR and mitral stenosis are not contraindications to LVAD implantation. Currently, severe MR does not require surgical repair unless there is expectation of recovery or LVAD explant. Mitral stenosis with a mean pressure gradient >10 mmHg should be considered for concomitant mitral valve repair.

### Previously Implanted Prosthetic Valves

#### Aortic Valve
For patients with preexisting bioprosthetic AV, a functioning valve does not require removal or replacement. For patients with previously implanted mechanical prostheses undergoing LVAD implantation, 2 options exist: (1) replacement with a bioprosthetic valve or (2) exclusion of the valve from circulation. For example, the Cohn sandwich plug technique uses a felt circular patch for outflow tract closure and excludes the metallic valve leaflets from affecting blood flow by creating a barrier on both the ventricular and aortic side of the prosthetic.

#### Mitral Valve
The presence of prosthetic or mechanical mitral valves is not a contraindication for LVAD placement. Prosthetic valves are exposed to normal blood flow after LVAD implantation and should not be at risk for thrombus formation. Thus, patients with previous prosthetic mitral valves typically do not require additional mitral valve surgery, but may require a higher level of anticoagulation postoperatively.

### Valvular Heart Disease and LVAD Speed Modification
Ideally, continuous-flow LVADs would operate with total systemic blood flow consisting of contributions from both the LVAD and the LV. The pump speed would therefore be low enough for the AV to intermittently open yet high enough to maintain adequate systemic perfusion and unloading of the LV with reduction in MR grade. Intermittent opening of the AV via optimized pump speed could be advantageous in delaying and preventing de novo pathology, as well as allowing myocardial recovery and remodeling through maintenance of native contractility. It has also been suggested that opening of the AV will more closely mimic physiological pulsatility, which may be helpful in delaying development of acquired von Willebrand disease and pathological gastrointestinal bleeding. Finally, incomplete unloading of the LV may help maintain a normal interventricular septal position, creating less distortion of the tricuspid apparatus and reduced TR. Although this provides an optimal scenario, the combination of fully unloading the LV and intermittent AV opening may not be achievable in many patients without recurrence of HF symptoms.
Currently, clinical management of pump speed is assessed through clinical history and serial echocardiograms, which assess LV unloading, opening of the AV, interventricular septum position, and degree of MR. Topilsky et al described use of echocardiography to adjust pump speed perioperatively and found that variables such as tricuspid lateral annulus velocity, estimated left atrial pressure, and mitral deceleration index may be useful for future ramp optimization studies. Identifying the ideal pump speed, individualized based on severity of HF and degree of MR, will be one of the most important factors in management of this unique population. A promising protocol by Columbia University provides a standardized echocardiographically guided assessment for speed optimization and diagnosis of device malfunction to be used at discharge. This elegant study made speed adjustments (mean±424 rpm) in 61% of subjects and provided an understanding of device settings to preserve LV geometry, reduce MR severity, and allow intermittent AV opening. To our knowledge, the Columbia Ramp Study is one of the first standardized clinical ramp tests that both optimizes pump settings and diagnoses device malfunction.

### Table 2. Current Approaches for Valvular Heart Disease in Patients Supported With LVADs

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Current Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic insufficiency</td>
<td>Correct moderate or greater AI at time of LVAD implantation (if patient deemed appropriate to receive LVAD)*</td>
</tr>
<tr>
<td></td>
<td>Consider surgical intervention for mild AI</td>
</tr>
<tr>
<td></td>
<td>Suture closure is preferred method</td>
</tr>
<tr>
<td>Aortic valve prostheses</td>
<td>Prefer bioprosthetic valve if replacement undertaken*</td>
</tr>
<tr>
<td></td>
<td>Cohn sandwich plug technique for previously implanted mechanical prostheses</td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>Not contraindication to LVAD implantation†</td>
</tr>
<tr>
<td></td>
<td>May require surgical repair if anticipation of ventricular recovery†</td>
</tr>
<tr>
<td>Mitral valve prostheses</td>
<td>Mean pressure gradient ≥10 mm Hg should be corrected at time of implantation</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>May require higher level of anticoagulation*</td>
</tr>
<tr>
<td></td>
<td>No need for routine replacement of a properly functioning mechanical valve</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>Moderate or greater lesion should prompt consideration for concomitant repair†</td>
</tr>
</tbody>
</table>

AI indicates aortic insufficiency; and LVAD, left ventricular assist device.
*In accordance with Recommendations for the Use of Mechanical Circulatory Support from American Heart Association.24
†In accordance with The 2013 International Society of Heart Lung Transplantation Guidelines for Mechanical Circulatory Support: Executive Summary (Level C recommendations).25

### Summary

Patients with advanced HF and coexisting VHD who undergo LVAD implantation constitute a growing population and pose unique challenges in clinical and surgical management. Contemporary continuous-flow LVADs alter blood flow dynamics and cardiovascular physiology and can induce progression of preexisting VHD or lead to de novo VHD. Although we have defined our recommendations for treatment options (Table 2), continued changes to device technology, patient selection, and surgical techniques will undoubtedly lead to further changes in practice. Finally, the rapid growth in the field of mechanical circulatory support necessitates collaborative multicenter approaches to study the impact of these practice changes in the form of prospective randomized trials.

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