Chapter

Aortic Insufficiency in LVAD Patients

Vi Vu and Karen May-Newman

Abstract

Aortic insufficiency (AI) is a common complication that increases morbidity and mortality in patients with left ventricular assist devices (LVAD). Significant AI during LVAD support creates a substantial regurgitant flow loop, negatively affecting cardiac recovery and exposing blood to longer residence time and higher shear stress. The mechanism of AI development and progression is linked to a lack of aortic valve opening, which alters the valvular tissue mechanics. Pre-existing AI also worsens following LVAD implantation, interfering with the pump benefits. This chapter will evaluate AI development with LVAD support compared with naturally occurring AI and present the features, mechanisms, and links to clinical treatment options.

Keywords: aortic valve, insufficiency, LVAD, flow

1. Introduction

Moderate-severe aortic insufficiency (AI) develops in more than 25% of left ventricular assist device (LVAD) recipients and reduces survival and freedom from other complications. Improvements in LVAD design have not addressed this problem, which continues to threaten the benefits of mechanical circulatory support. AI can develop de novo or progress from pre-existing AI conditions [1–7] and is associated primarily with rotary LVADs, also called continuous flow pumps. AI occurs when the mitral valve does not close completely during diastolic filling (**Figure 1**). The large pressure difference across the valve produces retrograde flow from the aorta to the LV. During LVAD support, the retrograde flow passes through the LVAD and into the ascending aorta, and a portion joins the regurgitant flow to repeat the cycle, exposing the blood to more shear. Significant AI diminishes cardiac output, negatively affects myocardial recovery and induces end-organ hypoperfusion [1]. Previous studies have linked a lack of aortic valve (AV) opening to the development of AI. Alterations in AV biomechanics during LVAD support can increase the activation of valvular interstitial cells, which transform into myofibroblasts that increase fibrosis preferentially at the ventricular face of the leaflets and fusion at the commissures. The subsequent contraction of fibrotic tissue and the fragmentation of elastin reduces coaptation, eventually resulting in AI. Assessment of AI in LVAD patients must be adapted from standard guidelines to determine when treatment is needed.

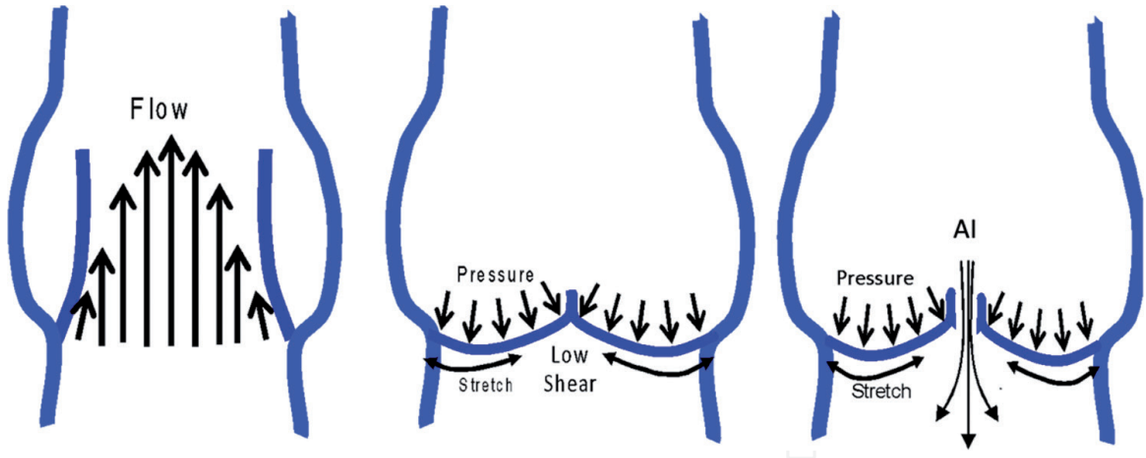

Figure 1.
Schematic of aortic insufficiency (AI), when the aortic valve leaks under high pressures, reducing forward flow.

2. Clinical complications of aortic insufficiency during LVAD support

Aortic insufficiency occurs when the AV does not close completely, thus inducing a backward flow from the aorta to the left ventricle (LV). As severe AI progresses, usually over many years, valve repair or replacement is needed to resolve the problem. Naturally occurring affects 0.5% of the general population and 2% of those over 75 years and is responsible for only 4% of all deaths from AV disease [8]. However, for LVAD patients, AI is a significant complication that occurs in more than 25% of recipients and has persisted despite improvements in design, surgical placement, and control.

The most recent INTERMACS report noted an average LVAD support duration of 1.7 years and a comparable survival rate in axial and centrifugal continuous-flow LVAD [9]. For axial and centrifugal LVAD designs, the leading causes of death are similar, including neurologic dysfunction, multisystem organ failure, infection, and stroke (ischemic or hemorrhagic) [9]. Moreover, the risk of readmission due to severe adverse events increases as patients stay longer in LVAD support [9]. Some recurrent adverse events with rates noted at 1 year post-implant are shown in **Figure 2** [9–12].

As LVADs are implanted for longer support durations, complications related to tissue remodeling or other adaptations to the altered physiology introduced by the LVAD arise. AI is one of those, appearing within a few months of LVAD support and worsening over time [6, 13, 14]. Reports of AI were not common for the early pulsatile LVADs but have risen with the implantation of rotary LVADs of axial and centrifugal designs. Many of these clinical studies are single-center with relatively few patients. Still, a consistent picture has emerged that ~15% of patients develop AI within three months of LVAD support, and the fraction increases to ~25% at 12 months and over 30% after 3 years (**Figure 3**) [1, 6, 12–16].

Rotary LVADs include axial designs, like the HeartMateII, which operate at high speeds and have a linear flow path through the housing. Centrifugal LVAD designs such as the HeartMate3 direct blood along a radial path, from the center towards the side, and operate at lower speeds which is gentler for the blood. Some LVADs have added speed modulation to introduce pulsatility to the flow, improving the washout to prevent thrombi from forming inside of the LVAD. These innovations have reduced hemolysis and thromboembolic complications but have not substantially reduced the occurrence of AI.

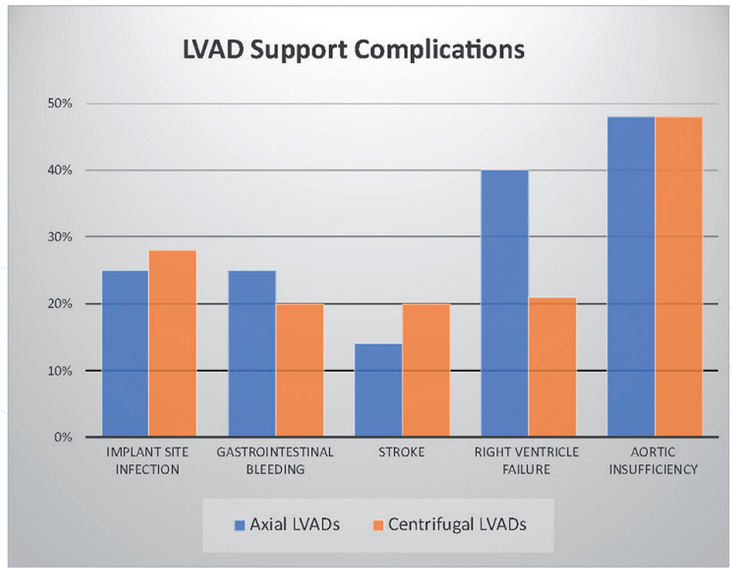

Figure 2.
Complications of left ventricular assist device (LVAD) support [9–12].

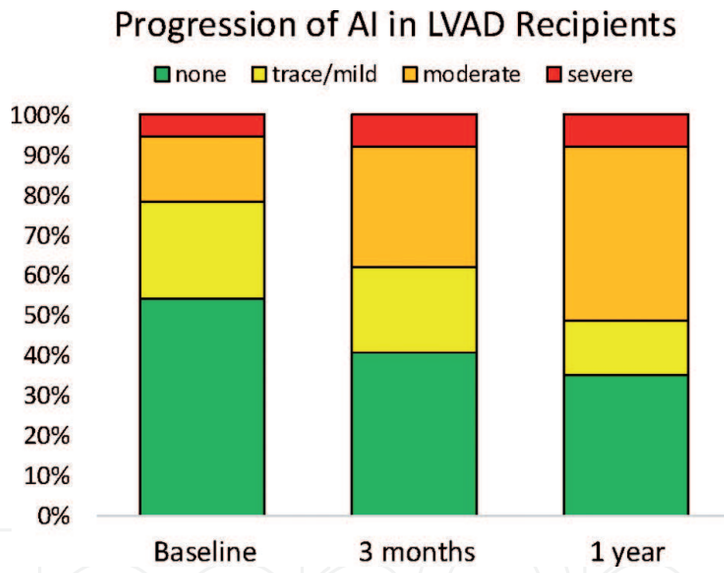

Figure 3.
Graphical illustration of AI progression in LVAD patients shows a progress worsening within the first-year post-implant. Adapted from Imamura 2020 [16].

The progression of AI with LVAD support is well documented, but the underlying mechanisms remain unclear [17, 18]. Even mild AI that is unrepaired is associated with a higher incidence of AI progression to moderate/severe and worse NYHA functional class compared to trace or less AI patients in mid-term after LVAD implantation [19]. AI in LVAD recipients can occur de novo or progress from pre-existing AI conditions [1–3, 5–7]. De novo AI develops as early as three months post-implant, and freedom from significant AI decreases as LVAD support duration increases [12, 13, 15]. Long LVAD support duration and low ejection fraction have been identified as independent predictors of de novo AI development [2, 7].

When pre-existing AI is present, the severity tends to increase with time post-implant [1, 16]. LVAD support induced a larger regurgitant flow resulting in lower cardiac output, higher preload, and impacting HF status [18, 20, 21]. Worsening of

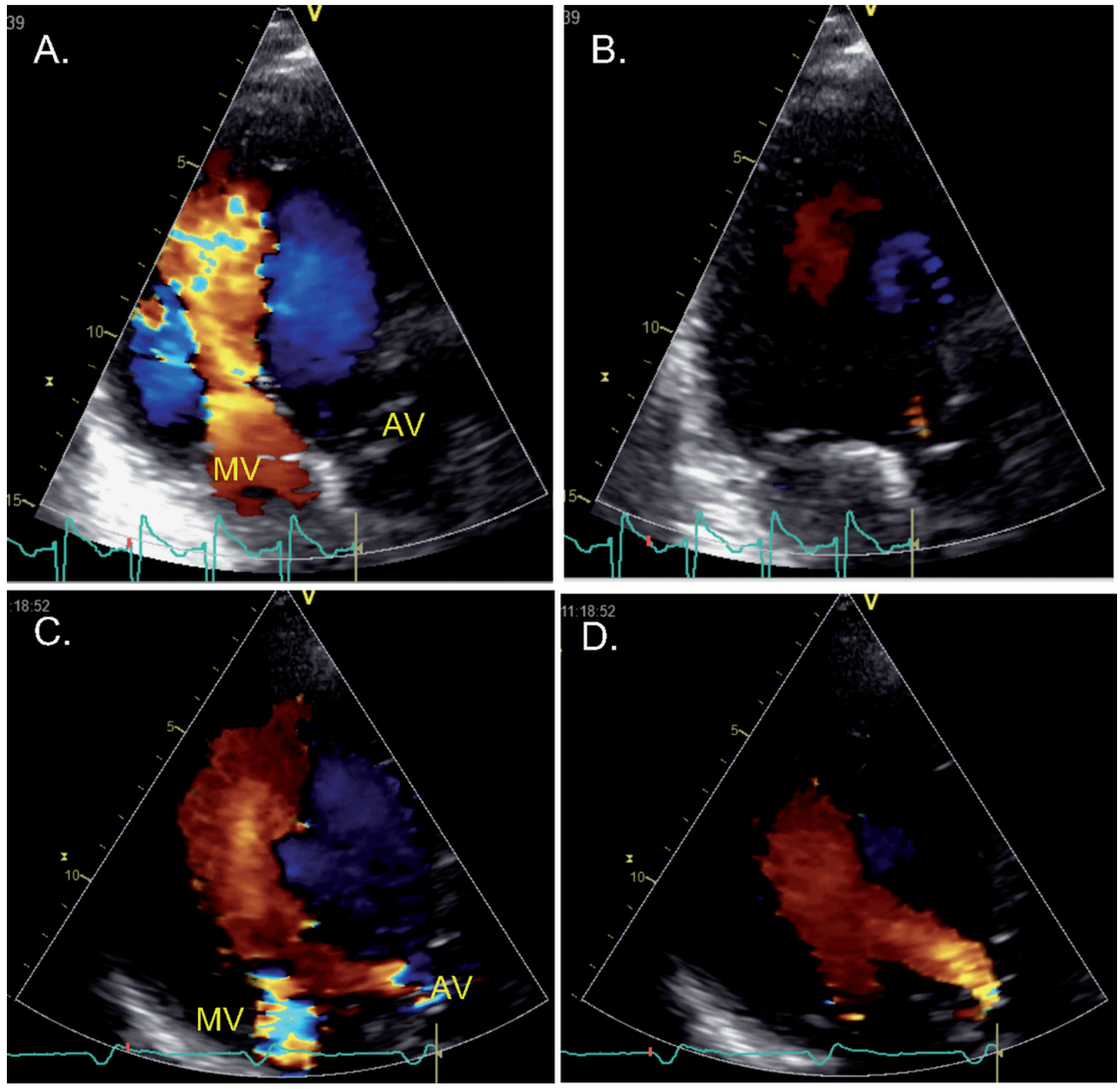

Figure 4.
Three-chambered echo view of LVAD patients with mild AI (top) and moderate/severe AI (bottom). A. Early diastolic filling through the mitral valve (MV). B. Mid diastole shows a small regurgitant jet through the aortic valve (AV). C-D. a large regurgitant jet appears in early diastole and merges with mitral inflow.

AI increases LVAD flow while systemic flow decreases, forming a regurgitant flow loop [21]. As shown in **Figure 4**, mild AI presents in mid-diastole but extends in magnitude and duration towards moderate/severe levels within a few months of LVAD support.

Moreover, LVAD patient with concurrent AI is associated with a higher readmission rate and adverse events, including mitral and tricuspid regurgitation, hemolysis, and worsening of right ventricle function [6, 20, 22]. Previous clinical studies have reported multiple factors associated with the worsening of pre-existing trivial AI in post-LVAD support. Patient-related factors included pre-existing valvular dysfunctions, old age, and abnormal cardiac function. Pre-existing valvular dysfunctions include uncorrected mild AI [23, 24], large aortic sinus diameters [6, 25], LVAD-related factors include reduction of AV opening area and duration, high LVAD speed, and types of LVAD [6, 25]. Previous studies have suggested that the higher rate of progressive AI with rotary LVAD support results from low pulsatility, which may induce a more significant regurgitant flow and a higher rate of valvular remodeling [22, 26–28].

3. Flow dynamics of aortic insufficiency during LVAD support

For the majority of rotary LVADs, the LVAD inlet is located at the LV apex, and the outlet anastomoses to the ascending aorta, bypassing the AV. Implantation of the LVAD immediately increases systemic blood flow and end-organ perfusion, providing an alternate pathway for blood to flow from the heart to the arterial system, as shown in **Figure 5**. LVAD support unloads the heart, decreasing the magnitude and pulsatility of LV pressure, which can fall below the level needed to open the AV fully during myocardial contraction. With sufficient contraction of the native heart, a fraction of the flow is ejected through the AV, and the heart and LVAD operate in parallel. In this condition, the AV does not open fully, exhibiting a reduced opening area and duration [29]. During periods of high LVAD support, the LV pressure is too small to open the AV, and blood flow occurs entirely through the LVAD, the heart, and the pump operating in series [30]. The AV is continuously closed for this condition and chronically exposed to high transvalvular pressure. For many patients, the level of LVAD support needed to relieve the HF symptoms results in complete and continuous closure of the AV, with all blood exiting the heart through the LVAD.

Adding a rotary LVAD to the native heart reduces the range of pressure and flow experienced in the cardiovascular system, diminishing pulsatility. The last decade of LVAD therapy has revealed several significant complications that worsen with reduced pulsatility, including thrombus formation, AV incompetence, and vascular smooth muscle response [17, 31]. The latter has been tied to arteriovenous malformations and gastrointestinal bleeding [17, 32]. Indices of pulsatility include pulse pressure, normalized flow range, and surplus hemodynamic energy [28, 30], which decrease as LVAD speed increases. When the AV ceases to open, the abnormal flow pattern creates a region of flow stasis adjacent to the AV, which creates a high risk for thromboembolism that could be embolized by a sudden strong contraction of the native heart [33].

Blood flow in the normal healthy heart is unsteady, 3-D and shows a range of different length scales [34]. A typical flow pattern in the LV has been described as consisting of a large diastolic vortex that channels the transit of incoming blood from the mitral valve towards the AV [35]. This vortex contributes to diastolic suction and minimizes kinetic energy losses and cardiac work [36]. The LV vortex has been shown to facilitate the blood mass coming into the normal LV during one beat washing out completely after a few beats [37], which prevents intraventricular blood stagnation [38].

In the LV of a diseased heart, progressive adverse remodeling leads to abnormal flow patterns that may impair pumping efficiency, and therefore affects blood transit within the ventricle. It is believed these abnormal intraventricular flow dynamics may contribute to the progression of certain diseases, leading to a final stage of HF or thrombus formation [39]. In addition, previous studies of flow transport through the heart have correlated dilated cardiomyopathy with increased vortex kinetic energy and decreased flow transport [40]. Models of this pathological condition have identified a high thrombus risk in DCM patients with large regions of blood flow with residence times greater than 2 s that also exhibit low kinetic energy [41]. When AI is present, retrograde flow mixing with the forward flow during diastole contributes to energy loss and increases residence time [41].

Thrombus formation and growth in several locations have been observed clinically, contributing to the high stroke rate in LVAD patients [42]. When AI develops in LVAD patients, the backward flow through the AV may improve pulsatility and flow stasis in

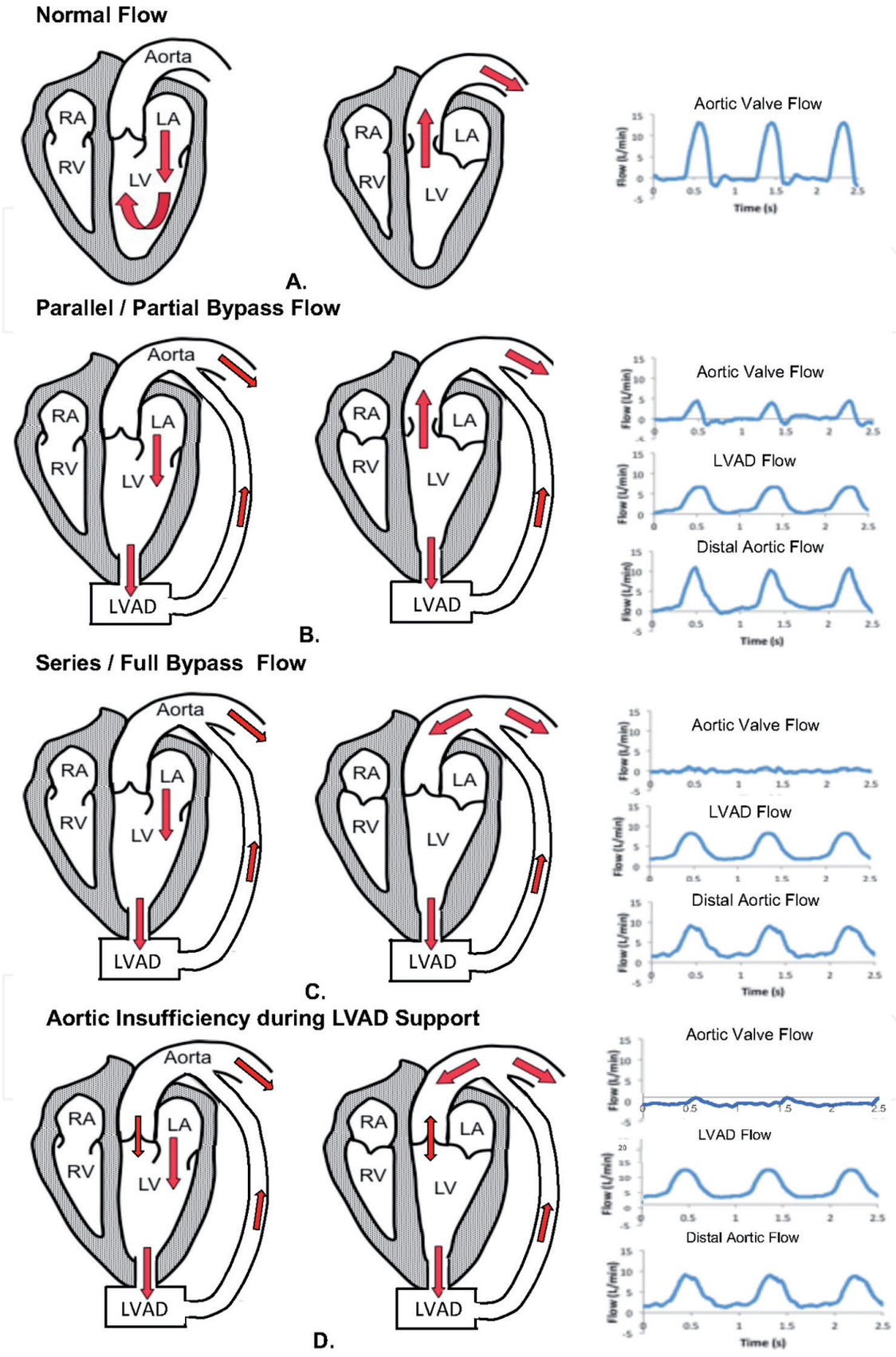

Figure 5.
Schematic of flow conditions. A. the normal flow path enters the left ventricle (LV) through the mitral valve and exits through the aortic valve and into the aorta. B. Low LVAD support works with the native heart to produce parallel flow through the LVAD and aortic valve. C. High LVAD support maintains continuous closure of the aortic valve during series flow. D. Aortic insufficiency produces retrograde flow through the aortic valve that can re-enter the LVAD in a regurgitant flow loop.

the aortic root, but over time results in reduced systemic flow. In particular, AI results in the formation of a regurgitant flow loop, in which blood from the LVAD flows retrograde through the AV, into the LV, and out through the LVAD again. This loop extends the amount and time-history of shear stress exposure to the blood, increasing hemolysis and thrombogenicity. The pump will also need to run at a higher speed to achieve the original cardiac output, which increases wear on the device. Hemostasis and thromboregulation are already compromised in LVAD patients, and AI adds to this liability.

During LVAD support, LV vortex formation is relatively unaffected, although vortex circulation and kinetic energy increase with LVAD speed, particularly in systole when all flow exits through the LVAD. When AI occurs, the regurgitant jet forms a vortex ring that normally dissipates in the mid-ventricle when no LVAD support is present but collides with the incoming mitral flow, as shown in **Figure 6**. When the LVAD is added, the regurgitant jet is drawn towards the LVAD inflow, impinging on the vortex ring generated by mitral inflow. The oppositely rotating vortices are partially annihilated, dissipating energy in the process. This flow pattern contributes to fluid stasis along the septal wall.

Recent device improvements include an "artificial pulse", based on a rapid LVAD speed change, that produces a small hemodynamic boost. While this artificial pulse provides substantial improvement in pulsatility, it is not synchronized with the native heartbeat and thus offers minimal improvement in the overall flow. The presence of speed modulation does not appear to impact the development of AI, which remains a significant complication of LVADs.

4. Aortic valve biomechanics during LVAD support

Human heart valves change their shapes and size during the cardiac cycle in response to their surrounding hemodynamics [43]. This mechanism helps facilitate the leaflet function and reduces the effect of flexural stress on the valve surface [43]. An average heart valve opens and closes more than three billion times in a lifetime and experiences various stress and strain types (e.g., tensile, compressive, stretching, and bending) [43]. The AV is a thin tissue structure with three leaflets attached to the aortic root wall in a u-shaped pattern in a roughly symmetric arrangement. Each leaflet forms a pocket with the corresponding sinus, which plays a vital role in the fluid mechanics of opening and closing [44]. During diastolic filling, the valve is closed, and the leaflets stretch in opposition to the high transvalvular pressure [17]. When the AV opens during systole, the leaflets relax as blood flows over the ventricular surface and into the aorta. Some of the flow is captured as vortices that form behind the valve leaflets, ensuring smooth closure. The unidirectional laminar blood flow produces shear stress of up to 80 dynes/cm^2 on the ventricular endothelial surface [45]. In contrast, the aortic surface has a small magnitude oscillatory flow in the range of ±10 dyn/cm^2 shear stress [46].

During LVAD support, the pressure difference across the AV remains high for a longer fraction of the cardiac cycle, producing a decrease in flow that corresponds to a reduction in valve opening. The valve opening area decreases with LVAD support, with more of the valve commissures coapted over the entire cardiac cycle. LVAD support also reduces the duration of AV opening, which increases the time that the leaflet tissue experiences maximum pressure loading. Simultaneously, the shear across the ventricular surface of the valve leaflet is reduced and eventually eliminated when the AV remains closed.

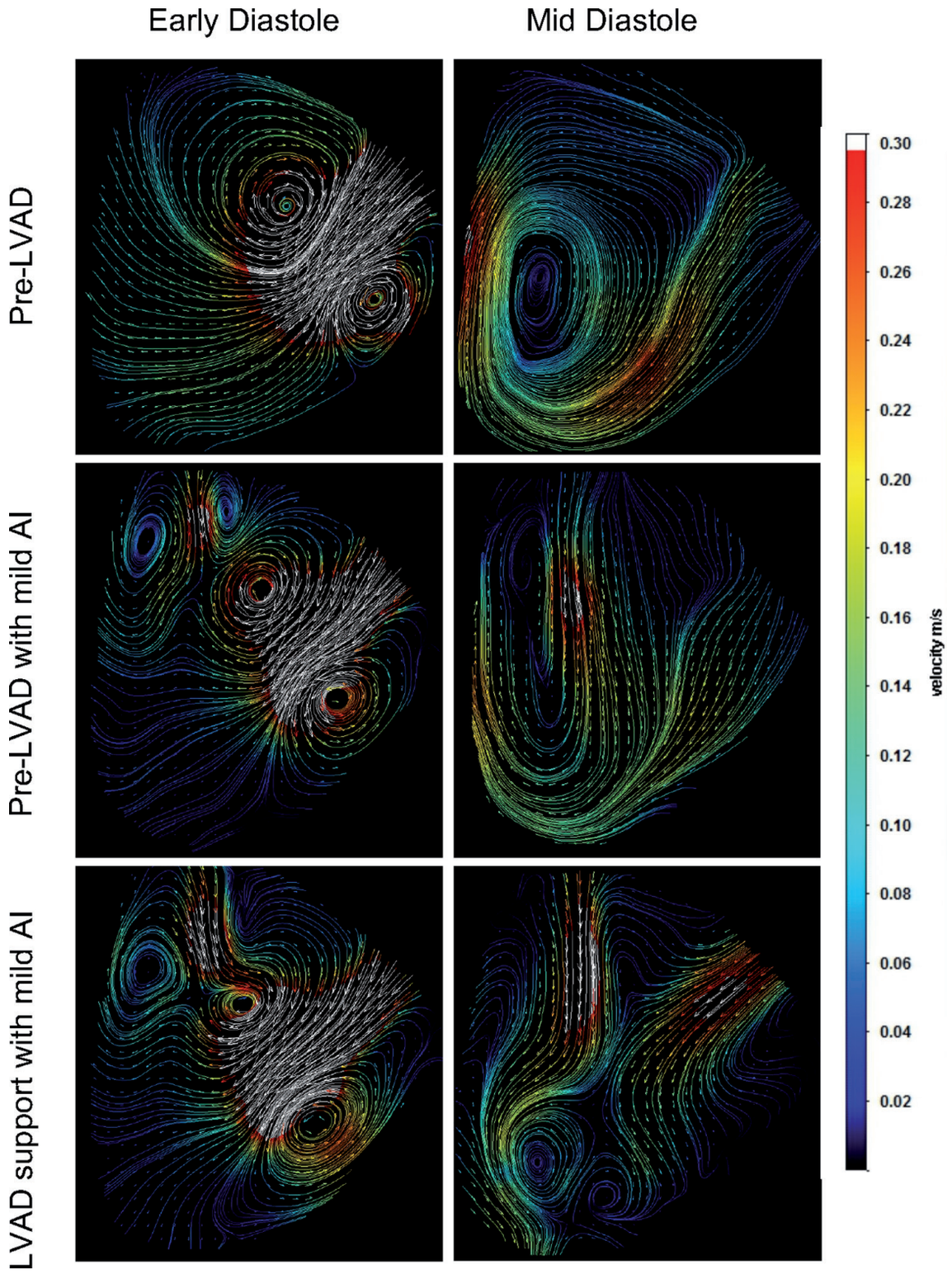

Figure 6.
Flow field images during early and mid-diastole illustrate the vortex ring generated by the regurgitant jet that collides with the mitral valve inflow.

At the level of the valve tissue and cells, the impact of LVAD hemodynamics produces a sudden change in the mechanical signals that can initiate a sequence of remodeling that results in AI. Measurements of valve tissue stretch during LVAD support show that the aortic leaflets are stiffer in the circumferential direction and

DOI: http://dx.doi.org/10.5772/intechopen.106173

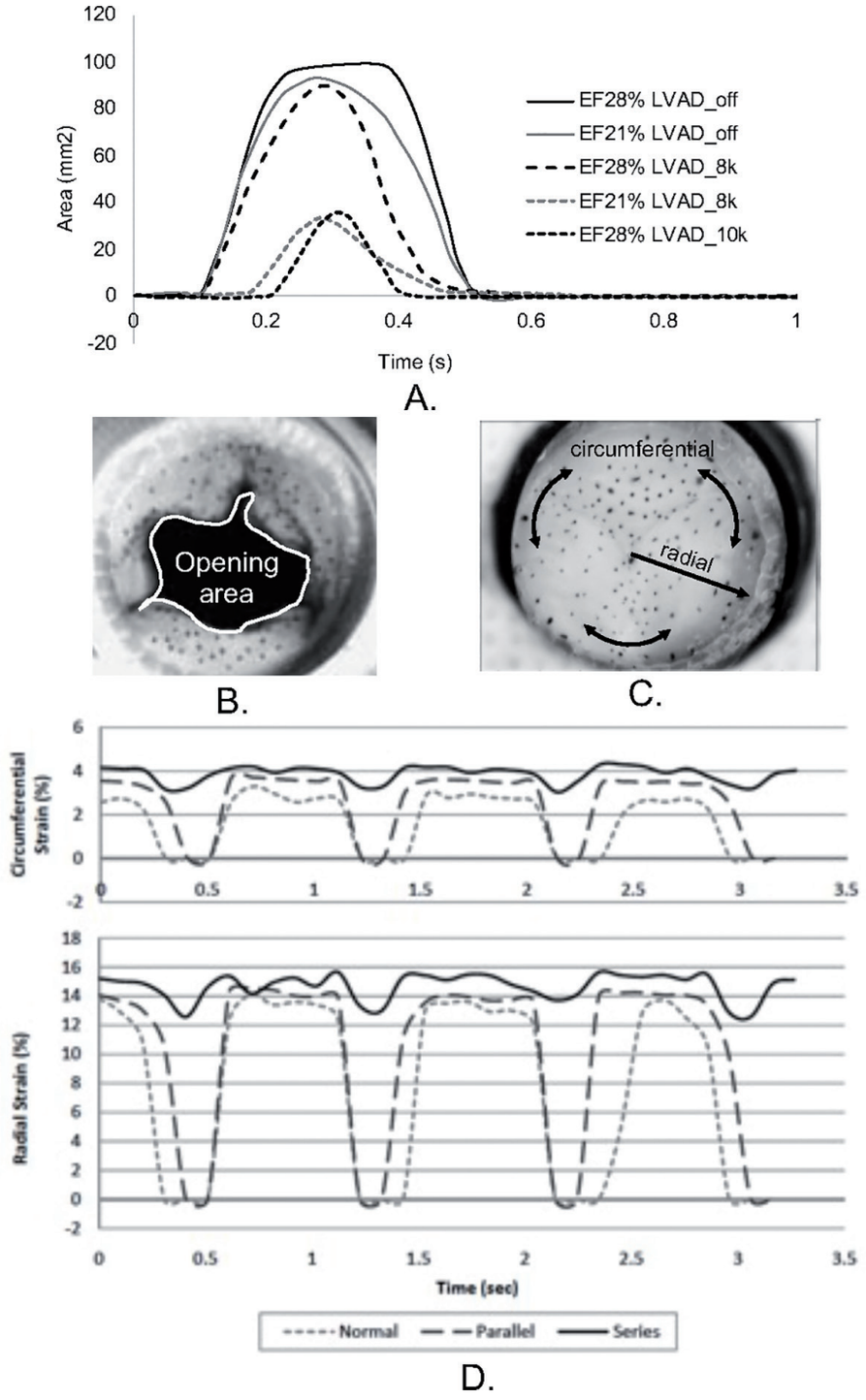

Figure 7.
A. Aortic valve opening area and duration with different cardiac function and LVAD support, B. Aortic valve opening area, C. Surface marker movement was used to measure stretch in the circumferential (hoop) and radial directions D. Stretch is highest for series flow when the aortic valve remains closed.

more compliant in the radial direction. This behavior corresponds to the alignment of collagen fibers with the circumferential direction, termed the anisotropy of the tissue. The peak stretch increases and extends for a longer duration as the normal flow pattern is compared to LVAD parallel and series conditions (**Figure 7**). Thus, the valve tissue experiences large and continuous tensile loading and significantly reduced ventricular shear during LVAD support.

5. Aortic valve commissural fusion during LVAD support

The AV leaflet tissue varies in thickness, being thicker at the free margin and annulus and thinner in the belly and coaptation areas. The leaflet tissue is composed of a layered structure of collagen, elastin, and proteoglycans. The textured fibrosa is a dense layer of circumferentially oriented collagen along the aortic face and bears most of the mechanical load [47]. The smooth ventricularis is an elastin layer adjacent to the ventricle, and the spongiosa is a central layer of loose connective tissue [47]. Naturally arising AV disease is preceded by tissue changes that occur over decades. Previous studies have shown that these are side-specific [48], manifesting as focal lesions that form preferentially from the aortic face, whereas the ventricular face is relatively disease-protected [49].

Post-transplant evaluation of LVAD-supported hearts has revealed the presence of extensive tissue remodeling of the AV, particularly commissural fusion, in 71–88% of LVAD patients [50, 51]. Aortic leaflet fusion creates adhesions between adjacent leaflets, preventing the complete opening of the valve [52, 53]. Increased fusion has been correlated with a longer duration of LVAD support [1, 6, 20] and with the development of AI [4, 51–53]. The aortic leaflets become more fibrotic and lose their elastic layer in the fusion areas, resulting in pathological remodeling, which progresses from the annulus towards the center of the valve (**Figure 8**). In contrast to naturally occurring AV disease, focal lesions arise from the ventricularis layer on the opposite side, as shown in **Figure 9** [17]. The hypothesis for this manifestation of valve dysregulation is that the high and continuous transvalvular pressure produces stretch and bending that is highest in the ventricular layer, activating a cellular process that results in extracellular matrix alterations. Fibrotic tissue often undergoes a consolidation and contraction stage, which preferentially affects the ventricular surface and may contribute to the improper coaptation that produces AI.

6. Valve mechanobiology during LVAD support

As explained previously, the addition of the LVAD to the heart results in a sudden increase in the pressure loading of the AV, in which tensile stress is increased, and shear is attenuated [54]. Each of these mechanical signals has been shown to play an important role in the progression of AV disease [43]. Evidence for the impact of LVAD-related increased tensile stretch and reduced shear stress on valve leaflets is found in extensive studies evaluating the role of mechanobiology in calcific AV

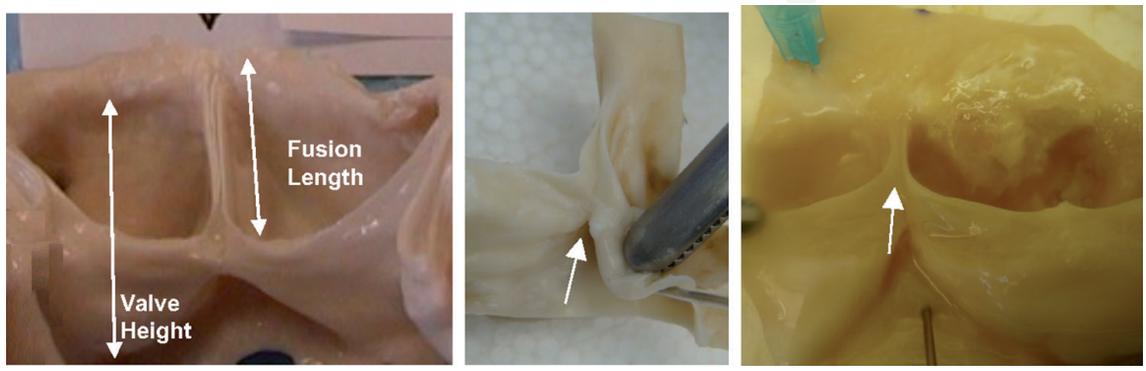

Figure 8.
Images of complete (left) and partial (center and right; location at the white arrow) commissural fusion of aortic valve leaflets following LVAD support.

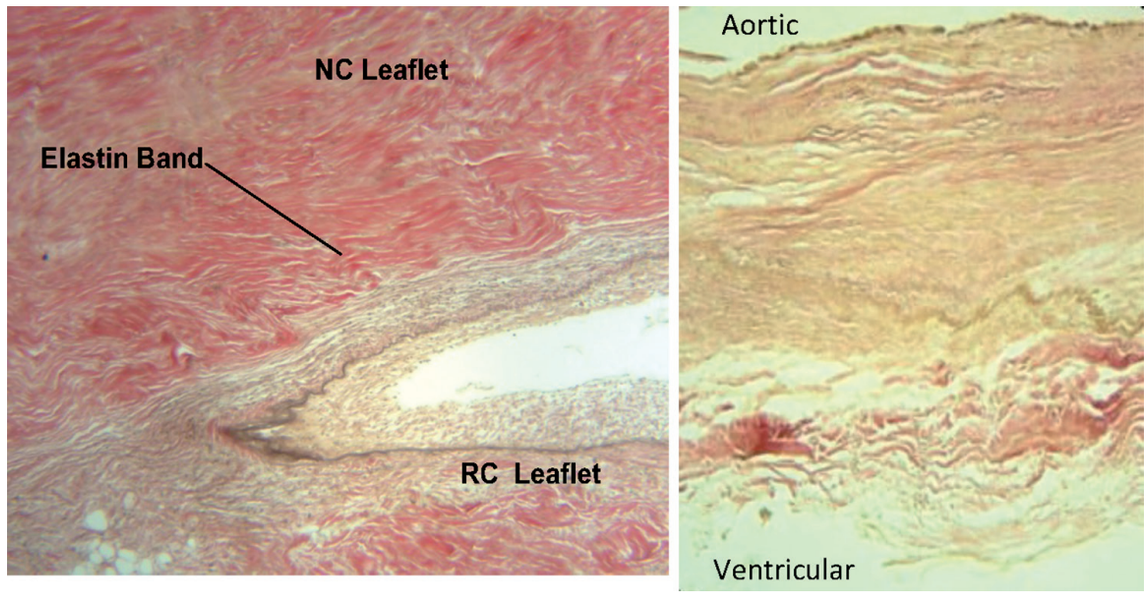

Figure 9.
Microscopic evaluation of aortic valve fusion from LVAD-supported hearts shows evidence of loss of the elastin band where the leaflets fuse together (left) and fibrosis arising from the ventricular face (right).

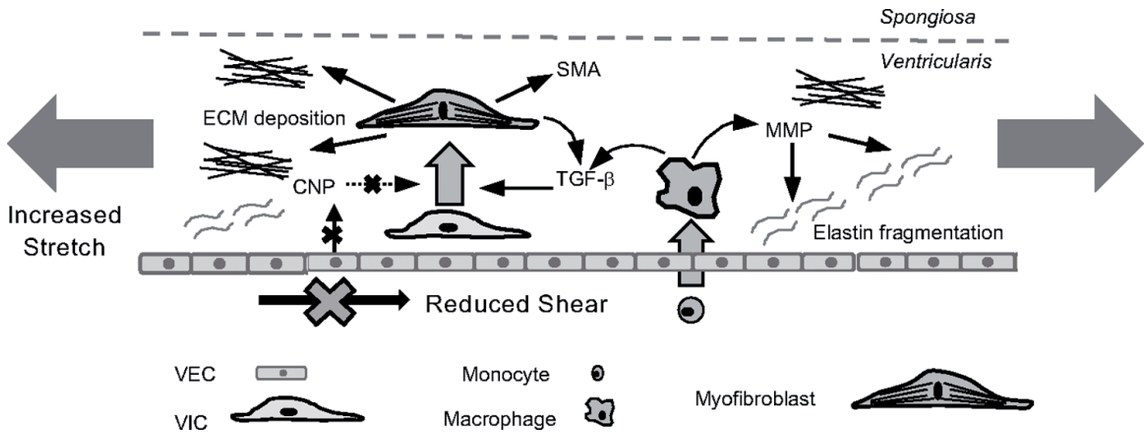

Figure 10.
LVAD support produces increased stretch and reduced shear in the ventricular layer of the aortic valve leaflet, which initiates a response resulting in ECM deposition and elastin fragmentation. The subsequent contraction of collagen in the ventricularis reduces leaflet coaptation, eventually resulting in AI.

disease and is illustrated in **Figure 10**. While this pathology manifests over a longer time and usually arises from the aortic surface of the leaflet, the same cell types are present in LVAD patients and respond to biochemical cues in the same way.

The cells responsible for valve tissue remodeling include the valvular endothelial cells (VECs), which reside in a single layer along the blood-contacting surfaces, and valvular interstitial cells (VICs), the more abundant cell type that resides throughout the tissue and is responsible for extracellular matrix maintenance [43]. VICs are usually quiescent and fibroblast-like but can be activated by abrupt changes in mechanical stress or when in a diseased state. VICs may translate between phenotypes to maintain homeostasis and can subsequently differentiate into other cell types, such as myofibroblasts, once activated [55]. Increased stretch provides a stimulus for VICs to increase collagen production and remodeling [56] by upregulating growth factors and integrins as cell-signaling mediators [57]. Stretch-activated VICs increase the production of

collagen and remodeling enzymes, which can lead to fibrosis and calcification. As the disease progresses, the differentiation of VICs to myofibroblasts can be identified by increased α smooth muscle actin (α-SMA) expression. Myofibroblasts secrete ECM such as collagen and increase tension in the matrix fibers [58, 59] and are associated with the formation of ECM disarray and fibrosis [17, 30, 60]. Tissue macrophages synthesize enzymes associated with pathological remodeling, such as MMPs, that are not released by VICs. These enzymes degrade elastin, disrupt collagen organization [61, 62] and potentiate the pathological differentiation of VICs into myofibroblasts.

The pathological differentiation of VICs into myofibroblasts is promoted by large numbers of tissue macrophages in the ventricularis layer, which contributes to the overproduction of TGF-β. Side-specific shear also plays a key role in modulating the valve tissue. VECs on the aortic side of normal valves, which experience low shear, have reduced expression of many cytokines that are known inhibitors of fibrosis and calcification compared with VECs on the ventricular side, which normally experience high shear [59]. When the high shear is virtually eliminated, as occurs with LVAD support, the expression of C-type natriuretic peptide (CNP), a paracrine factor shown to inhibit VIC differentiation, is reduced [59]. The reduction in CNP coupled with a dramatic increase in TGF-β further accelerates the population of myofibroblasts [63].

7. Prevention and treatment of AI in LVAD patients

The goals for AI management are to treat the symptoms, lower long-term consequences, and improve patient outcomes [64]. Patients with mild-moderate AI and normal aortic root size, or asymptomatic severe AI and regular LV size/function are usually managed with vasodilators [65], although many debates the effectiveness in delaying AV repair or replacement [64, 66]. Meanwhile, patients with symptomatic severe AI, asymptomatic severe AI, and systolic dysfunction/LV dilation require surgical management [67, 68]. Mild-moderate AI is often corrected at the time of LVAD implantation, especially in long-term supported patients, or in those with larger body sizes and large aortic root diameters (>3.3 cm) [6, 23, 69].

Surgical treatment is selected based on the candidate's underlying pathology, LVAD support duration, and INTERMACS classification to allow the possibility of LV recovery by maintaining the native AV structure and function (**Figure 11**) [6, 69–71]. Without any repair procedure, pre-existing mild AI is three times more likely to progress to moderate-severe AI [23]. Other complications worsen in the long term, including right ventricle dysfunction, mitral and tricuspid regurgitations [24].

7.1 Partial closure central park stitch/modified park stitch

The Park Stitch includes a single, pledgeted 4–0 Prolene suture placed at the central portion of the AV leaflets [70]. It is effective when the original valvular tissue is sufficiently thick and has enough tensile strength to hold the sutures. Alternatively, the modified Park stitch, consisting of stitches securing pledgets with individual commissural at the AV center, is recommended when the valve leaflets are relatively thin [72]. The recipients are monitored carefully during LVAD speed regulation and ramp testing to avoid stitch rupture from sudden AV opening [18]. These techniques have debatable durability: at 4–6 months post-implant, approximately 20% moderate-worse AI recurrence rate occurred in some centers [69, 73], while others reported a much lower rate (0 to 7%) [6, 72].

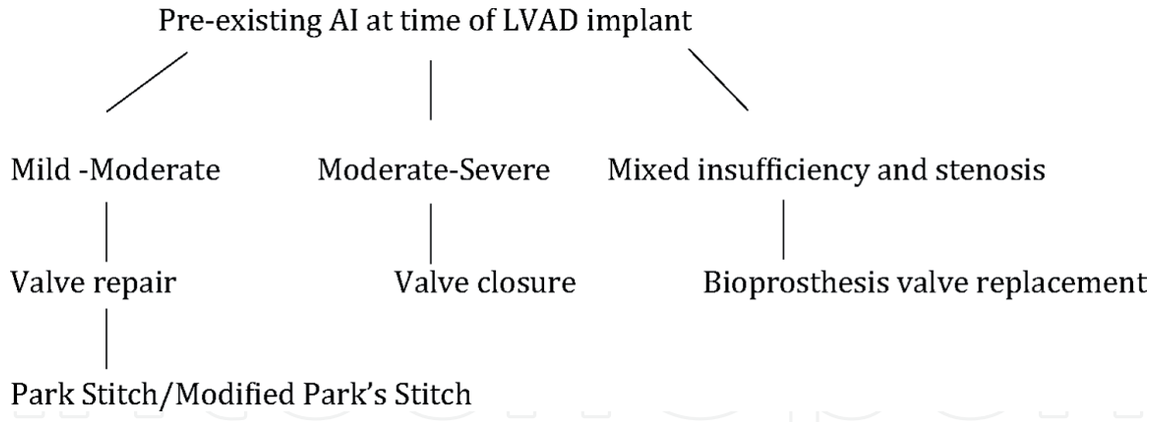

Figure 11.
Summary of the current treatment guidelines for pre-existing AI at the time of LVAD implant [6, 69–71].

7.2 Complete valve closure

Complete AV closure is recommended for patients with degenerative AV (leaflet prolapse or mal-coaptation) [18]. This procedure is performed by suturing felt strips to the leaflets or using a patch to cover the valve annulus directly. In the presence of a bioprosthesis, the valve is removed, and a pericardial patch is used to close the outflow tract [71, 74]. This procedure is durable with no AV deterioration or recurrent AI but induces a potential risk of thrombosis and restricts the possibility of myocardial recovery [18, 69, 71].

7.3 AV replacement

In patients with mixed stenosis or calcific pathology and insufficient AV, the valve can be replaced with a bioprosthesis. While allowing the possibility of AV opening, myocardial recovery, and pump removal, the limitations include a high risk of thrombosis, leaflet fusion, or stenosis [18, 21].

In post-LVAD patient management, AV structure and AI progression are monitored with routine echocardiography [75]. Intermittent AV opening was found to reduce the risk of AI development and improve LV systolic function and ejection fraction (especially in patients with preoperative short HF duration) [5, 6, 20, 22]. Optimization of pump speed (defined as the lowest possible LVAD support level to maintain adequate cardiac output and oxygen) is generally performed in case of mild AI to prevent worsening [6, 76]. If the patient's condition does not improve, surgical intervention will be performed. Approximately 5–10% of LVAD patients require AI-correction procedures after three or more years of LVAD support [6].

8. Conclusion

AI is a common complication affecting morbidity and mortality in LVAD patients. While the de novo AI development mechanism is unknown, it was linked to commissural fusion, lack of AV opening, and alteration of valvular tissue mechanics. Pre-existing AI also worsens in post-LVAD, interfering with the pump benefits.

Author details

Vi Vu* and Karen May-Newman
San Diego State University, San Diego, CA, USA

*Address all correspondence to: vtvu@sdsu.edu

IntechOpen

References

[1] Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. Circulation. Heart Failure. 2010;**3**(6):668-674

[2] Aggarwal A, Raghuvir R, Eryazici P, Macaluso G, Sharma P, Blair C, et al. The development of aortic insufficiency in continuous-flow left ventricular assist device–supported patients. The Annals of Thoracic Surgery. 2013;**95**(2):493-498

[3] Bryant AS, Holman WL, Nanda NC, Vengala S, Blood MS, Pamboukian SV, et al. Native aortic valve insufficiency in patients with left ventricular assist devices. The Annals of Thoracic Surgery. 2006;**81**(2):e6-e8

[4] Samuels LE, Thomas MP, Holmes EC, Narula J, Fitzpatrick J, Wood D, et al. Insufficiency of the native aortic valve and left ventricular assist system inflow valve after support with an implantable left ventricular assist system: Signs, symptoms, and concerns. The Journal of Thoracic and Cardiovascular Surgery. 2001;**122**(2):380-381

[5] Pak SW, Uriel N, Takayama H, Cappleman S, Song R, Colombo PC, et al. Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices. The Journal of Heart and Lung Transplantation. 2010;**29**(10):1172-1176

[6] Jorde UP, Uriel N, Nahumi N, Bejar D, Gonzalez-Costello J, Thomas SS, et al. Prevalence, significance, and Management of Aortic Insufficiency in continuous flow left ventricular assist device recipients. Circulation. Heart Failure. 2014;**7**(2):310-319

[7] Ben-ali W, Bouhout I, Lambert J, Bouchard D, Carrier M. Prevalence and impact of de novo aortic insufficiency during long-term support on a left ventricular assist device: A SYSTEMATIC review and META-analysis. Canadian Journal of Cardiology. 2017;**33**(10):S68-S69

[8] Coffey S, Cox B, Williams MJA. Lack of progress in valvular heart disease in the pre–transcatheter aortic valve replacement era: Increasing deaths and minimal change in mortality rate over the past three decades. American Heart Journal. 2014;**167**(4):562-567.e2

[9] Kormos RL, Cowger J, Pagani FD, Teuteberg JJ, Goldstein DJ, Jacobs JP, et al. The Society of Thoracic Surgeons Intermacs database annual report: Evolving indications, outcomes, and scientific partnerships. The Journal of Heart and Lung Transplantation. 2019;**38**(2):114-126

[10] Grant ADM, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. Journal of the American College of Cardiology. 2012;**60**(6):521-528

[11] Schlöglhofer T, Wittmann F, Paus R, Riebandt J, Schaefer AK, Angleitner P, et al. When nothing goes right: Risk factors and biomarkers of right heart failure after left ventricular assist device implantation. Life. 2022;**12**(3):459

[12] Malick A, Ning Y, Kurlansky PA, Melehy A, Yuzefpolskaya M, Colombo PC, et al. Development of De novo aortic insufficiency in patients with HeartMate 3.

The Annals of Thoracic Surgery. Aug 2022;**114**(2):450-456

[13] Truby LK, Garan AR, Givens RC, Wayda B, Takeda K, Yuzefpolskaya M, et al. Aortic insufficiency during contemporary left ventricular assist device support. JACC. Heart Failure. 2018;**6**(11):951-960

[14] Deo SV, Sharma V, Cho YH, Shah IK, Park SJ. De novo aortic insufficiency during long-term support on a left ventricular assist device: A Systematic review and Meta-analysis. ASAIO Journal. 2014;**60**(2):183-188

[15] Patil NP, Sabashnikov A, Mohite PN, Garcia D, Weymann A, Zych B, et al. De novo aortic regurgitation after continuous-flow left ventricular assist device implantation. The Annals of Thoracic Surgery. 2014;**98**(3):850-857

[16] Imamura T, Narang N, Kim G, Nitta D, Fujino T, Nguyen A, et al. Aortic insufficiency during HeartMate 3 left ventricular assist device support. Journal of Cardiac Failure. Oct 2020;**26**(10):863-869

[17] John R, Mantz K, Eckman P, Rose A, May-Newman K. Aortic valve pathophysiology during left ventricular assist device support. Journal of Heart and Lung Transplantation. Dec 2010;**29**(12):1321-1329

[18] Cowger J, Rao V, Massey T, Sun B, May-Newman K, Jorde U, et al. Comprehensive review and suggested strategies for the detection and management of aortic insufficiency in patients with a continuous-flow left ventricular assist device. Journal of Heart and Lung Transplantation. Feb 2015;**34**(2):149-157

[19] Tanaka Y, Nakajima T, Fischer I, Kotkar K, Moon M, Damiano R, et al. The Impact of Uncorrected Mild Aortic Insufficiency at the Time of Left Ventricular Assist Device Implantation. Toronto, Canada: AATS Annual Meeting; 2019

[20] Cowger JA, Aaronson KD, Romano MA, Haft J, Pagani FD. Consequences of aortic insufficiency during long-term axial continuous-flow left ventricular assist device support. The Journal of Heart and Lung Transplantation. 2014;**33**(12):1233-1240

[21] Garcia MAZ, Enriquez LA, Dembitsky W, May-Newman K. The effect of aortic valve incompetence on the hemodynamics of a continuous flow ventricular assist device in a mock circulation. ASAIO Journal. 2008;**54**(3):237-244

[22] Imamura T, Kinugawa K, Fujino T, Inaba T, Maki H, Hatano M, et al. Aortic insufficiency in patients with sustained left ventricular systolic dysfunction after axial flow assist device implantation. Circulation Journal. 2014;**79**(1):104-111

[23] Fukuhara S, Ikegami H, Polanco AR, Song JJ, Han J, Takeda K, et al. Concomitant repair for mild aortic insufficiency and continuous-flow left ventricular assist devices. European Journal of Cardio-Thoracic Surgery. 2017;**52**(6):1062-1068

[24] Tanaka Y, Nakajima T, Fischer I, Wan F, Kotkar K, Moon MR, et al. The impact of uncorrected mild aortic insufficiency at the time of left ventricular assist device implantation. The Journal of Thoracic and Cardiovascular Surgery. Dec 2020;**160**(6):1490-1500.e3

[25] Imamura T, Kinugawa K. Preoperative prediction of aortic

insufficiency during ventricular assist device treatment. International Heart Journal. 2016;**57**(1):3-10

[26] Gregory SD, Stevens MC, Wu E, Fraser JF, Timms D. In vitro evaluation of aortic insufficiency with a rotary left ventricular assist device. Artificial Organs. Sep 2013;**37**(9):802-809

[27] Stanfield JR, Selzman CH. In vitro Pulsatility analysis of axial-flow and centrifugal-flow left ventricular assist devices. Journal of Biomechanical Engineering. 2013;**135**(3):034505

[28] Soucy KG, Koenig SC, Giridharan GA, Sobieski MA, Slaughter MS. Defining pulsatility during continuous-flow ventricular assist device support. The Journal of Heart and Lung Transplantation. 2013;**32**(6):581-587

[29] Tolpen S, Janmaat J, Reider C, Kallel F, Farrar D, May-Newman K. Programmed speed reduction enables aortic valve opening and increased Pulsatility in the LVAD-assisted heart. ASAIO Journal. 2015;**61**(5):540-547

[30] Travis AR, Giridharan GA, Pantalos GM, Dowling RD, Prabhu SD, Slaughter MS, et al. Vascular pulsatility in patients with a pulsatile- or continuous-flow ventricular assist device. Journal of Thoracic and Cardiovascular Surgery. 2007;**133**(2):517-524

[31] May-Newman K, Wong YK, Adamson R, Hoagland P, Vu V, Dembitsky W. Thromboembolism is linked to intraventricular flow stasis in a patient supported with a left ventricle assist device. ASAIO Journal. 2013;**59**(4):452-455

[32] Lopilato AC, Doligalski CT, Caldeira C. Incidence and risk factor analysis for gastrointestinal bleeding and pump thrombosis in left ventricular assist device recipients: Hemostastic complications in LVAD recipients. Artificial Organs. 2015;**39**: 11, 939-944

[33] Mahr C, Chivukula VK, McGah P, Prisco AR, Beckman JA, Mokadam NA, et al. Intermittent aortic valve opening and risk of thrombosis in ventricular assist device patients. ASAIO Journal. 2017;**63**(4):425-432

[34] Hendabadi S, Bermejo J, Benito Y, Yotti R, Fernandez-Aviles F, del Alamo JC, et al. Topology of blood transport in the human left ventricle by novel processing of Doppler echocardiography. Annals of Biomedical Engineering. 2013;**41**:12, 2603-2616

[35] Martinez-Legazpi P, Bermejo J, Benito Y, Yotti R, Perez Del Villar C, Gonzalez-Mansilla A, et al. Contribution of the diastolic vortex ring to left ventricular filling. Journal of the American College of Cardiology. 2014;**64**(16):1711-1721

[36] Pedrizzetti G, Domenichini F. Nature optimizes the swirling flow in the human left ventricle. Physical Review Letters. 2005;**95**(10):1-4

[37] Watanabe H, Sugiura S, Hisada T. The looped heart does not save energy by maintaining the momentum of blood flowing in the ventricle. American Journal of Physiology Heart and Circulatory Physiology. 2008;**294**(5):H2191-H2196

[38] Hong GR, Pedrizzetti G, Tonti G, Li P, Wei Z, Kim JK, et al. Characterization and quantification of vortex flow in the human left ventricle by contrast echocardiography using vector particle image velocimetry. JACC Cardiovascular Imaging. 2008;**1**(6):705-717

[39] Carlha CJ, Bolger A. Advances in heart failure passing strange flow in the failing ventricle. Circulation Heart Failure. 2010;**3**:326-331

[40] Bermejo J, Benito Y, Alhama M, Yotti R, Martinez-Legazpi P, Del Villar CP, et al. Intraventricular vortex properties in nonischemic dilated cardiomyopathy. American Journal of Physiology Heart and Circulatory Physiology. 2014;**306**(5):H718-H729

[41] Rossini L, Braun OÖ, Brambatti M, Benito Y, Mizeracki A, Miramontes M, et al. Intraventricular flow patterns in patients treated with left ventricular assist devices. ASAIO Journal. 2021;**67**(1):74-83

[42] Kirklin JK, Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, et al. Interagency registry for mechanically assisted circulatory support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. Journal of Heart and Lung Transplantation. 2014;**33**(1):12-22

[43] Sacks MS, Yoganathan AP. Heart valve function: a biomechanical perspective. Philosophical Transactions of the Royal Society B: Biological Sciences. 2007;**362**(1484):1369-1391

[44] Beck A, Thubrikar MJ, Robicsek F. Stress analysis of the aortic valve with and without the sinuses of valsalva. The Journal of Heart Valve Disease. 2001;**10**(1):1-11

[45] Weston MW, LaBorde DV, Yoganathan a P. Estimation of the shear stress on the surface of an aortic valve leaflet. Annals of Biomedical Engineering. 1999;**27**(4):572-579

[46] Ge L, Sotiropoulos F. Direction and magnitude of blood flow shear stresses on the leaflets of aortic valves: Is there a link with valve calcification? Journal of Biomechanical Engineering. 2010;**132**(1):14505

[47] Thubrikar M. The Aortic Valve. Boca Raton, FL: CRC Press; 1989

[48] Sider KL, Blaser MC, Simmons CA. Animal models of calcific aortic valve disease. International Journal of Inflammation. 2011;**2011**:364310

[49] Yip CYY, Simmons C. a. the aortic valve microenvironment and its role in calcific aortic valve disease. Cardiovascular pathology: the Official Journal of the Society for Cardiovascular Pathology. 2011;**20**(3):177-182

[50] Mudd JO, Cuda JD, Halushka M, Soderlund KA, Conte JV, Russell SD. Fusion of aortic valve commissures in patients supported by a continuous axial flow left ventricular assist device. The Journal of Heart and Lung Transplantation. 2008;**27**(12):1269-1274

[51] May-Newman K, Mendoza A, Abulon DJK, Joshi M, Kunda A, Dembitsky W. Geometry and fusion of aortic valves from pulsatile flow ventriuclar assist device patients. The Journal of Heart Valve Disease. 2011;**20**(2):149-158

[52] Rose AG, Park SJ, Bank AJ, Miller LW. Partial aortic valve fusion induced by left ventricular assist device. The Annals of Thoracic Surgery. 2000;**70**(4):1270-1274

[53] Connelly J. Acquired commissural fusion of aortic valves in patients with left ventricular assist devices. The Journal of Heart and Lung Transplantation. 2003;**22**(12):1291-1295

[54] Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL,

et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. The Journal of Heart and Lung Transplantation. 2017;**36**(10):1080-1086

[55] Bouabdallaoui N, El-Hamamsy I, Pham M, Giraldeau G, Parent MC, Carrier M, et al. Aortic regurgitation in patients with a left ventricular assist device: A contemporary review. The Journal of Heart and Lung Transplantation. 2018;**37**(11):1289-1297

[56] Tilea I, Suciu H, Tilea B, Maria C, Ispas M, Constantin R. Anatomy and Function of Normal Aortic Valvular Complex. London, UK: Calcific Aortic Valve Disease. InTech; 2013

[57] Denolin H, Kuhn H, Krayenbuehl H, Loogen F, Reale A. The defintion of heart failure. European Heart Journal. 1983;**4**(7):445-448

[58] Walker GA, Masters KS, Shah DN, Anseth KS, Leinwand LA. Valvular Myofibroblast activation by transforming growth factor-β: Implications for pathological extracellular matrix remodeling in heart valve disease. Circulation Research. 2004;**95**(3):253-260

[59] Rajamannan NM, Evans FJ, Aikawa E, Grande-Allen KJ, Demer LL, Heistad DD, et al. Calcific aortic valve disease: Not simply a degenerative process: A review and agenda for research from the National Heart and lung and Blood institute aortic stenosis working group executive summary: Calcific aortic valve disease – 2011 update. Circulation. 2011;**124**(16):1783-1791

[60] Gharib M, Kremers D, Koochesfahani M, Kemp M. Leonardo's vision of flow visualization. Experiments in Fluids. 2002;**33**(1):219-223

[61] Fondard O, Detaint D, Iung B, Choqueux C, Adle-Biassette H, Jarraya M, et al. Extracellular matrix remodelling in human aortic valve disease: The role of matrix metalloproteinases and their tissue inhibitors. European Heart Journal. 2005;**26**(13):1333-1341

[62] Aikawa E, Aikawa M, Libby P, Figueiredo JL, Rusanescu G, Iwamoto Y, et al. Arterial and aortic valve calcification abolished by Elastolytic Cathepsin S deficiency in chronic renal disease. Circulation. 2009;**119**(13):1785-1794

[63] van Rijswijk JW, Vink A, Martina JR, Ramjankhan FZ, Goldschmeding R, de Jonge N, et al. Pathology of aortic valve remodeling after continuous-flow left ventricular assist device support. The Journal of Heart and Lung Transplantation. 2017;**36**(1):113-116

[64] Maurer G. Aortic regurgitation. Heart. 2006;**92**(7):994-1000

[65] Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation. 2002;**106**(21):2687-2693

[66] Carabello BA. Vasodilators in aortic regurgitation — Where is the evidence of their effectiveness? The New England Journal of Medicine. 2005;**353**(13):1400-1402

[67] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the Management of Patients with Valvular Heart Disease. Journal of the American College of Cardiology. 2014;**63**(22):e57-e185

[68] Nash PJ, Vitvitsky E, Li J, Cosgrove DM, Pettersson G, Grimm RA. Feasibility of valve repair for Regurgitant bicuspid aortic valves—An echocardiographic study. The Annals of Thoracic Surgery. 2005;**79**(5):1473-1479

[69] Robertson JO, Naftel DC, Meyers SL, Kirklin JK, Mertz GD, Prasad S, et al. Concomitant aortic valve procedures in patients undergoing implantation of continuous-flow LVADs: An INTERMACS database analysis. The Journal of Heart and Lung Transplantation. 2015;**34**(6):797-805

[70] Park SJ, Liao KK, Segurola R, Madhu KP, Miller LW. Management of aortic insufficiency in patients with left ventricular assist devices: a simple coaptation stitch method (Park's stitch). The Journal of Thoracic and Cardiovascular Surgery. 2004;**127**(1):264-266

[71] Adamson RM, Dembitsky WP, Baradarian S, Chammas J, May-Newman K, Chillcott S, et al. Aortic valve closure associated with HeartMate left ventricular device support: Technical considerations and long-term results. The Journal of Heart and Lung Transplantation. 2011;**30**(5):576-582

[72] Morgan JA, Brewer RJ. Modified central closure technique for treatment of aortic insufficiency in patients on left ventricular assist device support. ASAIO Journal. 2012;**58**(6):626-628

[73] Goda A, Takayama H, Pak SW, Uriel N, Mancini D, Naka Y, et al. Aortic valve procedures at the time of ventricular assist device placement. The Annals of Thoracic Surgery. 2011;**91**(3):750-754

[74] Savage EB, d'Amato TA, Magovern JA. Aortic valve patch closure: An alternative to replacement with HeartMate LVAS insertion. European Journal of Cardio-Thoracic Surgery. Sep 1999;**16**(3):359-361

[75] Estep JD, Stainback RF, Little SH, Torre G, Zoghbi WA. The role of echocardiography and other imaging modalities in patients with left ventricular assist devices. JACC: Cardiovascular Imaging. 2010;**3**(10):1049-1064

[76] Holtz J, Teuteberg J. Management of Aortic Insufficiency in the continuous flow left ventricular assist device population. Current Heart Failure Reports. 2014;**11**(1):103-110