Preoperative Prediction of Aortic Insufficiency During Ventricular Assist Device Treatment

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SUMMARY

Survival rate in patients with stage D heart failure has improved significantly owing to the development of continuous flow left ventricular assist devices (LVAD), but aortic insufficiency (AI) still remains one of the major unsolved complications that impair patient quality of life. There are no established treatments for AI, and preoperative prediction and prevention of AI is needed. The opening of a native aortic valve (AV) is a sufficient condition for prevention of AI, and improvement of LV ejection fraction due to LV reverse remodeling (LVRR) is essential to open a native AV. Preoperative insufficient β-blocker treatment and pulsatile flow LVAD usage are keys for LVRR, opening of an AV, and prevention of AI. The second mechanism that leads to AI is remodeling of the aortic root and degeneration of a native AV, which results from reduced pulse pressure during LVAD support. Pulsatile LVAD usage has an advantage in terms of preserving pulsatility, and may prevent AI compared with an axial pump. There is less probability of avoiding AI with sufficient β-blocker treatment, and these patients may be good candidates for concomitant surgical intervention to a native AV at the time of LVAD implantation. (Int Heart J 2016; 57: 3-10)

Key words: Pulsatility, VAD, Carvedilol, Aortic valve

Currently, the survival rate in patients with advanced heart failure (HF) has improved due to the development of continuous flow (CF) left ventricular assist device (LVAD) treatment and improvement of perioperative management procedures. However, quality of life during CF LVAD is still not satisfactory because of several unresolved postoperative complications. One of the major complications is aortic insufficiency (AI), which is characterized as continuous aortic regurgitation during both systolic and diastolic phases through a degenerated and occasionally fusional native aortic valve (AV) (Figure 1AB). Native AV, which is apparently normal before LVAD implantation, can be associated with a considerable level of AI after LVAD implantation. Post-LVAD AI can develop even in the preoperative setting in which there is no aortic regurgitation at all.

In 2000, Rose, et al first documented acquired AV disease during pulsatile flow (PF) LVAD. They identified evidence of commissural fusion of native AV. In 2006, Frazier, et al summarized the relationship between commissural fusion of native AV and development of AI during CF LVAD treatment. We also showed that AI was more frequently observed in patients with CF LVAD as compared with PF pump in 2011 (Figure 1C). Since then, a number of single-center studies have documented a wide-ranging prevalence of AI during LVAD treatment.

The development of AI during LVAD treatment is considered to be a multifactorial phenomenon and a result of altered AV and aortic root biomechanics due to chronic and continuous ventricular unloading. Unloading of LV results in ventricular decompression, and the combination of systolic dysfunction and low preload cannot generate sufficient pressure to open the native AV. With scarce opening of a native AV, arterial pressure becomes minimally pulsatile. Thus, a native AV is exposed to elevated diastolic aortic pressure and increased transvalvular pressure. The incremental transvalvular pressure is reversely directed toward native AV since aortic pressure is higher than LV pressure for most of the cardiac cycle, and it is not at all physiological. The increases in magnitude and duration of transvalvular pressure load may make native AV degenerate along with annular deformation, which ultimately lead to regurgitation.

AI reduces systemic output because LVAD flow is stolen backward. Not surprisingly, AI worsens the HF symptoms with elevated LV filling pressure due to retrograde aortic flow as we showed previously. Consistently, AI decreases patient exercise tolerability, because LVAD flow alone cannot satisfy output demand during exercise (Figure 2A). Many studies including ours (Figure 2B) have agreed that the development of AI did not increase mortality, although this is still controversial. However, the re-admission rate due to cardiovascular events (ventricular tachyarrhythmias or stroke) was higher in patients with AI (Figure 2B). Enhanced intra-cardiac pressure may precipitate the risk of ventricular tachyarrhythmias. Turbulence due to scarce forward flow through a native AV may facilitate the formation of thrombus in the aortic root.
Figure 1. A typical case of AI in a patient with EVAHEART. A long-axis parasternal view of transthoracic echocardiography (A). Partial fusion formation of native AV between right coronary and non-coronary cusps was observed at the timing of heart transplantation (B). Freedom rate from AI is compared between patients with PF and those with CF LVAD (C).

Figure 2. Exercise tolerability (A) and prognosis in patients (B) with or without AI. PVO₂ indicates peak oxygen consumption; and 6MWD, 6-minute walk distance. *P < 0.05 by the log-rank test, †P < 0.05 by unpaired t-test compared with AI group.
According to the ISHLT guidelines, more than mild aortic regurgitation should prompt consideration for surgical intervention at the time of LVAD implantation (Class I, Level of Evidence C) to avoid hemodynamic loss of LVAD flow. Aortic mechanical prostheses are never recommended because subvalvular thrombosis is more likely to occur with infrequent opening of the AV. Therefore, a bioprosthetic valve is a common choice for this situation.

On the other hand, there are no established treatments for post-LVAD AI. Lower rotation speed is sometimes indicated to reduce the grade of AI, but it may be associated with a higher risk of pump thrombosis, lower exercise tolerability, or inadequate stimulation of sympathetic activity. Some authors reported successful trans-catheter aortic valve replacement during LVAD support, but the procedure has a risk of migration of the replaced device owing to the strong vacuum of blood into apical VAD inflow. Native AV can be replaced with a bioprosthetic valve, but newly placed biologic valves are still at risk for the development of postoperative AI. Park, et al first reported a simple technique of concomitant AV repair at the time of LVAD implantation (Park’s stitch), but the repair also carries a risk for recurrence of AI. Patch closure of the outflow tract is another strategy. While the procedure can be a definite solution for AI, it ruins the possibility of myocardial recovery, and increases the risk of serious decompensation or mortality. Native AV closure by an Amplatzer septal occluder has also been reported.

As such, once AI develops during LVAD treatment, another open-heart surgical procedure or catheter-based intervention may be needed with inevitably high risk. If a precise prediction of AI before LVAD implantation can be made, some appropriate intervention may be performed concomitantly with LVAD surgery at a relatively low risk. Recently, we have reported several predictors for AI development after LVAD implantation, and we will summarize them in this review.

Previously Reported Predictors of Post-LVAD AI

So far, several preoperative predictors of post-LVAD AI have been reported: CF LVAD usage, smaller body size, female gender, and large baseline aortic root diameter. We observed a consistently higher prevalence of AI in patients with CF LVAD. A recent meta-analysis revealed that preoperative predictors of AI were higher age and CF LVAD usage. Correlates of development or worsening of AI following LVAD implantation include increasing aortic root diameter, less frequent opening of native AV, AV commissural fusion, higher pump speeds, increased mitral regurgitation, and higher levels of B-type natriuretic peptide.

We recently proposed a “2-hit” theory for the development of AI (Figure 3). Few patients suffer AI when a native AV is open at rest. Slaughter, et al have stated that the opening of native AV at least once per 3 native heart beats may be sufficient to avoid development of AI and we and others define the opening of a native AV at > 30% of the native heart beats as “open.” On the other hand, AI always develops in patients with closed native AV. Closed AV is the first and sufficient condition for the development of AI.

**Figure 3.** A scheme of “2-hit theory” for the development of AI.

**Preoperative β-blocker Treatment and LV Reverse Remodeling (LVRR)**

Native AV opens when the intra-cardiac pressure exceeds the pressure of the aortic root during the systolic phase. Under the circumstances with decreased preload by LV unloading, considerable recovery of systolic function may be indispensable to generate sufficient systemic pressure. As is well known, improvement of LV systolic function as well as reduction in LV cavity are observed among many patients under LVAD support, ie, LVRR. Therefore, we believe that LVRR is a key to open native AV and prevent AI.

As for the etiology, fulminant myocarditis or peripartum cardiomyopathy often recovers in terms of cardiac function and has an advantage over ischemic cardiomyopathy from the viewpoint of LVRR. Patients with a broad scar lesion, which is assessed by endomyocardial biopsy, cardiac magnetic resonance imaging, or myocardial scintigraphy, have less chance to achieve LVRR. Simon, et al showed that a short duration of HF is a positive factor to achieve LVRR during LVAD treatment, because remodeling is not severe in such myocardium and there is a chance to recover.

We have demonstrated that preoperative “insufficient” β-blocker treatment is a strong predictor of LVRR during LVAD treatment. The amount of β-blocker treatment here is quantified as a cumulative dose of β-blocker during the entire duration of HF. Patients with preoperative insufficient β-blocker treatment typically have too short a period to try sufficient β-blocker titration because of acute deterioration in hemodynamics, but many of them are responders to the post-LVAD titration of β-blocker. Cases with acute myocarditis or peripartum cardiomyopathy are usually treated for a relatively short period (less than 6 months) before LVAD insertion, and the etiology is by itself closely related with the cumulative amount of β-blocker in such cases. A low cumulative dose of β-blocker (less than 4.5 g of carvedilol-equivalent dose) was associated with considerable improvement of LVEF (> 25%). Among them, patients with a very low cumulative dose of β-blocker (less than 1.6 g of carvedilol-equivalent dose) were super-responders in terms of LVRR (LVEF ≥ 35% and/or explantation of LVAD within 6 months).

In contrast, patients who eventually received LVAD implantation despite preoperative sufficient β-blocker treatment are inevitably non-responders to β-blockers, and such patients rarely achieve LVRR even with unloading by LVAD. In animal
models, prolonged sufficient LV unloading by LVAD without \( \beta \)-blocker treatment could not facilitate LVRR, but rather increased the ratio of the myocardial fibrotic area, myocardial apoptosis, and cardiac stiffness.\(^{51,52}\) Considering the results, postoperative responsiveness to \( \beta \)-blocker may be essential to achieve LVRR in addition to the LV unloading.

We would like to note that this theory does not at all recommend intentional insufficient \( \beta \)-blocker treatment. We cannot predict responders to \( \beta \)-blocker beforehand. In many cases, we initiate and titrate the drug with every effort, and after 3-6 months of treatment we can finally determine the responsiveness of a \( \beta \)-blocker.\(^{53}\) Our idea for the cumulative dose of \( \beta \)-blocker with respect to LVRR is based on such a clinical setting that all cardiologists must have made every attempt in order to introduce a higher dose of \( \beta \)-blocker.\(^{59}\) If we are somehow able to determine the responsiveness to a \( \beta \)-blocker without treatment of the drug by a certain novel technique in the future, we may not need to take into account the history of HF treatment before LVAD implantation. We would have to completely rewrite our paper then, but we believe that it is not yet the time to do that.

**Pulsatile Device and LVRR**

Not only preoperative \( \beta \)-blocker therapy but also device selection may have a huge impact on the achievement of LVRR. PF devices unload the ventricle only during a certain part of the cardiac cycle, whereas CF devices do so continuously throughout the overall cardiac cycle.\(^{54}\) In animal experimental models, Bartoli, et al demonstrated that continuous unloading altered the physiologic profile of myocardial and vascular hemodynamic energy utilization, in contrast to pulsatile unloading that preserved normal physiology.\(^{55}\) Ootaki, et al showed a decrease in coronary blood flow by strong continuous LV unloading.\(^{56}\) Loebe, et al revealed that a PF LVAD was associated with less stimulation of the systemic inflammatory system as compared with a CF device.\(^{57}\) Accordingly, intermittent LV unloading may correlate positively to successful LVRR. We have also demonstrated in a clinical setting that PF LVAD had an advantage over CF pumps in terms of LVRR.\(^{58,59}\)

Now is the era of CF LVAD, and PF devices have a number of drawbacks compared with CF devices in terms of higher morbidity and mortality rates.\(^{3,4,7}\) However, when patients receive significantly insufficient \( \beta \)-blocker treatment preoperatively, it may be preferable to consider PF LVAD as a tar-
Opening of Native AV and AI

Responders to $\beta$-blocker treatment experience LVRR with LVEF $> 25\%$, and their native AV are open for at least $30\%$ of total heart beats at rest. With sufficient opening of native AV, such patients can avoid development of AI. Super-responders to $\beta$-blockers can achieve significant improvement of LVEF during LVAD treatment (LVEF $\geq 35\%$), and their native AV opens in $100\%$ of heart beats. They never experience AI, and we can even explant LVAD in some of them.

We have recently shown that some patients experience the opening of native AV only during exercise (see the typical case in Figure 4AB). LVRR is never observed since their LVEF remain $\leq 25\%$ and their native AV does not open at rest. In this sense, they are non-responders to $\beta$-blocker treatment, but they somehow maintain cardiac reserve for exercise. Such patients also avoid AI. Native AV might open frequently during daily life under light exertion. Although the “intermittent low speed” mode of the Jarvik 2000 may have an advantage in the prevention of AI due to the forced opening of native AV for 8 seconds per minute, no studies including ours have thus far demonstrated its clinical advantage.

Definite non-responders to $\beta$-blocker treatment, who received sufficient $\beta$-blocker treatment preoperatively, rarely achieve LVRR, and their LVEF remains at a low level ($\leq 25\%$), and their native AV never opens at rest or during exercise. Not surprisingly, we observed AI development in these patients very frequently.

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remodeling of the aortic root emerges along with thinning of the aortic wall under reduced pulsatility, which is attributable to apoptosis of smooth muscle cells and fragmentation of elastic fibers.\textsuperscript{56,59} Remodeling and dilatation of the aortic root is associated with a higher prevalence of AI as well as the degeneration of the aortic valve and enlargement of the aortic ring.\textsuperscript{20} Other than reduced pulsatility, we have to take into consideration geometric alteration of AV by commissural fusion and flow turbulence in the ascending aorta. Commisural fusion of native AV is not always observed in patients with AI,\textsuperscript{60} and may not be a mainstay of AI development. In contrast, flow turbulence, which increases wall shear stress and retrograde pressure in the aortic root, develops during LVAD support, especially when a native AV is closed.\textsuperscript{61} The degree of turbulence may also be affected by the location or direction of the LVAD outflow conduit anastomosis on the aorta.\textsuperscript{62} Inadequately excessive flow into the ascending aorta by LVAD pump may be another factor for increasing turbulence.\textsuperscript{56}

Although lower rotation speed is usually associated with higher pulse pressure and appears to have an advantage in preventing AI, it has a risk of pump thrombosis or low output syndrome. Pulsatility is more preserved during centrifugal LVAD support than during axial pump support, because pump flow changes more dramatically depending on the pressure gradient between the LV and aorta in a centrifugal pump as compared with an axial device.\textsuperscript{63,64} Consistently, we previously showed that patients receiving a centrifugal pump had larger pulse pressure than those with an axial pump.\textsuperscript{123} The differences in pulse pressure may be attributable to a less enlarged aortic root and less frequent AI in patients with centrifugal LVAD.\textsuperscript{63} When patients received sufficient \(\beta\)-blocker treatment during long-term HF duration preoperatively, a centrifugal pump may be a better selection than an axial pump, targeting both preservation of pulse pressure and prevention of AI (Figure 7D).

Although the clinical relevance of pulsatile device is decreasing nowadays, pulsatility can be best preserved with PF LVAD by its nature. Pulsatile flow by itself facilitates LVRR as described above, but preserved pulsatility in the aortic pressure also contributes to minimize the development of AI. Accordingly, both LVRR and preserved pulsatility well explain the advantage of PF LVAD over CF LVAD in terms of AI development.\textsuperscript{65}

The advantage of preserved pulsatility has increasingly been acknowledged, and several attempts during CF LVAD treatment are emerging.\textsuperscript{9} A centrifugal HeartWare LVAD has a cyclic controlled speed change function (Lavare Cycle) mode; this allows for changes in LV filling and flow rate.\textsuperscript{66} Another centrifugal HeartMate III LVAD has an induced pulse mode for achieving an increased level of pulsatility with CF assistance.\textsuperscript{67} An effort to preserve pulse pressure during LVAD therapy would be a future direction, although the precise target level of pulsatility remains uncertain.

**Relationship Between Preoperative Condition and Post-LVAD AI**

Finally, we would like to summarize the relationship between the preoperative condition and post-LVAD AI in Figure 7. Patients with insufficient \(\beta\)-blocker treatment (in other words, those who do not have enough time for the titration of \(\beta\)-blocker) can achieve LVRR with full opening of a native AV, and avoid AI. HF duration in these patients is usually less than 1 year. Such patients enjoy good clinical courses including explantation of LVAD or at least stable hemodynamics without AI (Figure 7A). Some patients can achieve partial LVRR, and they experience the partial opening of native AV at rest (Figure 7B). Others do not achieve LVRR but maintain cardiac reserve for exercise. They do not have any opening of their native AV at rest but do during exercise (Figure 7C). These two scenarios also avoid AI, and are good indications for stable LVAD treatment. With respect to HF duration, they typically have suffered for a couple of years.

In contrast, patients with preoperative sufficient \(\beta\)-blocker treatment (ie, those with a long history of HF > 3 years) rarely achieve LVRR and lose cardiac reserve along with a persistently closed native AV (Figure 7D). In these cases, a centrifugal pump may have an advantage with respect to preventing AI during LVAD support. Concomitant surgical intervention of native AV at the time of LVAD implantation may also be considered in such patients.

Concomitant patch closure may be the most reasonable choice to prevent AI, considering the low recurrence rate after the procedure. However, candidates should be carefully selected, because the procedure eliminates the possibility of future explantation of LVAD and increases the risk of sudden death with device malfunction. In Japan, patients often wait several years on LVAD support for a transplant, and AI becomes a serious threat that can decrease the quality of life of the patient for a long time. Therefore, concomitant patch closure may be better indicated for not only the candidates of destination therapy but also for those of bridge to transplantation when patients have received sufficient \(\beta\)-blocker treatment preoperatively (Figure 7D).

**Conclusion:** Preoperative insufficient \(\beta\)-blocker treatment and pulsatility-preserving device usage such as PF or a centrifugal pump are keys to prevent AI during LVAD treatment.

**DISCLOSURE**

None
REFERENCES


