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Pathophysiology and management of valvular lesions in the setting of LVAD support

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Pathophysiology and management of valvular lesions in the setting of LVAD support

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A computational study of aortic insufficiency in patients supported with continuous flow left ventricular assist devices: Is it time for a paradigm shift in management?

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Background: *De novo* aortic insufficiency (AI) following continuous flow left ventricular assist device (CF-LVAD) implantation is a common complication. Traditional early management utilizes speed augmentation to overcome the regurgitant flow in an attempt to augment net forward flow, but this strategy increases the aortic transvalvular gradient which predisposes the patient to progressive aortic valve pathology and may have deleterious effects on aortic shear stress and right ventricular (RV) function.

Materials and methods: We employed a closed-loop lumped-parameter mathematical model of the cardiovascular system including the four cardiac chambers with corresponding valves, pulmonary and systemic circulations, and the LVAD. The model is used to generate boundary conditions which are prescribed in blood flow simulations performed in a three-dimensional (3D) model of the ascending aorta, aortic arch, and thoracic descending aorta. Using the models, impact of various patient management strategies, including speed augmentation and pharmacological treatment on systemic and pulmonary (PA) vasculature, were investigated for four typical phenotypes of LVAD patients with varying degrees of RV to PA coupling and AI severity.

Results: The introduction of mild/moderate or severe AI to the coupled RV and pulmonary artery at a speed of 5,500 RPM led to a reduction in net flow from 5.4 L/min (no AI) to 4.5 L/min (mild/moderate) to 2.1 L/min (severe). RV coupling ratio (Ees/Ea) decreased from 1.01 (no AI) to 0.96 (mild/moderate) to 0.76 (severe). Increasing LVAD speed to 6,400 RPM in the severe AI and coupled scenario, led to a 42% increase in net flow and a 16% increase in

regurgitant flow (RF) with a nominal decrease of 1.6% in RV myocardial oxygen consumption (MVO2). Blood pressure control with the coupled RV with severe AI at 5,500 RPM led to an 81% increase in net flow with a 15% reduction of RF and an 8% reduction in RV MVO2. With an uncoupled RV, the introduction of mild/moderate or severe AI at a speed of 5,500 RPM led to a reduction in net flow from 5.0 L/min (no AI) to 4.0 L/min (mild/moderate) to 1.8 L/min (severe). Increasing the speed to 6,400 RPM with severe AI and an uncoupled RV increased net flow by 45%, RF by 15% and reduced RV MVO2 by 1.1%. For the uncoupled RV with severe AI, blood pressure control alone led to a 22% increase in net flow, 4.2% reduction in RF, and 3.9% reduction in RV MVO2; pulmonary vasodilation alone led to a 18% increase in net flow, 7% reduction in RF, and 26% reduction in RV MVO2; whereas, combined BP control and pulmonary vasodilation led to a 113% increase in net flow, 20% reduction in RF and 31% reduction in RV MVO2. Compared to speed augmentation, blood pressure control consistently resulted in a reduction in WSS throughout the proximal regions of the arterial system.

Conclusion: Speed augmentation to overcome AI in patients supported by CF-LVAD appears to augment flow but also increases RF and WSS in the aorta, and reduces RV MVO2. Aggressive blood pressure control and pulmonary vasodilation, particularly in those patients with an uncoupled RV can improve net flow with more advantageous effects on the RV and AI RF.

KEYWORDS

aortic insufficiency (AI), left ventricular assist device (LVAD), computational fluid dynamics, myocardial efficiency, right ventricular (RV) function

Introduction

The development of *de novo* aortic insufficiency (AI) while on continuous flow left ventricular assist device (CF-LVAD) support is a common complication with up to 25% of patients developing mild to moderate AI within the first year after implantation (1–3). The severity of AI appears to be time-dependent with patients with longer durations of support developing more severe regurgitation. Nearly a third of patients will develop moderate or greater AI within 2–3 years of CF-LVAD implantation (1, 3). Over time, progressive AI may lead to LV chamber dilation followed by left-sided pressure elevation leading to pulmonary congestion. Eventually, secondary pulmonary hypertension leading to right-sided dysfunction may ensue.

Whereas, the prevalence of the disease is unmistaken, considerable controversy remains regarding the clinical significance and management of AI in patients supported with CF-LVADs. Cowger et al. performed serial echocardiograms on 166 patients following implantation with a CF-LVAD and found no difference in survival rates or rates of urgent transplantation following the development of moderate or worse AI (3). Despite the lack of a survival benefit, patients with moderate AI were more likely to develop mitral regurgitation, hemolysis, and worsening right ventricular (RV) dysfunction than patients without AI. In the subgroup of patients with pre-existing RV dysfunction prior to device implantation, patients who developed moderate or worse AI after CF-LVAD implantation had worse survival than those without important AI (3). Conversely, Jorde et al. followed 232 patients with CF-LVADs and found that 7 of 21 patients (33%) with moderate or greater AI developed symptoms of heart failure requiring urgent transplantation or aortic valve closure/repair (1). Forty percent of their cohort required an intervention within 3 months of developing symptomatic AI. Given the divergent conclusions from outcome studies examining the clinical consequences of AI in CF-LVAD patients, it is not surprising that there is a paucity of guidelines to help manage patients who develop important AI (4).

In practice, most clinicians increase LVAD speed in an attempt to overcome the regurgitant flow introduced by AI (5, 6). This increased speed increased the reverse transvalvular pressure gradient across the aortic valve which further results in earlier closure of the aortic valve, increases the regurgitant fraction and volume load on the LV and pulmonary circulation and consequently can lead to more pulmonary vascular

remodeling and RV dysfunction over time. In severe cases of AI, surgical or transcatheter aortic valve replacement or closure can be performed although technical challenges related to lack or annulus calcification and progressive RV failure from abrupt changes in RV preload and afterload can ensue (7–9). It has been hypothesized that the ability of the right ventricle to handle volume challenges of AI and its management may be influenced by the RV coupling ratio. The RV coupling ratio defines the relationship of RV contractility, which can be estimated by the end-systolic elastance (Ees) of the RV, to the afterload or effective arterial elastance (Ea) of the pulmonary circulation. A coupled RV has sufficient contractile reserve to eject blood into the pulmonary circulation, whereas, an uncoupled RV struggles to eject blood, especially when challenged with high preload conditions.

Currently little is known about the functional impact of varying LVAD speed, blood pressure control and pulmonary vasodilators on patients with AI. The specific effects of different management strategies can often be hard to assess in clinical practice. Therefore, the development of strategies to help estimate the hemodynamic and clinical effects of these management strategies is of the utmost importance. We herein present a computational model of CF-LVAD patients with varying degrees of AI and RV-arterial coupling to determine, *in silico*, the effects of different management strategies, such as regulation of LVAD speed, blood pressure control, and administration of pulmonary vasodilator medications on cardiac function and shear stress distribution on the aortic wall.

Materials and methods

The methodology is split into two phases. First, we built a closed-loop lumped-parameter model of the cardiovascular system to analyze global circulatory phenomena, with emphasis in the cardiac performance and its interaction with the LVAD. Second, we retrieved the hemodynamic conditions, specifically blood flow rates through the LVAD cannula and aortic root, and used them as boundary conditions to perform three-dimensional (3D) blood flow simulations using a patient-specific geometric model of the aorta and LVAD outflow cannula.

Global circulation model

The closed-loop model accounts for the arterio-venous circulation, the four cardiac chambers with corresponding valves, the pulmonary circulation and the LVAD connecting the LV to the arterial system. Model parameters were selected to emulate the different physiological conditions of relevance for this study. We placed a HeartMate 3 (Abbott, Abbott Park, IL, United States) coupled with the LV in the closed-loop model. The model was developed and implemented in an in-house Python code. Full details of the model, including the model parameters used, have been previously reported (10). Ten cardiac cycles were simulated to ensure that all the variables in the model were in a periodic regime. Specifically, for the considerations of AI, the aortic valve was modeled taking into account the valve opening-closing dynamics (10). The pressure loss on the valve partially takes into account the high Reynolds number when the pressure-flow relation becomes non-linear (also known as turbulent loss). Evidently since there is no 3D modeling, the 0D representation is a simplified view of reality. The AI is modeled by modifying the parameters that control the minimum angle the valve can reach when it closes. Hypothetically, a perfect valve has a minimum angle of 0 degrees. In our model, we have modified this parameter so that the regurgitant fraction fell into the mild/severe classification (see definition below).

Study cases and cardiovascular scenarios

Typical phenotypes of patients with LVAD and relevant clinical scenarios were defined by altering model parameters such as systemic and pulmonary resistance and compliance, cardiac elastance, and closing valve capabilities. To this aim, we used the computer simulations performed with the compartmental model. We hypothesized that the ability of the right ventricle to handle LVAD speed and volume changes may be dependent on the degree RV to pulmonary artery coupling. As study cases we defined four conditions combining the state of the right ventricle (RV) and the aortic insufficiency (AI):

1. Coupled RV and severe AI.
2. Uncoupled RV and severe AI.
3. Coupled RV and mild/moderate AI.
4. Uncoupled RV and mild/moderate AI.

The RV was deemed to be uncoupled when the ratio of RV Ees relative to the pulmonary effective arterial Ea was <0.7 and coupled when the ratio RV Ees/Ea was >0.7. Severe AI was defined as a regurgitant fraction (RF) of $>50\%$ and mild/moderate AI as a RF of $<50\%$.

As cardiovascular scenarios we investigated the following protocols to counteract the pathophysiological conditions:

a) Baseline condition (HR 60 bpm, central MAP 80–90 mmHg, CO 5.0 L/min, mean pulmonary artery pressure 20–25 mmHg, LVAD operated at 5,500 RPM).
b) Left ventricular assist device speed augmentation (5,500 → 6,400 RPM).

c) Blood pressure (BP) control (target mean central aortic pressure 70–75 mmHg by reducing vascular resistance to 50–60% of its baseline value).
d) Pulmonary vasodilation (for the uncoupled scenarios, target systolic pulmonary pressure ∼25 mmHg by increasing pulmonary compliance by a factor of ∼10, and reducing vascular resistance to 80% of its baseline value).
e) Pulmonary vasodilation and BP control (for the uncoupled scenarios).

Local circulation model

We simulated the 3D local blood flow in a patient-specific model of the aorta obtained through the segmentation of a computed tomography angiography dataset of a 50 years-old male patient who had a heartmate 3 (HM3, Abbott, Chicago, IL, United States) implanted at University of Chicago Hospital. Prior consent was obtained from patient, following the Declaration of Helsinki, and the imaging protocol as well as the use of the data was approved by the local ethics committee. We prescribed flow rate boundary conditions at the cannula inlet and at the aortic root as predicted by the global circulation model. At the five outlets (two subclavian arteries, two carotid arteries, and the descending aorta), resistance boundary conditions were prescribed to mimic the flow rate split occurring in the 0D model. Three cardiac cycles were simulated to ensure the solution becomes periodic, and the time-average wall shear stress (WSS) was computed for the last cardiac cycle in four different regions of the aortic model (outflow cannula, ascending aorta, aortic arch, and descending aorta). Details of the local circulation model have been previously reported (10). All simulations were conducted using an in-house simulation software (11). Simulations for the global circulation were run on a standard laptop, while simulations for the local circulation (3D) model were run in the Santos Dumont high performance facility (12).

Model calibration

The proposed global-local model aims at characterizing the pathophysiological conditions encountered in a prototypical patient, to illustrate a proof-of-concept. The global circulation model was adjusted by performing a sensitivity analysis of the model predictions with respect to the main model parameters (perturbation in the range ± 40%). Specifically, these parameters were the systemic/pulmonary resistance/compliance, maximum/baseline cardiac elastances, and minimum valve opening angle. This sensitivity analysis led us to a baseline scenario, which was defined as the case that mimicked the main physiological conditions, as defined by physiological variables such as cardiac output, systemic/pulmonary blood pressure, end-systolic elastance, arterial elastance, and regurgitation fraction. From the baseline model, and exploiting the sensitivity analysis performed previously, we modified the model parameters to build virtual scenarios as those described in the previous section [state of the RV and the AI severity, see Table 14 in Blanco et al. (10)]. Concerning the local circulation model, although the 3D model of the aorta was built from patient-specific data, this 3D anatomical model was used here also as a typical anatomical model to investigate the sensitivity of the blood flow under the different conditions proposed above.

Results

Coupled right ventricular conditions

The introduction of mild/moderate or severe AI to the coupled RV and pulmonary artery at a speed of 5,500 RPM led to a reduction in net flow from 5.4 L/min (no AI) to 4.5 L/min (mild/moderate) and to 2.1 L/min (severe). RV Ees/Ea decreased from 1.01 (no AI) to 0.96 (mild/moderate) and to 0.76 (severe).

Effect of speed augmentation

Increasing LVAD speed to 6,400 RPM in the severe AI led to a 42% increase in net flow and a 16% increase in regurgitant flow (RF) with a nominal decrease of 1.6% in RV MVO2 (**Table 1** and **Figure 1A**). Wall shear stress increased in the aortic tree and especially in the ascending aorta and was found to be two times higher than the baseline (average of 4.7 dyn/cm^2 at baseline to 9.8 dyn/cm^2 with speed augmentation) (**Figures 2**, **3**). Speed augmentation in mild/moderate AI led to a 39% increase in net flow, 12% increase in RF and 8% reduction in RV MVO2 (**Table 1** and **Figure 1B**) while the WSS was uniformly increased throughout the vascular tree with speed augmentation (**Figures 2**, **3**).

Effect of blood pressure control

Blood pressure control in severe AI at 5,500 RPM led to an 81% increase in net flow with a 15% reduction RF and an 8% reduction in RV MVO2 while BP control with mild/moderate AI led to 30% increase in net flow, 18% decrease in RF and 8% reduction in RV MVO2 (**Figures 1A,B**). Blood pressure control in this setting was associated with a 15 and 13% reduction in WSS compared to speed augmentation in the outflow cannula and ascending aorta, respectively (**Figures 2**, **3**).

Effect of simultaneous speed augmentation and blood pressure control

The combination of speed augmentation together blood pressure control in the scenario with severe AI and coupled RV led to a 48% increase in net flow compared to speed augmentation alone (4.40 vs. 2.97 L/min) and a 16% increase

TABLE 1 Intracardiac hemodynamics, energetics, left ventricular assist device (LVAD), and aortic flow with a coupled right ventricle with varying degrees of aortic insufficiency.

		Coupled RV–severe AI			Coupled RV–mild/moderate AI		
	Units	Baseline	Speed augmentation	BP control	Baseline	Speed augmentation	BP control
EesRV	mmHg/ml	0.364	0.360	0.356	0.364	0.351	0.354
EaRV	mmHg/ml	0.477	0.408	0.333	0.379	0.273	0.271
EesRV/EaRV	–	0.762	0.884	1.069	0.959	1.285	1.310
SWRV	mmHg.ml	851	860	827	862	805	816
MVO2RV	mlO2	0.0447	0.0440	0.0413	0.0435	0.0401	0.0398
PERV	mmHg.ml	726	684	589	659	555	532
PVARV	mmHg.ml	1,577	1,544	1,416	1,520	1,360	1,348
EffRV	–	0.127	0.130	0.133	0.132	0.134	0.136
Psa	mmHg	92	99	73	92	88	72
Psamax	mmHg	97	101	78	94	89	75
Psamin	mmHg	88	96	69	90	87	70
Ppa	mmHg	24	22	20	22	19	18
Ppamax	mmHg	28	28	26	27	25	25
Ppamin	mmHg	19	18	16	17	14	14
DPAoV	mmHg	57	67	43	58	63	44
Qao	l/min	−3.33	−4.07	−2.47	−0.87	−0.99	−0.42
Qlvad	l/min	5.42	7.05	6.26	5.35	7.20	6.22
Vback	ml	−59	−68	−50	−15	−16	−12
Net flow	l/min	2.10	2.97	3.80	4.47	6.21	5.80
Regurgitant fraction	–	61.3%	57.8%	39.4%	16.3%	13.7%	6.7%

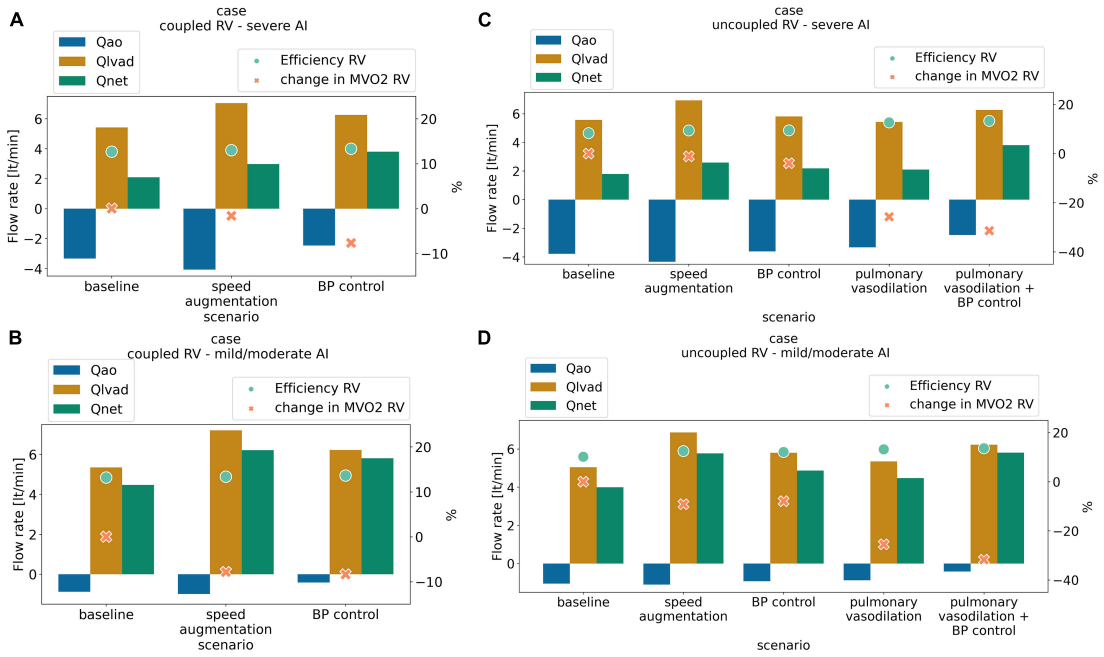

FIGURE 1
Antegrade flow (L/min) (orange), retrograde flow (L/min) (blue) net flow (L/min) (green) right ventricular cardiac efficiency (%) (dot light green), and change in right ventricular oxygen consumption (%) (RV MVO2, cross light orange) with medical management and LVAD speed augmentation in a scenario of **(A)** coupled right ventricular (RV) with severe aortic insufficiency (AI), **(B)** coupled RV with mild/moderate AI, **(C)** uncoupled RV with severe AI, **(D)** uncoupled RV with mild/moderate AI.

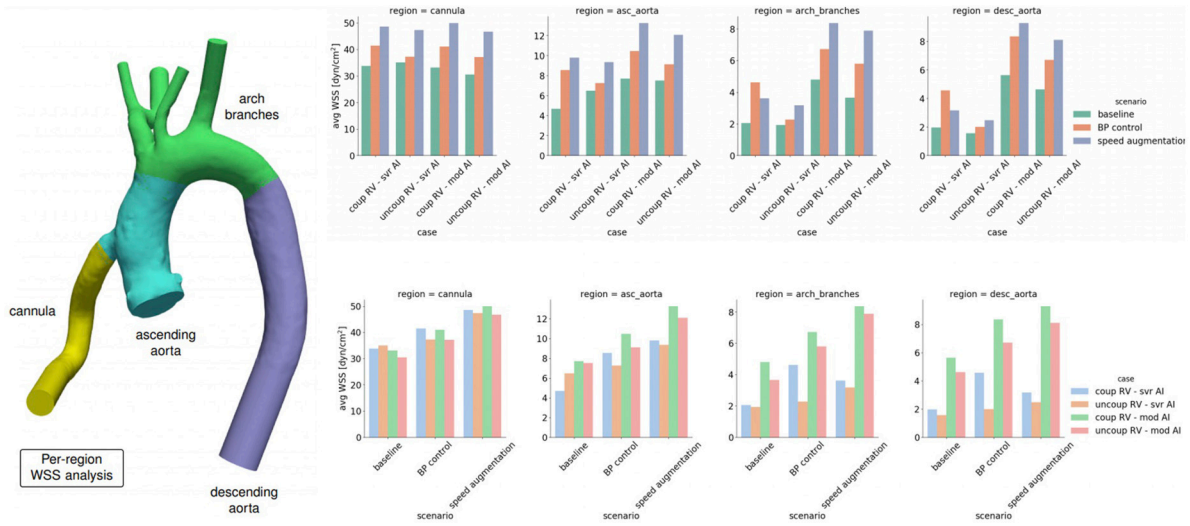

FIGURE 2
Average wall shear stress (WSS) by location within the left ventricular assist device (LVAD) outflow cannula or aorta stratified by degree of right ventricular (RV) coupling, aortic insufficiency (AI) severity and medical and device management.

in net flow compared to BP control alone (4.40 vs. 3.80 L/min). Simultaneous speed augmentation and BP control modestly increased the regurgitant fraction of flow back across the aortic valve compared to BP control alone (42.8 vs. 39.4%) but was lower than isolated speed augmentation (57.8%). Overall, a strategy of simultaneous speed augmentation with blood pressure control was the most effective at improving net flow and only led to a modest increase in regurgitant flow when the RV is coupled.

Management strategy and regional wall shear stress

Local variations in WSS have been hypothesized to contribute to both the development and progression of AI. Here were observed regional variations in WSS by management strategy and degree of AI severity. With severe AI, WSS was lower in the cannula and ascending aorta but higher in the aortic arch and descending aorta using a blood pressure control strategy in favor of speed augmentation. Conversely, with mild or moderate AI, a blood pressure control strategy resulted in a uniform decreased in WSS throughout the entirety of the thoracic aorta when compared to a speed augmentation strategy (**Figures 2**, **3**). Additional information on the pressure and velocity fields including the peak systolic to end-diastolic (S/D) velocity ratio and diastolic acceleration can be found in **Supplementary Figure 1**.

Uncoupled right ventricular conditions

With an uncoupled RV, the introduction of mild/moderate or severe AI at a speed of 5,500 RPM led to a reduction in net flow from 5.0 L/min (no AI) to 4.0 L/min (mild/moderate) and to 1.8 L/min (severe). RV Ees/Ea decreased from 0.47 (no AI) to 0.38 (mild/moderate) and to 0.29 (severe).

Effect of speed augmentation

Increasing the speed to 6,400 RPM in severe AI scenario increased net flow by 45%, RF by 15% and decreased RV MVO2 by 1.1% (**Table 2** and **Figure 1C**). WSS increased in all regions with the most notable augmentation occurring in the outflow cannula (35 dyn/cm^2 at baseline vs. 47 dyn/cm^2 with speed augmentation) (**Figures 2**, **3**). With mild AI, speed augmentation led to a 44% increase in net flow, 4.5% increase in RF and 9% reduction in RV MVO2 (**Table 2** and **Figure 1D**) with a consistent increase in WSS throughout.

Effect of blood pressure control

Blood pressure control alone in severe AI led to a 22% increase in net flow, 4.2% reduction in RF and 3.9% reduction in RV MVO2. Compared to speed augmentation, blood pressure control consistently resulted in a lower WSS in the entire aorta. More specifically, the WSS decreased in the aorta and especially in the outflow cannula by 21%, in the ascending aorta by 22%, in the aortic arch by 28%, and in the descending aorta by 19% (**Figures 2**, **3**).

Effect of pulmonary vasodilation and combined pulmonary vasodilation and blood pressure control

Pulmonary vasodilation alone led to a 18% increase in net flow, 7% reduction in RF and 26% reduction in RV MVO2. A strategy that combined blood pressure control and pulmonary vasodilation led to a 113% increase in net flow, 20%

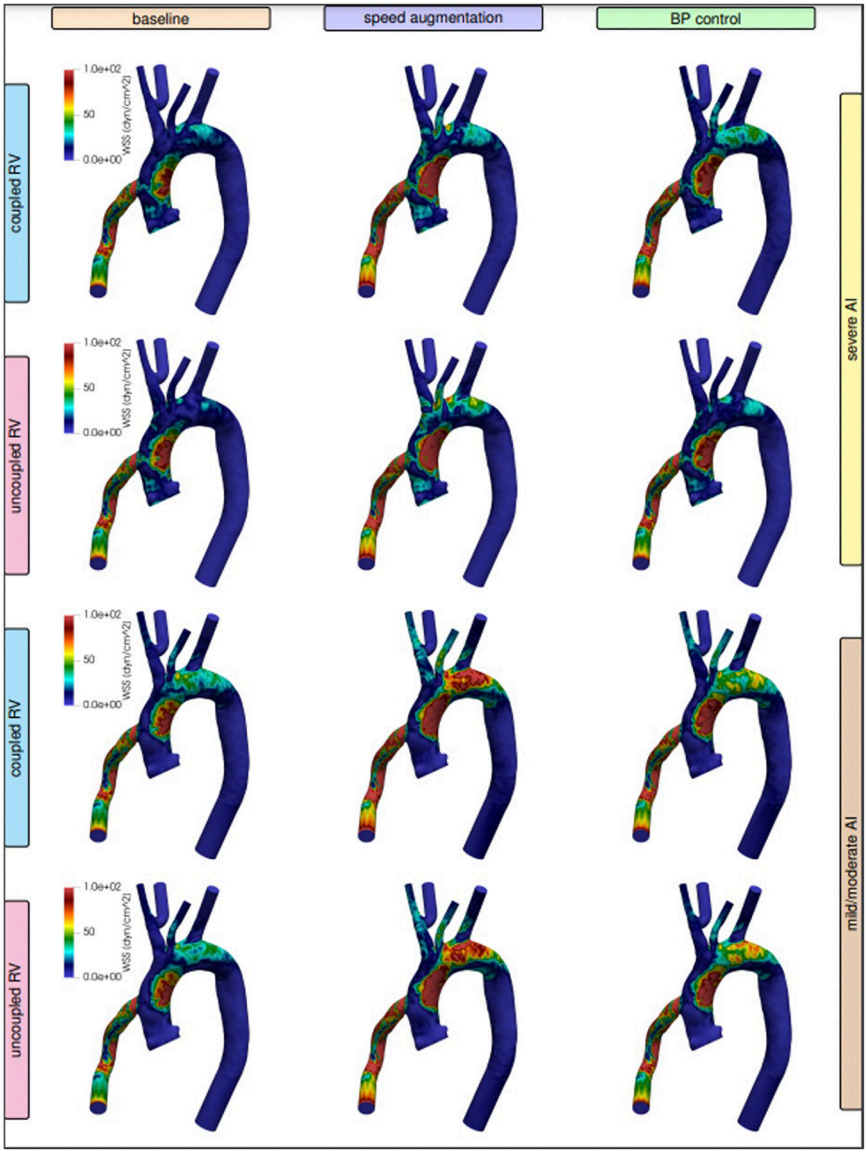

FIGURE 3
Visualized wall shear stress stratified by degree of right ventricular (RV) coupling and aortic insufficiency (AI) severity when comparing speed augmentation to blood pressure (BP) control.

reduction in RF and 31% reduction in RV MVO2 (Table 2 and Figure 1D). A strategy of simultaneous blood pressure control and pulmonary vasodilation was the most effective at improving net flow and reducing regurgitant fraction when the RV is uncoupled.

Management strategy and regional wall shear stress

Unlike with the coupled scenarios, there was no regional variation in vascular WSS when comparing a blood pressure control strategy vs. a speed augmentation strategy. Blood pressure control was associated with less WSS in the outflow cannula, ascending aorta, aortic arch, and descending aorta in both the uncoupled severe AI and uncoupled mild/moderate AI scenarios (Figures 2,3). While the S/D ratio was low for all scenarios, the diastolic acceleration was better able to discriminate mild/moderate from severe AI, especially when RV uncoupling was present (Supplementary Figure 1).

Discussion

It is well-established that AI in patients supported with CF-LVAD has different pathophysiological implications than AI that

TABLE 2 Intracardiac hemodynamics, energetics, left ventricular assist device (LVAD), and aortic flow with an uncoupled right ventricle with varying degrees of aortic insufficiency.

		Uncoupled RV–severe AI					Uncoupled RV–mild/moderate AI				
	Units	Baseline	Speed augmentation	BP control	Pulmonary vasodilation	Pulmonary vasodilation + BP control	Baseline	Speed augmentation	BP control	Pulmonary vasodilation	Pulmonary vasodilation + BP control
EesRV	mmHg/ml	0.340	0.331	0.339	0.364	0.356	0.327	0.315	0.326	0.364	0.354
EaRV	mmHg/ml	1.192	0.979	0.918	0.477	0.333	0.857	0.585	0.597	0.379	0.271
EesRV/EaRV	–	0.285	0.338	0.370	0.762	1.069	0.381	0.540	0.547	0.959	1.310
SWRV	mmHg.ml	754	842	822	851	827	891	994	977	862	816
MVO2RV	mlO2	0.0602	0.0595	0.0578	0.0447	0.0413	0.0584	0.0530	0.0538	0.0435	0.0398
PERV	mmHg.ml	1,564	1,445	1,384	726	589	1,345	988	1,038	659	532
PVARV	mmHg.ml	2,318	2,287	2,206	1,577	1,416	2,235	1,982	2,015	1,520	1,348
EffRV	–	0.083	0.094	0.095	0.127	0.133	0.101	0.125	0.121	0.132	0.136
Psa	mmHg	83	89	79	92	73	84	82	72	92	72
Psamax	mmHg	88	92	82	97	78	86	82	73	94	75
Psamin	mmHg	79	87	76	88	69	82	82	71	90	70
Ppa	mmHg	21	21	21	24	20	20	19	19	22	18
Ppamax	mmHg	41	39	39	28	26	38	34	34	27	25
Ppamin	mmHg	13	13	13	19	16	13	12	13	17	14
DPAoV	mmHg	57	72	53	57	43	69	75	55	58	44
Qao	l/min	−3.78	−4.34	−3.62	−3.33	−2.47	−1.05	−1.10	−0.93	−0.87	−0.42
Qlvad	l/min	5.56	6.92	5.80	5.42	6.26	5.05	6.86	5.80	5.35	6.22
Vback	ml	−63	−72	−60	−59	−50	−17	−18	−15	−15	−12
Net flow	l/min	1.78	2.59	2.19	2.10	3.80	4.00	5.77	4.87	4.47	5.80
Regurgitant fraction	–	67.9%	62.6%	62.4%	61.3%	39.4%	20.8%	16.0%	16.0%	16.3%	6.7%

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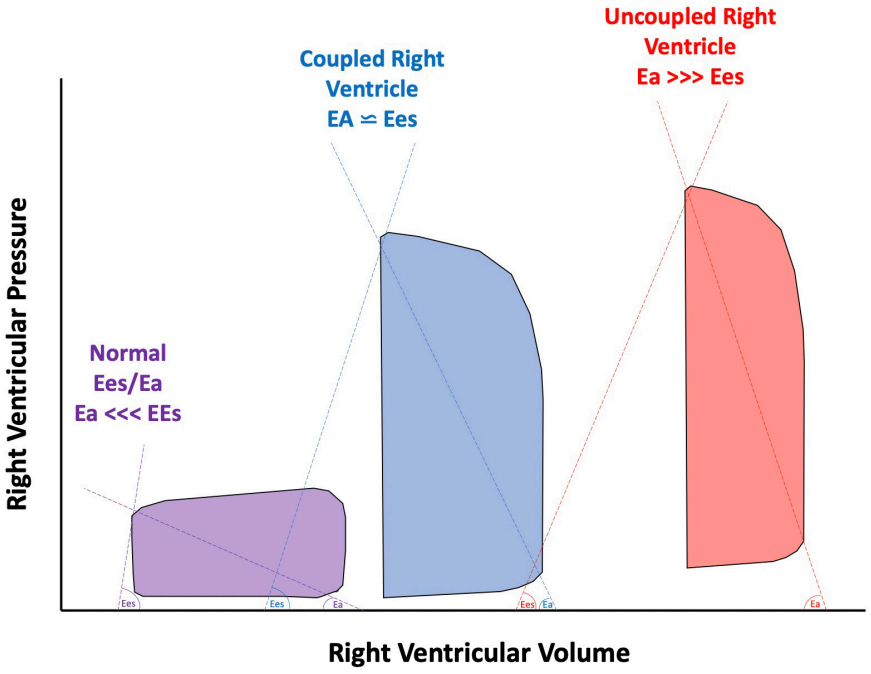

FIGURE 4
Pressure volume loops of a normal right ventricle (RV) compared to a compensated, coupled RV, and uncoupled RV. Ees, end systolic elastance; Ea, effective arterial elastance.

develops in patients with unassisted hearts. With continuous unloading of the LV and return of blood to the ascending aorta, patients supported with CF-LVAD develop a constant trans-aortic pressure gradient which allows for continuous or pan-cyclical regurgitation of blood flow (13, 14). Therefore, the regurgitant blood volume is greater in AI in patients supported with CF-LVAD than in AI in native hearts where regurgitation only happens during diastole. This increased regurgitant volume increases LV filling pressures which over time can lead to both pre- and post-capillary pulmonary hypertension and increased myocardial workload for the RV (3, 15). With vascular remodeling, the effective arterial Ea increases and the ratio of the Ees of the RV to the effective arterial elastance (Ees/Ea) decreases. A coupled RV allows for a more efficient transfer of energy. Fortunately, the RV can maintain adequate efficiency up until an Ees/Ea of 0.7–0.8. Below this value, the RV becomes uncoupled and thus the mechanical efficiency of the RV reduces (**Figure 4**; 16–18). Receiver operating characteristic analysis has shown that an Ees/Ea of 0.7 has the greatest prognostic impact for a variety of clinical settings including chronic heart failure and pulmonary arterial hypertension (19).

Traditional management strategies in AI include speed augmentation in an attempt to overcome the regurgitant flow, and boost net forward flow into the aorta. With enhanced speed, an improvement in net flow can often be achieved but this strategy can cause progression in the aortic valve pathology by increasing the trans-aortic pressure gradient. From our simulations, speed augmentation led to an increase in average transvalvular pressure gradient that ranged from 8 to 26%, while blood pressure control led to reduction in mean pressure gradient values between 8 and 25%, with respect to the baseline case. A high trans-aortic pressure gradient promotes a better closure of aortic valve but could also induce aortic root dilation from increased circumferential stress (20). With more advanced disease, aortic valve replacement or occlusion can be considered although outcomes with these procedures have been variable and complicated by device migration, perivalvular leak and right ventricular dysfunction (6–8, 21, 22).

Here we showed that the optimal management strategy for AI differs by disease severity and the degree of RV coupling to the pulmonary circulation. Based on computational models of the circulation including the LVAD, the main findings of our work are as follows. (1) Speed augmentation increases net flow regardless of the degree of RV coupling and AI severity although it comes at the expense of increased WSS, increased regurgitant volume and transaortic pressure gradient promoting an AV closure. (2) In the setting of uncoupled RV, speed augmentation is less advantageous for the RV MVO2. (3) Tight blood pressure control either in isolation or combined with aggressive pulmonary vasodilation in those with uncoupled RV can achieve similar or greater augmentation in net flow with a reduction in RV MVO2, regurgitant volume and a reduction in the transvalvular gradient which will promote aortic valve opening. An aggressive management strategy was shown to be

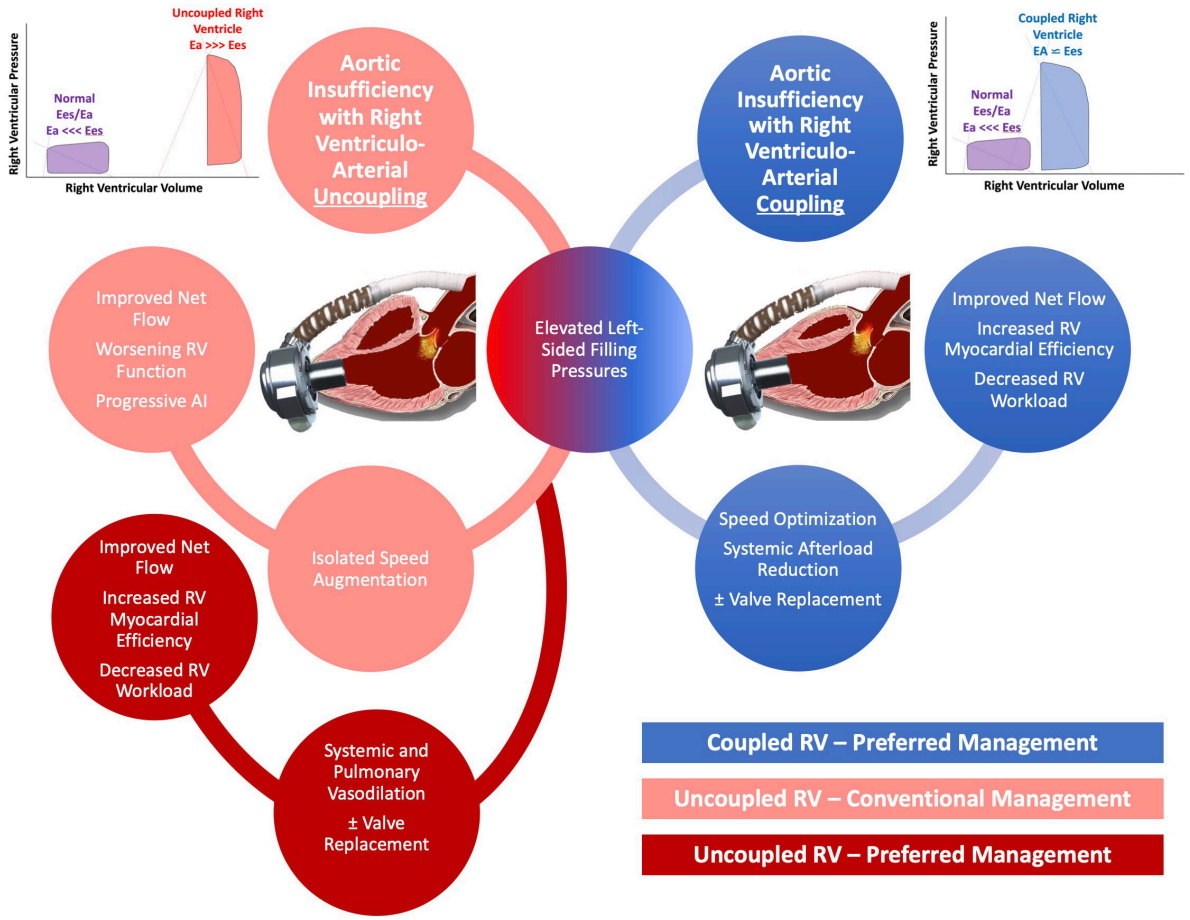

FIGURE 5
Schematic of proposed management of aortic insufficiency (AI) based on degree of right ventricular (RV) uncoupling.

attainable in the Endurance Supplement trial where the HVAD arm had an average mean arterial pressure of less than 80 mmHg throughout the duration of the 24 months follow up (23).

Timely recognition of AI severity is of the utmost importance as management options are more abundant before fixed pre-capillary pulmonary hypertension and RV dysfunction ensues. Speed augmentation will increase preload to the RV but at the same time will reduce the elastance of the pulmonary circulation and thus the RV afterload. When AI is only mild/moderate or when the RV is coupled to the pulmonic circulation, our computer simulations showed that speed augmentation in addition to blood pressure control can improve net flow while having either neutral effects or even beneficial effects on RV energetics and workload. Conversely, when AI is more severe, particularly when the RV is uncoupled to the pulmonary circulation, speed augmentation has less advantageous effects on RV workload. Under these settings, the elastance of the pulmonary circulation is too high to accommodate the increased flow returning back to the RV which leads to an increase in RV pressure hence RV wall tension, and elevated myocardial workload. Unfortunately, these patients often already have a vulnerable RV and thus this management strategy can accelerate RV failure. In these setting, a strategy that aggressively reduces systemic and pulmonary pressures with a more judicious use of LVAD speed can augment net flow while at the same time reduce RV workload (**Figure 5**).

Recently, it has been recognized that traditional methods of quantifying AI may delay the diagnosis and underestimate disease severity. Instead, novel echocardiographic parameters obtained from the outflow cannula, the systolic to diastolic peak velocity ratio (S/D ratio) and the diastolic acceleration better prognosticate AI severity (24, 25). In our model, the diastolic acceleration was more predictive than the S/D ratio to discriminate mild/moderate from severe AI, especially when RV uncoupling was present. Better recognition and appreciation of the true AI severity in patients supported with CF-LVAD may allow for more timely non-invasive and invasive interventions that may improve clinical outcomes (26). In the absence of clinical symptoms, AI is often managed with diuresis, LVAD speed optimization and afterload reduction (4). Considerable

uncertainty exists about the optimal strategy for adjusting the LVAD speed, especially when the AI becomes more severe. Reducing the speed of the LVAD to allow for at least intermittent aortic valve opening has been shown to reduce the rate of AI progression early in its course but the effect of aortic valve opening on the natural history of more severe AI is unknown (1, 27). Increasing the LVAD speed will unload the LV and reduce left-sided filling pressures but this will further increase the positive trans-aortic pressure gradient and the severity of regurgitation (1, 28). Increasing LVAD speeds during a hemodynamic ramp study can successfully overcome pulmonary capillary wedge pressure elevations in patients with AI to degrees comparable to those without AI (28). In the same study, AI severity worsened in nearly two thirds of patients who had AI at higher LVAD speeds although pulmonary capillary wedge pressure was successfully reduced in all but one patient despite the higher degree of AI. Increased LVAD speeds also led to normalization of low cardiac index in the majority of patients although cardiac index may remain low despite speed optimization if considerable RV dysfunction is present (28). Our work here suggests that when RV dysfunction is present or when a patient has an uncoupled RV, aggressive systemic blood pressure control and pulmonary vasodilation and to a lesser degree speed augmentation may be the preferred management strategy. The definitive management for AI in patients on LVAD support remains aortic valve replacement or closure or cardiac transplantation for appropriate candidates.

Limitations

The computer simulations were performed using a model which was developed based on the physiologic and anatomical data for a single virtual patient with a HM3. Physiological data for this kind of patients was contrasted to model predictions to guide the selection of model parameters through a sensitivity analysis. Several variables including properties related to vessel and chamber elastance, and pulmonary and systemic resistance, had to be assumed based on previously published work to reflect prototypical patient phenotypes and treatment conditions. From the modeling perspective, the weak coupling between the 0D and the 3D models is a limitation. However, the pressure drop is mainly given by the cannula (see pressure field in the **Supplementary Figure 1**), and so the flow split in the major branches of the aorta will not be different from those prescribed from the 0D to the 3D model (which is actually determined by the downstream peripheral vasculature). Therefore, the only notorious discrepancy between the 3D and 0D models is the pressure pulse in the 3D, which is not realistic because of the rigid wall assumption (see systolic and diastolic pressure fields in the **Supplementary Figure 1**). In addition, since we employ the 3D model to estimate the regional WSS, and this depends on the flow rate, these results will not be greatly affected by the 3D–0D weak coupling. As said above, the velocity field is a direct consequence of the flow split among branches, being this the main determinant of the WSS regional distribution (see systolic and diastolic velocity fields in the **Supplementary Figure 1**). The pathogenesis of *de novo* AI in patients supported by LVADs can be heterogeneous and difficult to predict. Our model lacks a geometrically accurate representation of the aortic valve. The jet of RF can be eccentric or central and depends on the degree of commissural fusion, which could translate into different level of RF for the same geometrical area insufficiency. That being said, this assumption is commonly accepted in lumped-parameter model simulations. Moreover, our analysis focused on the effects of AI on the vasculature and RV and less on the impact on the LV. Lastly, our model assumed that RV Ees was relatively fixed with speed changes. With extremes of speed, the septal position can shift leftward which would impair RV Ees although in our experience, extreme shifts to this nature are rare in patients with AI as the regurgitant flow and concomitant elevated left-sided filling pressures tend to keep the septum in a more neutral position.

Conclusion

Speed augmentation to overcome AI in patients supported by CF-LVAD will augment flow but at the expense of RV MVO2, RF, and WSS. Aggressive blood pressure control and pulmonary vasodilation, particularly in those patients with an uncoupled RV can improve net flow with more advantageous effects on the RV and aortic valve function.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of Chicago. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JG, PB, RT, and HG-G: study design. JG, PB, and CAB: study completion and data collection. JG, PB, and RT: clinical

data analysis. JG, PB, CAB, CVB, PL, and HG-G: writing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

JG was a speaker for Abbott. HG-G's institution received research grants from Medtronic and Abbott. PL reported: (i) institutional research funding, and/or unpaid advisory board member, and/or unpaid member of the steering/executive/data safety and monitoring group of trials, and/or unpaid interventional proctor by Abbott, Corindus, Scietch, Boston Scientific, and Flouit but had not received personal payments by pharmaceutical companies or device manufacturers; (ii) being part of Argonauts, an innovation facilitator.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Role of the mitral valve in left ventricular assist device pathophysiology

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Functional mitral regurgitation (MR) in the setting of heart failure results from progressive dilatation of the left ventricle (LV) and mitral annulus. This leads to leaflet tethering with posterior displacement. Contrary to common assumptions, MR often does not resolve with LVAD decompression of the LV alone. The negative impact of significant (moderate-severe) mitral regurgitation in the LVAD setting is becoming better recognized in terms of its harmful effect on right heart function, pulmonary vascular resistance and hospital readmissions. However, controversies remain regarding the threshold for intervention and management. At present, there are no consensus indications for the repair of significant mitral regurgitation at the time of LVAD implantation due to the conflicting data regarding potential adverse effects of MR on clinical outcomes. In this review, we summarize the current understanding of MR pathophysiology in patients supported with LVAD and potential future management strategies.

KEYWORDS

advanced heart failure, functional mitral regurgitation, mitral valve, left ventricular assist device, transcatheter edge-to-edge therapy, right heart failure, aortic valve, tricuspid valve

Introduction

Functional mitral regurgitation (MR) occurring in end-stage heart failure results from progressive dilatation of the left ventricle (LV) and mitral annulus driven by progressive left ventricular dysfunction. LV dilation leads to leaflet tethering with posterior displacement (1) accompanied by change of LV geometry from an elliptical

to a spherical shape (2, 3). Outward papillary muscle displacement also contributes to mitral leaflet tethering (4, 5). This pathological cardiac remodeling process can occur in both ischemic and non-ischemic cardiomyopathies (6). It is more recently recognized that "atrial functional mitral regurgitation" plays an important role for MR pathogenesis in heart failure. This describes structural left atrial remodeling and dilatation which is commonly associated with atrial fibrillation. This atrial enlargement occurs and contributes to the normal elliptical and saddle shaped mitral annulus becoming rounder and flatter (7). Atrial functional MR is also characterized by isolated mitral annular dilatation, inadequate leaflet growth/adaptation as well as impaired atrial and annular contractile dynamics (8). Interestingly, the association of left atrial dilatation with functional MR was initially described in patients with atrial fibrillation (9).

The occurrence of functional MR in the heart failure setting is common. There is a 44.5% prevalence of moderate-severe MR in patients with acute heart failure with reduced ejection fraction (10). As expected, this correlated closely with the 39–43% incidence of preoperative significant MR in patients undergoing left ventricular assist device (LVAD) implantation (11, 12). The large majority (∼94%) of MR in LVAD patients are a result of restricted leaflet motion during systole from tethering (type IIIb) along with components of reduced leaflet motion from thickening and calcification (type IIIa) and annular dilatation (type I) (13). It should be noted that there are significant challenges in evaluating the burden of preoperative and residual MR given its underlying dynamic nature where MR severity is modulated by conditions such as pump speed, afterload and volume status. Aggressive medical optimization to promote euvolemia, blood pressure control and speed adjustments to promote optimal LVAD support should be carried out prior to assessing MR severity with subsequent interventions.

Despite common assumptions, MR often does not resolve with LVAD support alone. In patients with preoperative moderate-severe MR, up to 34% had persistent significant MR on follow-up. This is more likely with greater posterior displacement of the coaptation point (1). Therefore, a significant number of patients have moderate to severe MR following LVAD implant. This proportion is particularly high in those with severe MR preoperatively. Despite recent reports citing the negative impact of persistent MR after LVAD implantation, reaching a consensus on interventions for moderate-severe MR remains controversial (14).

This impact of significant (moderate-severe) mitral regurgitation (SMR) in the LVAD setting is gradually being recognized. However, there remain important controversies regarding its implications as well as management. There are a number of explanations for these. Several studies have found that preoperative SMR does not impact post-LVAD surgical outcomes or survival, but many studies did not specifically examine those patients with persistent SMR following LVAD implantation (1, 12, 15, 16). Intuitively, it would be the persistence of post-LVAD SMR that are more likely impact LVAD outcomes over time, not preoperative MR severity *per se*. At present, there are no consensus indications for repair of SMR at the time of LVAD implantation due to the conflicting data regarding its potential adverse effects on clinical outcomes (14).

Mitral regurgitation and its impact on left ventricular assist device outcomes

Residual SMR after LVAD can increase pulmonary vascular resistance, negatively impact right ventricular function, promote right ventricular failure, increase hospital readmissions, and likely reduce survival in settings such as destination therapy (17, 18). While it is recognized that LVAD therapy will improve pulmonary hypertension over time (19), Kassis et al. reported that the presence of residual SMR after LVAD implantation are more likely to have persistent pulmonary hypertension, and increased mortality (20). Importantly, Taghavi et al. observed in patients with significant preoperative MR that concomitant mitral surgery with LVAD implant led to a greater reduction in mean pulmonary artery pressures and pulmonary vascular resistance (PVR) compared to those without concomitant mitral intervention (16). Computational modeling showed that at LVAD speeds where AV opening occurs, moderate-severe MR was associated with significant increases in pulmonary artery and left atrial pressures (21). Elevations in pulmonary vascular pressures and resistance will also negatively impact heart transplant candidacy (16). The impact of residual significant MR on right ventricular failure (RVF) will be discussed in the section below.

Given the purported negative impact of residual SMR on right heart physiology, a number of studies investigated its impact on defined clinical outcomes. However, the results of these studies have yielded varying results. One group of studies found that moderate-severe MR did not adversely impact LVAD outcomes. Kawabori et al. retrospectively studied patients with preoperative severe MR ($n = 108$) and found that those who underwent mitral valve (MV, $n = 26$) repair did not influence survival, postoperative right heart failure, or readmission (22). Studies by Stulak et al. concluded that preoperative significant MR ($n = 189$, 39%) did not adversely impact outcomes. In fact, the presence of larger preoperative end-diastolic dimensions was actually marker by improved survival after LVAD implant, particularly in those with centrifugal devices (12).

Conversely, other studies found mitral regurgitation had significant effects on quality of life, hospital readmissions and survival. Robertson et al. conducted an INTERMACS registry study ($n = 4,930$) for patients with preoperative significant MR and found that mitral intervention ($n = 263$) only demonstrated a trend toward improved survival ($P = 0.089$) in those with

destination therapy indications (17). However, when examining the entire INTERMACS population, MV repair/replacement did not impact 2-year survival compared to those who did not. Despite this, patients who underwent MV procedures had a lower rate of readmission and a better quality of life (17). The clinical impact of significant residual MR translates most consistently with its influence on increased readmission rates. This is most likely the result of a higher incidence of RVF in those with residual SMR (13, 23).

Residual mitral regurgitation and right ventricular failure

Postoperative RVF occurs in 29.8 to 38.5% following LVAD implant and is an important challenge to successful durable LVAD therapy (24, 25). RVF is associated with serious complications such as postoperative bleeding, multi-organ failure, and thromboembolic issues (26). Severe RVF requiring right ventricular assist device (RVAD) support increases hospital mortality. Despite eventual successful RVAD weaning, these patients still often experience an increased incidence of future heart failure (27). Several right ventricular failure (RVF) risk prediction models have been developed for use in patient selection for LVAD therapy (28). Unfortunately, the accuracy of these models have been modest in predicting postoperative RVF. Multiple well-recognized RVF prediction models have only a 60% positive predictive value at best (29). This is likely because existing models only reflect an incomplete portion of a myriad risk factors that all contribute to RVF in the LVAD setting. These unaccounted for risk factors may include intrinsic myocardial biology, systemic inflammatory milieu and/or associated valvular pathologies. For the purpose of this review, the discussion will be focused on mitral regurgitation as a contributor to RVF.

We found that patients with larger preoperative cardiac dimensions had a higher incidence of significant residual MR. These patients were two times more likely to have severe RV dysfunction and over three times the rate of manifesting the clinical symptoms of late RV failure. Late RV failure also highly correlated with lower survival ($P = 0.006$) (30). Kassis et al. reported similar findings where postoperative LVEDD and RV dimensions was larger in patients with significant residual MR and this was associated with worse RV function by quantitative parameters (20). This is likely a result of consistently elevated afterload demands on the RV resulting from increased pulmonary vascular resistance which contributes to RV failure over a prolonged period (30). Kapelios et al. also reported the entity of late-onset RVF during LVAD support where RVF can occur many months to years from device implantation. This was show to be associated with poorer outcomes such as mortality and survival to heart transplantation (31).

While preoperative MR severity is important for subsequent decision making on anticipated need for mitral intervention, it is actually the postoperative residual MR that understandably determines eventual impact. We examined 159 patients with pre-LVAD severe MR and determined the impact of MR resolution after LVAD. Our studies show that persistent post-LVAD SMR in combination with moderate-severe RV dysfunction had very poor outcomes. We documented a high rate of stroke (30.2%), RVF (20.9%), hemolysis (39.5%) and RVAD use (18.6%) in this group which likely contributed to a lower survival in this population (32). However, in patients with post-LVAD significant RV dysfunction but resolution of MR, there was a relatively low incidence of RVF (9%) and RVAD use (7.5%) (32). On the other hand, in patients with more preserved RV function, the presence of SMR post-LVAD was well-tolerated with a very low incidence of RVF (2%) (32). Thus, in patients presenting with moderate-severe MR for LVAD implantation, a favorable outcome is associated with MR that improves to mild or less in severity and/or the RV function is relatively normal after continuous flow LVAD implantation (**Figure 1**; 32).

Resolution of mitral regurgitation in the left ventricular assist device setting

There is controversy regarding the indications for surgical intervention for significant mitral regurgitation (MR) associated with continuous flow left ventricular assist device (cfLVAD) therapy (12). Concomitant mitral surgery during LVAD implantation is performed only in about 5% of patients with preoperative significant MR (17). The International Society of Heart Lung Transplantation (ISHLT) guidelines do not provide a recommendation for concomitant mitral surgery at the time of LVAD implantation (14, 33). This "no-intervention" approach is based on the expectation that LVAD support itself will decrease the ventricular dimensions to resolve MR (34). However, there may be non-responders for MR improvement after LVAD implant. Increasing LVAD speed alone to resolve MR may conflict with competing goals of optimizing right ventricular function, promoting aortic valve opening and avoidance of suction events.

Pawale et al. reported that MV repair can be done safely with excellent outcomes in reducing MR during cfLVAD implant (35). However, Tanaka et al. reported that in patients with significant preoperative MR who spontaneously corrected their MR without a MV procedure after cfLVAD implant, recurrent MR occurred in 23–25% during mid-term follow up at just over 1 year. Additional reports of recurrent MR were also observed by other investigators (1, 36, 37). It is should be highlighted that mitral valve repair may lead to greater reductions in PVR which reduces right ventricular work and may also lower the incidence of heart failure related readmissions (38). While severe MR can

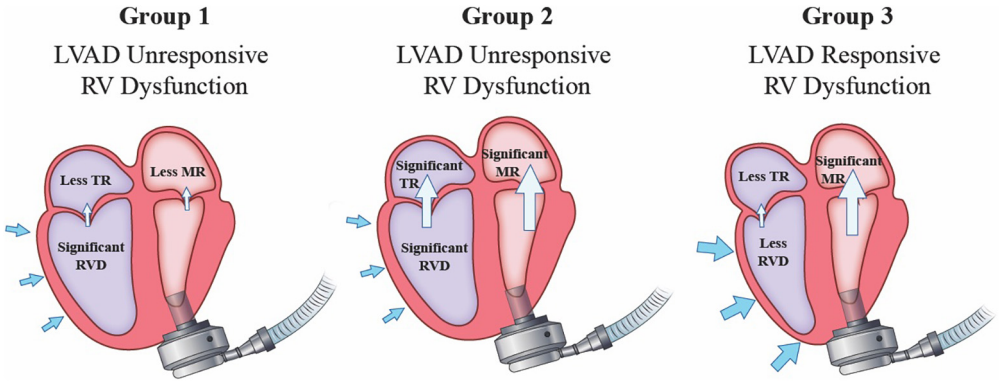

FIGURE 1
Post-LVAD implantation echocardiographic findings on atrioventricular valve competency and underlying right heart function determines the risk of postoperative right ventricular failure.

predict postoperative RVF and RVAD use in the immediate postoperative setting, persistent MR also likely has important implications for long term outcomes (39).

The rate of MR resolution following LVAD implantation likely varies according to the severity of pre-LVAD MR. Studies commonly grouped together pre-LVAD moderate and severe MR when assessing MR resolution (1, 12, 40). Morgan et al. reported that while 76% of patients had either moderate or severe MR pre-LVAD, this declined to 8% at 6 months post-LVAD following LVAD implantation (40). In the Momentum trial, Kanwar et al. studied 403 patients undergoing LVAD implant with preoperative moderate or severe MR. At 1 month, only 6.2% of patients with HM3 and 14.3% with HMII had significant residual MR (11). Further analysis showed that patients are more likely to have significant residual MR if they have MR classified as severe, larger preoperative left ventricular dimension and use of a HeartMate II device (11). Therefore, patients with pre-LVAD severe MR are likely to be an important target population when designing interventions that address residual SMR. When we focused on patients with pre-LVAD severe MR, we found that LVAD support only reduced MR to mild or less in 69.3% of patients. After LVAD implantation in this population, MR remained severe in 10.7% and moderate in 27.0% (32). By comparison, only 16% of those with pre-LVAD moderate MR had significant residual MR after LVAD implantation (41). Posterior displacement of the coaptation point was also an important predictor of MR non-resolution (1). This suggests that while a significant majority resolved SMR with LVAD support alone, those meeting criteria for pre-LVAD severe MR are much less likely to do so.

Building upon findings by previous groups on predictor of residual SMR, we employed a non-hypothesis driven statistical phenotyping of cardiac chamber dimensions. This revealed the correlations between pre-cfLVAD chamber size to MV tenting, early and late post-cfLVAD MR resolution and the occurrence of RV failure (30). Interestingly, LV and left atrial

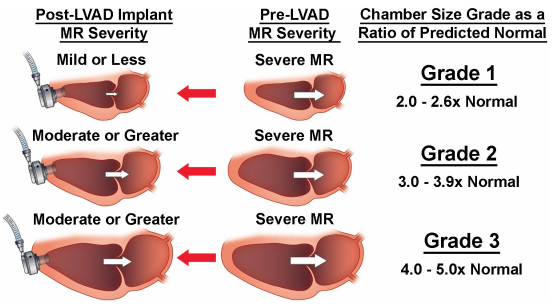

FIGURE 2
Despite decompression by left ventricular assist device (LVAD) implantation, larger pre-LVAD left heart dimensions (grades 2 and 3) are less likely to down size sufficiently to allow mitral leaflet coaptation due to severe tethering.

(LA) sizes greater than 3 times the normalized dimensions had twice the risk of having residual SMR at last follow up compared to those less than 3 times the normal size (50–55% vs. 25% respectively). Increased LA, LV, and mitral annular sizes were all significantly associated with post-cfLVAD MR severity. However, LA dimensions had the strongest correlation which is consistent with the now recognized contribution of LA dilatation to functional MR. Larger LA are more likely to have elevated atrial pressures, mitral annular dilatation, LA fibrosis, impaired atrial systole/diastolic function (8). Indeed, very large hearts (**Figure 2**; 30) had the greatest LA volumes despite LVAD decompression of the ventricle and also had the largest incidence of residual SMR (55.6%) (30).

It is important to note while LVAD decompression greatly reduced cardiac volume, mitral annular dimensions, and leaflet tenting, this may did not correlate with leaflet coaptation nor MR resolution in patients with very large hearts (30). This is congruent with Kitada et al.'s findings where preoperative posterior displacement of the mitral leaflet coaptation point

was a predictor for significant residual MR at 1 week following LVAD implant (1). Thus, in the setting of extreme baseline leaflet tethering associated with a very dilated LV, mitral leaflet coaptation may not be achieved despite the maximum degree of LVAD decompression. LVADs decompression of the LV is limited by its negative impact on right ventricular (RV) function as well as competing goals of promoting aortic valve (AV) opening and native LV ejection.

While 37.7% of patients with pre-LVAD severe MR had residual SMR, only 16% of those with moderate MR pre-LVAD had residual SMR (41). Therefore, a great majority (84%) of patients with pre-LVAD moderate MR had improvement to mild or less following device implant (41). Indeed, indications for surgical intervention for moderate MR in other non-heart failure settings (e.g., coronary bypass grafting) have been more controversial than the general consensus to correct severe MR (42–44). Given data suggesting a different rate of preoperative moderate vs. severe MR resolution after LVAD, there are unique considerations when faced with moderate MR in a LVAD candidate. Importantly, patients with residual SMR had greater preoperative LVEDD and LVESD and this population may be further defined in future studies for prediction of MR resolution. This also supports findings in the Momentum 3 trial where greater LV dimensions were predictive for residual significant MR in the combined moderate and severe MR groups (45). It is possible that moderate MR patients with larger LV dimensions may be identified for MV intervention. However, the patient population selected for mitral intervention during LVAD implantation needs to be accurately selected to avoid unnecessary procedures and prolonged cardiopulmonary bypass times in these high-risk patients.

Interaction of residual mitral regurgitation with aortic and tricuspid valve pathologies

Mitral regurgitation and the tricuspid valve

Patients with heart failure often have associated single or multi-valvular pathologies (46). However, most studies have focused on single valvular lesions when assessing their impact on postoperative outcomes such as impact on right ventricular (RV) function. The complexity of RVF pathogenesis post-cfLVAD means that it is unlikely to be fully accounted for by a single valvular lesion. Concomitant tricuspid regurgitation is highly prevalent in those presenting with mitral valve pathologies (47, 48), and is also frequently observed in patients undergoing surgical or transcatheter aortic valve replacement (TAVR) for aortic stenosis (49–51). For example, the mitral and tricuspid valves exist in series with the tricuspid valve being upstream in location and subject to forces exerted in a retrograde direction. Indeed, severe regurgitation of both mitral and tricuspid valve in the setting of biventricular failure had the highest incidence of post-LVAD RVF (20.3%) and RVAD use (17.2%) (39). The presence of significant tricuspid regurgitation may reflect several contributing mechanisms to RV dysfunction. Increased PVR from pre-LVAD persistent MR may lead to long standing RV dysfunction with remodeling and enlargement of the tricuspid annulus. This is a good indicator and likely contributes to predictably poor RV function after LVAD implant. Indeed, Accordingly, in the absence of associated moderate-severe TR in LVAD patients with severe MR, this phenotype is associated with a low incidence of RVF (5.5%) and RVAD utilization (4.5%) (39). In this setting associated pre-LVAD right ventricular dysfunction will likely be improved with LVAD support and diuresis since the tricuspid annulus is no chronically dilated from long standing RV dysfunction.

The presence of both severe TR and RV dysfunction is also highly associated with RVF with an Odds Ratio (OR) of 3.22. Echocardiographic evidence of moderate-severe RV dysfunction with moderate or less TR is a much weaker RVF predictor with an OR 1.78 ($P = 0.009$). This association with RVF is further strengthened if the patient also has severe MR along with significant RV dysfunction (39). A plausible explanation is that if severe TR persists despite diuresis and medical optimization, then this likely indicates long standing tricuspid structural remodeling with annular enlargement associated with chronic RV dysfunction as distinct from acute volume overload (39). Whether the finding of severe TR is a marker of significant underlying RV dysfunction as opposed to having an independent role in reducing RV forward flow remains less well-defined. Nevertheless, the implication is that TV repair for severe TR may not significantly improve RV function if residual SMR is present after LVAD implantation. Residual SMR will likely impair RV performance by increasing pulmonary artery pressures and afterload.

Indeed, we demonstrated that greater postoperative MR severity correlated independently with RVF (OR = 1.6) and RVAD use (OR = 1.6). We also excluded patients who underwent concomitant TV surgery and showed a strong positive correlation between the degree of post-cfLVAD MR and TR severity which suggests that residual MR imposes significant afterload on the right heart (32). It is likely that the population with significant residual MR coupled with moderate-severe RV dysfunction are most likely to benefit from restoring MV competency.

Currently, our practice is that severe TR especially in patients with a dilated tricuspid annulus are addressed with TV repair. The decision for TV repair is also determined by surgeon preference, and moderate TR is increasingly intervened upon over time. Until recently, MR was typically not repaired even if severe. Moderate-severe AI is uniformly addressed

intraoperatively but lesser degrees of AI have also been addressed by our group more recently as per surgeon preference.

Mitral regurgitation and the aortic valve

The combined effects of aortic and mitral regurgitation in the LVAD setting are not well-studied. However, studies of double left sided valve regurgitations in the non-LVAD literature have documented severe volume and pressure overload which is poorly tolerated as expected. LV remodeling in this setting is characterized by severe dilatation combined with an eccentric hypertrophic remodeling pattern (that is lower wall thickness to cavity ratio). Importantly, the presence of premature mitral valve closure which limits the flow reversal into the left atrium in severe aortic regurgitation contributes to poor clinical outcomes (52). Symptomatic patients with this pattern of valve lesions have worse LV function than those with isolated aortic or mitral regurgitation (53, 54). In the LVAD setting it would be expected that regurgitant volumes will be larger than the non-LVAD setting given mechanically driven continuous flow which is rapidly re-circulated. Native ejection if any, would also be reduced given greatly impaired forward flow.

Cowger et al. described progressive aortic insufficiency (AI) in LVAD patients contributing to worsening MR and this adversely impacted RV function (55). Indeed, in patients with pre-LVAD significant (moderate-severe) aortic insufficiency (AI) there was already a very high incidence of moderate-severe RV dysfunction (62.5%) and severe MR (38.9%) (39). While several studies have focused on new-onset AI after a lengthy duration of LVAD support (56), the implications of preoperative isolated AI are less clear. Interestingly, we showed that preoperative RV dysfunction associated with concomitant significant AI rarely results in severe RV dysfunction after LVAD implant especially when it is not accompanied by mod-severe TR (39). Since temporary mechanical circulatory support is generally contraindicated in the presence of severe AI, this may have contribute to timely LVAD implantation with AV intervention in this group. Furthermore, concomitant significant MR and AI can present with early symptoms resulting in prompt intervention. This may reduce the duration of exposure of the RV to elevated left sided pressures.

Approach to presence of MitraClip during left ventricular assist device implant

The MitraClip is increasingly used to address functional mitral regurgitation through transcatheter coaptation of mitral leaflets (57, 58). Although improvement of clinical symptoms and better exercise tolerance has been reported (57, 59, 60), controversies exist as to whether it translates into reduced heart failure admissions or improved survival (58, 59, 61–63). Regardless, a portion of patients treated with MitraClip do subsequently undergo LVAD implantation. The average mitral orifice area reduction from MitraClip is about 40–50% (64). It is important to carefully echocardiographically assess the mitral valve pre-LVAD, intraoperatively and post-LVAD. When LVAD candidates with MitraClip are assessed, the implanting team should ascertain how many Clips were placed as greater than 3 clips is likely to increase transmitral gradients after the low flow state is corrected by the LVAD (65). In practice, any clips causing more than mild stenosis pre-LVAD will likely need to be addressed (65). In the MitraBridge study, where 119 patients on the heart transplant list was treated with MitraClip, about 12.5% of patients had 3 or more Clips (66).

It is important to assess whether significant MR is present following MitraClip placement. This may indicate Clip dehiscence, single leaflet device implant, mitral leaflet injury (e.g., perforation) or thrombus formation on the Clip that may need to be addressed intraoperatively (67). In the absence of mitral stenosis or MitraClip specific issues, the clips can generally be left in place as it will help mitigate against significant residual MR. It is critical to re-assess intraoperative mitral gradients following full LVAD support to rule out mitral stenosis in the presence of normal flow volumes across the mitral annulus.

If mitral stenosis or MitraClip complications are present however, the surgical team needs to assess mitral apparatus integrity, mitral annulus and orifice size, magnitude of the transmitral gradient, and overall left heart dimensions. Indeed, larger left atrial and ventricular volumes are associated with an increased incidence of significant residual MR (30). If mitral stenosis is deemed present or likely, an attempt can be made to remove excess MitraClips if the mitral valve apparatus is not compromised. However, scarring around the device can be a barrier to effective removal. If all MitraClips are removed and cardiac dimensions are high, then an annuloplasty ring and/or an Alfieri central coaptation stitch should be considered to minimize the negative impact of significant residual MR.

Concomitant mitral repair with annuloplasty

Persistent MR also works against the LV pressure that can be produced by the ventricular myocardium to augment cardiac output as well as negatively impacting the ability to open the aortic valve consistently (68). Importantly, the use of cfLVAD support to reduce chamber and annular size needed to be balanced with the risk of septal shift resulting in worsened RV function (21). While it has been suggested that MR may not be relevant when considering the average lifespan of 4 years

for destination therapy patients (69), this rationale may become less relevant as LVAD technology increases in effectiveness, reliability and longevity. As suggested by Taghavi et al. and Tanaka et al., surgical correction of MR is an effective and reliable intervention for those who are likely to remain with significant MR following cfLVAD implant and can improve LVAD outcomes (36).

We find that a full annuloplasty ring that is 30 mm or greater will not usually cause stenosis in the LVAD setting. However, if the mitral valve apparatus is irrevocably damaged, we recommend mitral valve replacement (bioprosthesis) with chordal sparing. We prefer a transseptal approach to the mitral valve in this setting as it allows access to the tricuspid valve if intervention is planned and provides excellent hemostasis. The left atrium is often very large in patients with severe pre-LVAD MR and affords an excellent view of the mitral valve. Mitral intervention can often be performed without aortic cross-clamping in the presence of a competent aortic valve. To minimize the risk of air embolism in this setting, we vent the heart through the left atrium (*via* right superior pulmonary vein), left ventricular apex and ascending aorta. The iatrogenic atrial septal defect from the 24 French MitraClip catheter often resolves in 73% of patients by 1 year (70). If present however, we do close this to avoid systemic thromboembolic events, worsening of right ventricular function by left to right shunting or arterial desaturations from right to left shunting (70). More technical details on mitral surgery during LVAD implantation will be discussed separately in this topic series.

There have been concerns that concomitant MV surgery may increase the surgical risk due to increased cardiopulmonary bypass times and needing to cross-clamp the aorta in select settings such as aortic insufficiency. Indeed, longer cardiopulmonary bypass duration during LVAD surgery contributes to per-operative vasoplegia (71). We suggest that although aortic cross-clamping is at times necessary, concomitant MV intervention can often be done without cardioplegic arrest thus avoiding ischemic injury to the right heart (36). Furthermore, we target patients with larger cardiac sizes that are less likely to resolve MR with LVAD alone. These candidates often have very large atria and ventricles which afford excellent visualization of the mitral valve for expeditious surgical intervention.

Intervention for atrial fibrillation during left ventricular assist device implant

Co-existing atrial fibrillation and heart failure with reduced ejection fraction (HFrEF) commonly occur. Importantly, this combination of pathologies is associated with an increased risk of all-cause mortality and morbidity compared to either condition alone. Presence of both atrial fibrillation and HFrEF is associated with a higher risk of hospitalization, stroke, myocardial infarction, renal failure and death than in patients with either condition in isolation (72, 73). About 50% of patients presenting for mitral valve surgery have atrial fibrillation (74, 75). In comparison, a history of atrial fibrillation is present in 21–54% of LVAD patients (72, 76–79). Atrial fibrillation associated with LVAD therapy increases thromboembolic events such disabling strokes as well as pump thrombosis (72, 76, 80–82). Furthermore, atrial fibrillation in the LVAD setting is associated with right ventricular failure and elevated right atrial pressures (83). Increased ventricular rate from atrial fibrillation can contribute to right ventricular failure (84–86). Left atrial appendage ligation is associated with reduced risk of stroke in patients with atrial fibrillation (87, 88). Left atrial appendage ligation at the time of LVAD implantation has been performed either routinely (80) or only in the setting of atrial arrhythmias (81). This has been shown to decrease the rate of disabling stroke in LVAD patients (80). Our group currently performs left atrial appendage ligation in patients with atrial arrhythmias. This is achieved using the commercially available AtriClip or with an excise-and-sew technique with 4-0 or 5-0 prolene in 2 layers. It should be noted that the AtriClip will need to be excised if subsequent heart transplantation is performed but this is can usually be accomplished without great inconvenience.

Transcriptomic biology of mitral regurgitation in end-stage heart failure

It is known that greater MR severity during LVAD support is associated with a reduced likelihood of myocardial recovery (89). In comparison, MR resolution after LVAD was associated with partial or complete myocardial recovery (89, 90). While quantification of MR mainly focuses on hemodynamic parameters and imaging, myocardial biology is expected to have an important impact on MR improvement and myocardial recovery. End stage heart failure itself is well known to demonstrate elevated myocardial inflammatory responses (e.g., innate and adaptive immunity, complement activation) coupled with reduced expression of contractile and energetic/oxidative related proteins (91, 92). We previously reported that increased MR severity is associated with increasing myocardial immune transcriptomic responses (e.g., complement and innate/adaptive immune responses) in patients undergoing LVAD implantation. MR is also associated with decreased expression of transcripts related to structural and proliferative pathways (**Figure 3**; 91). Consistent with these biological findings, cardiac imaging in patients with degenerative MR show greater myocardial fluorine 18-lebeled fluorodeoxyglucose uptake which reflect increased myocardial inflammation (93). It is recognized that myocardial inflammation with the sequalae of cardiac injury can contribute to worsening of MR (93–95). Sarcoplasmic endoplasmic

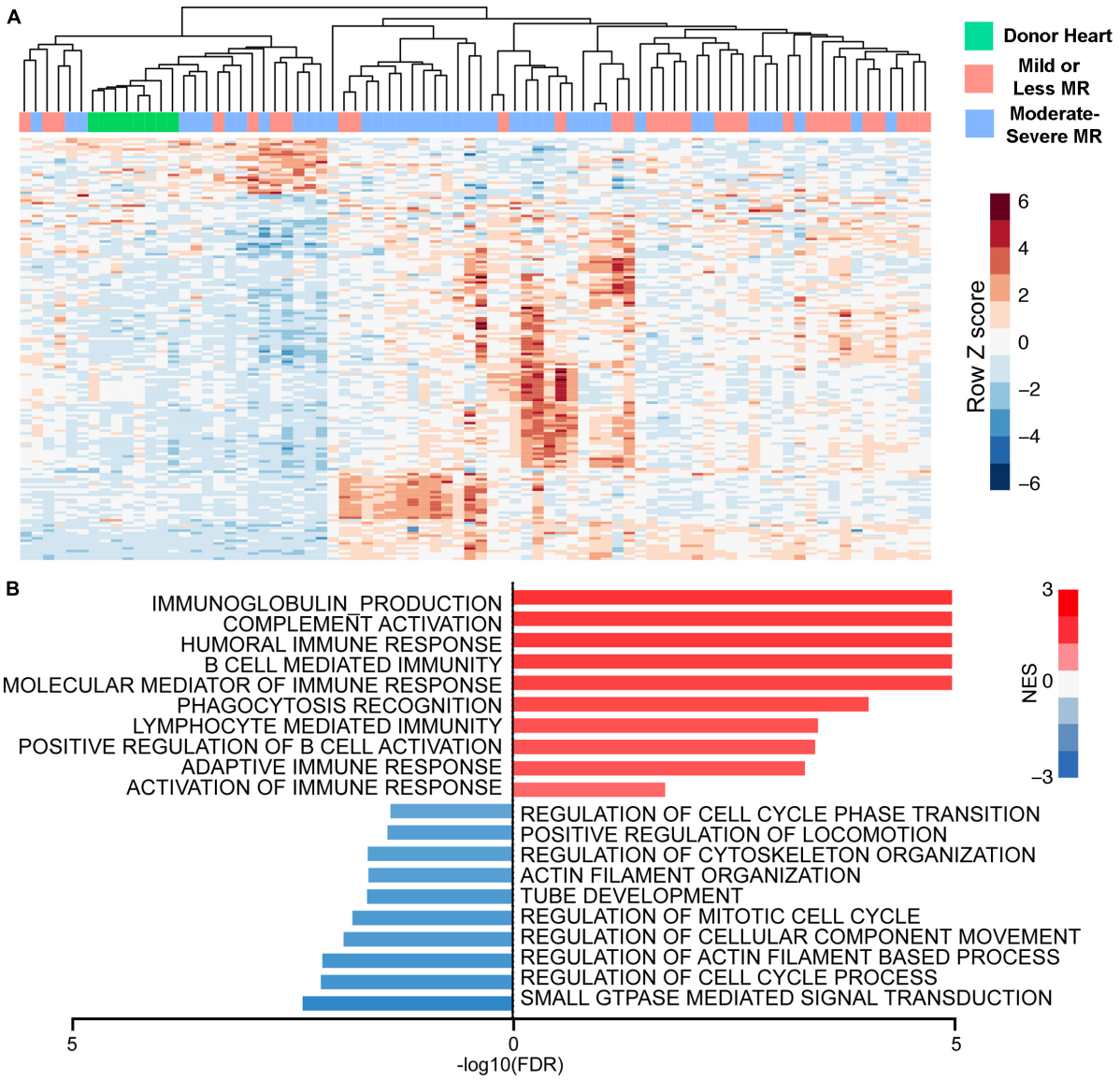

FIGURE 3
Greater mitral regurgitation (MR) severity is associated with heightened expression of immune response genes and down-regulation of genes associated with cellular proliferation and structure. **(A)** Heatmap of subtype specific differentially expressed genes (DEGs). **(B)** Gene set enrichment analysis using moderate-severe MR-specific regulated genes.

reticulum Ca^{2+} ATPase 2a (SERCA2a) expression is reduced in the presence of MR and is also associated with worsened LV function and increased ventricular dimensions (96).

Despite the diversity of myocardial molecular signaling underlying the clinical manifestations of MR, this aspect has received relatively little attention for clinical consideration. Published prediction models for LVAD outcomes such as right heart failure and myocardial recovery mainly utilized clinical parameters, imaging, and hemodynamics (28, 29), but not specific biological markers. We previously showed that patients with pre-LVAD moderate-severe MR expressing more myocardial inflammatory transcripts are more likely to resolve their MR (91). Conversely, reduced myocardial inflammation in patients with pre-LVAD moderate-severe MR may indicate a "burnt-out" phenotype with a non-viable and non-contractile LV wall with reduced compliance. These patients are more likely to have persistent MR after LVAD implant due to persistent mitral annular dilatation and poor leaflet coaptation. This is consistent with findings by our group and others that larger LV dimensions represent a more advanced stage of heart failure that is associated with persistent residual MR after LVAD (30, 97). Since severe MR resolves without intervention in about 62–80% of patients, using biomarkers

(e.g., inflammation) to identify those likely to have SMR and would benefit from concomitant mitral valve repair can help avoid unnecessary surgical interventions with inherent risks (20, 98).

Return of mitral competence with myocardial recovery during LVAD support may be contributed by reduced myocardial inflammation with the lack of significant MR (89). While inflammatory mediators such as IL-6 and TNFα are known to reduce cardiac function in myocarditis (99, 100). The sustained impact of low simmering degrees of inflammation associated with preoperative and/or residual post-LVAD moderate-severe MR is unknown. However, clinical drug regimens used to promote myocardial recovery in the LVAD setting all have significant anti-inflammatory actions. These agents include mineralocorticoid receptor inhibitors (101), ACE inhibitors or angiotensin receptor blockers (102) and beta-blockers (103). It should be emphasized that correcting the mechanical aspects of mitral regurgitation with valve repair or replacement is also critical. This can restore ventricular geometry, improve contractile mechanics and increase native cardiac ejection (104). Cardiac biology is highly complex in the setting of mechanical circulatory support for end stage heart failure. Molecular biological factors should be incorporated in our prognostic paradigms and therapeutic approaches when managing patients supported durable mechanical devices. It is also likely that novel circulating biomarkers can personalize our approach to targeted surgical heart failure therapies.

Challenges with evaluating the mitral valve in the left ventricular assist device setting

There are a number of challenges in the study of mitral regurgitation in the LVAD setting, Unfortunately, many studies of the mitral valve in the LVAD setting consists of single institution studies (19, 22, 32, 35, 36) with a low number of patients and thus underpowered. Institutional patient selection also has inherent biases which limit the validity of conclusions. For the relative few multi-institutional studies examining registries (17) and clinical trial data (11), the low data granularity limits our ability to detect patient subsets that may benefit from mitral intervention. Combining the analysis of patients with moderate versus severe MR or not comparing against an appropriate denominator population for example can limit our ability to draw relevant conclusions. Echocardiographic assessment for residual MR is often limited by artifacts from the inflow cannula of the LVAD which makes it difficult to align image windows with the MV (105, 106). Furthermore, the complication of RV failure is often not defined by a quantitative hemodynamic metric which leads to subjectivity. Detailed echocardiographic measurements describing RV function (e.g., tricuspid annular plane systolic excursion, RV ejection fraction, RV dimension) are often not available. Ventricular contractility is also load-dependent and can be temporally variable on echocardiographic examination. RVF was often not defined by a quantitative parameter of RV contractility which contributes to subjectivity. Other concomitant valvular interventions may have also influenced outcomes. Majority of studies are also limited by the retrospective single institutional design with associated biases. Future research protocols would likely benefit from the use of more comprehensive imaging modalities (e.g., 3-dimensional echocardiogram, cardiac computerized tomography or cardiac magnetic resonance imaging) to provide a more detailed assessment of heart function and anatomy before and after LVAD support.

TABLE 1 Features suggesting concomitant mitral repair for pre-LVAD severe mitral regurgitation should be considered.

Concomitant mitral valve repair may benefit those with the features below
1. Moderate or severe right ventricular dysfunction
2. Moderate or severe tricuspid regurgitation
3. Dilatation of the left ventricle to > 7 cm in diastole
4. Posterior displacement of the mitral coaptation point

Conclusion and considerations for future studies

Future studies about MR in the LVAD setting may be designed to consider a number of important issues. Multi-institutional studies enrolling many patients are needed to reveal the impact of significant MR on non-mortality related outcomes in the early to mid-term. The impact of MR on mortality may be better appreciated when improvements in LVAD technology allows longer support durations extending beyond 3 years and/or in those with destination therapy indications. Heart transplantation truncates the duration of LVAD therapy and likely blunts our ability to detect the impact of MR and/or its interventions. Future studies utilizing echocardiography can benefit by incorporating quantitative MR features (e.g., leaflet tethering measurements, quantitative assessment of MR severity, measuring mitral annular diameters, quantifying ventricular morphology), detailed description of hemodynamic parameters with right heart catheterization data (e.g., right heart hemodynamic measurement), and documenting relevant pump settings. Importantly, the duration of LVAD support (e.g., bridge to transplant, destination therapy) will likely determine the impact of residual MR. We have summarized some patient

factors that would support concomitant mitral intervention during LVAD implant in **Table 1**.

Since forward left-sided flow is generally excellent in the presence of a LVAD, the impact of residual significant MR likely rests with increased afterload imposed on the right ventricle. A longer period of exposure would be needed to manifest the negative impact of this on survival and readmissions. Future studies incorporating this interacting variable would be revealing (i.e., duration that the right heart is exposed to significant residual MR). Ultimately, larger studies on this topic including randomized clinical trials will be key. Finally, novel therapies to improve LVAD outcomes (e.g., myocardial recovery) with valvular lesions may incorporate several treatment goals including: (1) reducing wall stress, (2) correction of valve dysfunction to improve hemodynamics, (3) Use of pharmacological therapies that inhibit inflammation, promote cellular (e.g., cardiomyocytes) survival and increase myocardial energy production through activation of beneficial metabolic pathways.

Author contributions

P-EN, ND, FP, TC, and PT contributed to conception and design of the review. P-EN, MJ, and PT wrote the first draft of the manuscript. ND, MB, and IL wrote the sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pathophysiology and management of valvular disease in patients with destination left ventricular assist devices

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Over the last two decades, implantable continuous flow left ventricular assist devices (LVAD) have proven to be invaluable tools for the management of selected advanced heart failure patients, improving patient longevity and quality of life. The presence of concomitant valvular pathology, including that involving the tricuspid, mitral, and aortic valve, has important implications relating to the decision to move forward with LVAD implantation. Furthermore, the presence of concomitant valvular pathology often influences the surgical strategy for LVAD implantation. Concomitant valve repair or replacement is not uncommonly required in such circumstances, which increases surgical complexity and has demonstrated prognostic implications both short and longer term following LVAD implantation. Beyond the index operation, it is also well established that certain valvular pathologies may develop or worsen over time following LVAD support. The presence of pre-existing valvular pathology or that which develops following LVAD implant is of particular importance to the destination therapy LVAD patient population. As these patients are not expected to have the opportunity for heart transplantation in the future, optimization of LVAD support including ameliorating valvular disease is critical for the maximization of patient longevity and quality of life. As collective experience has grown over time, the ability of clinicians to effectively address concomitant valvular pathology in LVAD patients has improved in the pre-implant, implant, and post-implant phase, through both medical management and procedural optimization. Nevertheless, there remains uncertainty over many facets of concomitant valvular pathology in advanced heart failure patients, and the understanding of how to best approach these conditions in the LVAD patient population continues to evolve. Herein, we present a comprehensive review of the current state of the field relating to the pathophysiology and management of valvular disease in destination LVAD patients.

KEYWORDS

heart failure, left ventricular assist device, LVAD, tricuspid regurgitation, aortic insufficiency, mitral regurgitation

Introduction

Albeit the term "destination" appeared in the literature in the mid-nineties (1), destination therapy (DT) in reference to the implantation of durable mechanical support devices for advanced heart failure became embedded in the heart failure lexicon with the publication of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study in 2001 (2). In this multicenter prospective randomized trial, 128 end-stage heart failure patients ineligible for heart transplantation were randomized to either left ventricular assist device (LVAD) with the first-generation HeartMate VE (Thoratec Corporation, Pleasanton, CA) or to receive optimal medical management. Investigators reported a 48% reduction in the risk of death from any cause in the LVAD group as compared with the medical-therapy group, with Kaplan–Meier estimates of survival at 1 and 2 years being 52 vs. 25%, and 23 vs. 8%, respectively. In November 2002 the Food and Drug Administration (FDA) expanded the approved indications for the HeartMate^{TM} SNAP VE LVAS device from bridge to transplantation to include DT; the approval order stated that the device "is now also indicated for use in patients with New York Heart Association Class IV end-stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, who have a life expectancy of $<$2 years, and who are not eligible for cardiac transplantation" (3).

Since this initial FDA approval of implantable LVAD for DT, LVAD technology and strategies for managing LVAD patients have evolved considerably. Pre-existing native valvular heart disease as well as in-situ valvular prostheses were traditionally considered a contraindication to LVAD implantation (4). Due to the rapid initial expansion seen in the field of mechanical circulatory support, it was shown early on that surgical intervention could be undertaken to facilitate LVAD candidacy in patients with pre-existing valvular pathology with acceptable early morbidity or mortality (4, 5). The International Society for Heart and Lung Transplantation (ISHLT) in 2013 issued a list of recommendations providing guidance to all aspects of clinical management including associated valvular heart disease; an evidence-based approach was followed with majority of recommendations being level of evidence C or consensus agreement (6). Since then, the literature has been enriched by numerous clinical studies providing further insight into the underlying pathophysiology and associated mid- and long-term clinical outcomes.

In this review, we critically appraise the impact of valvular heart disease on LVAD patient outcomes and delineate the current state of the field regarding how concomitant valve disease is addressed both medically and surgically in this population. Furthermore, we review current concepts of development of de-novo valvular pathology post LVAD implantation and proposed preventative strategies.

Aortic valve

In a conventional arrangement, continuous-flow LVADs funnel left ventricular blood into the ascending aorta creating a transvalvular pressure gradient across the aortic valve. Theoretically, when the gradient is $>$0, the aortic valve remains persistently closed throughout the cardiac cycle altering not only physiological flow patterns within the aortic root, but also the distribution of mechanical stress on the proximal ascending aorta and aortic valve apparatus. The ensuing pathophysiological changes of leaflet deterioration, commissural fusion, and aortic sinus dilation may lead to worsening of pre-existing aortic insufficiency (AI) or lead to the development of *de novo* AI.

AI in the context of LVAD physiology effectively creates a closed-loop circulation between the ascending aorta and left ventricle, leading to suboptimal left ventricular unloading, reduced peripheral perfusion, and eventually recurrence of heart failure symptoms. Multiple studies have documented an increasing incidence of AI with the introduction of second-generation LVADs (7, 8). Furthermore, in a systematic review and meta-analysis of *de novo* AI during log-term LVAD support, investigators reported a pooled incidence of significant AI of 25% (11%−42%) during a support period of 412 $\pm$ 281 days (9). ISHLT guidelines have recommended consideration for surgical intervention during device implantation in cases with more than mild aortic insufficiency (Class 1, Level of evidence 3) (6). A comprehensive list of representative studies regarding the interplay of AI during LVAD implantation is provided in Table 1.

Patients developing moderate to severe AI during follow-up exhibit significantly higher left ventricular end-diastolic diameter, reduced cardiac output, and higher levels of brain natriuretic peptide. Furthermore, reduced left ventricular unloading in this circumstance is ultimately reflected back toward the unsupported right ventricle, increasing right ventricular afterload. This predisposes to right ventricular failure and potentially limits the duration in which a single ventricular support configuration will be viable for the patient, which of course is paramount concern for the DT patient who is unlikely to have an alternative viable support strategy. With these thoughts in mind, it is unsurprising that significant AI after LVAD implantation has correlated with higher rates of rehospitalization and mortality conditional upon survival to 1 year (17). Another extremely rare but dreaded complication that may be seen in this clinical setting is aortic valve and aortic root thrombosis (20).

TABLE 1 Key studies in chronological order of publication reporting on the interaction of AI and LVAD implantation.

References	Design	Year	Study groups	*N*	Main outcome
Cowger et al. (7)	Retrospective Single institutional	2010	LVAD (HM-XVE/HM II)	78	Early evidence of progressive nature of AI post LVAD implantation
Pak et al. (8)	Retrospective Single institutional	2010	LVAD (HM-XVE/HM II)	130	*De novo* AI with LVADs shown to occur frequently
Toda et al. (10)	Retrospective Single institutional	2011	LVAD (Toyobo-VAS/HM II/Novacor)	47	Significantly worse survival in patients who developed *de novo* AI at 1 year after LVAD implantation
Dranishnikov et al. (11)	Retrospective Single institutional	2012	LVAD (HVAD/HM II/Incor) with -AV replacement -No AV procedure	 19 299	Concomitant aortic valve replacement and LVAD implantation is not associated with an impaired outcome
Rajagopal et al. (12)	Retrospective Single institutional	2013	LVAD (HM-XVE/Novacor/HM II/HVAD/Ventracor VentaAssist) Control	184 132	*De novo* or progression of native AI more pronounced with Cf-LVADs to control cohort (medical treatment)
Cowger et al. (13)	Retrospective Single institutional	2014	LVAD (HM II)	166	Albeit common post LVAD implantation, AI was not seen to affect survival
Hiraoka et al. (14)	Retrospective Single institutional	2015	LVAD (HM II/HVAD/Ventracor VentaAssist)	99	AI was not seen to affect survival at 1 year
Robertson et al. (15)	Retrospective Registry (INTERMACS)	2015	LVAD (mostly HM II) with -AV closure -AV repair -AV replacement	 125 95 85	AV closure was associated with increased mortality when compared with repair or replacement in patients with AI who underwent LVAD implantation
Holley et al. (16)	Retrospective Single institutional	2017	LVAD (HM II)	237	AI was seen to increase over time without having an impact on long-term mortality
Truby et al. (17)	Retrospective Registry (INTERMACS)	2018	LVAD (Continuous Flow LVADs)	10,603	1,399 patients on LVAD support developed moderate to severe AI; investigators showed negative impact on hemodynamics, hospitalizations, and survival
Tanaka et al. (18)	Retrospective Single institutional	2020	LVAD (HM II/HVAD) with -mild AI -trace or no AI	 111 493	Uncorrected mild aortic insufficiency had a higher risk of progression to moderate or greater aortic insufficiency after left ventricular assist device implantation with worse functional status and higher incidence of heart failure related readmission
Jimenez Contreras et al. (19)	Retrospective Single institutional	2022	LVAD -HM II -HM 3	 452 252	A trend for less progression to moderate/severe AI seen with HM3 implantation

AI, aortic insufficiency; AV, aortic valve; LVAD, left ventricular assist device; HM2, heartmate 2; HM3, heartmate 3; HVAD, heartware ventricular assist device.

Aortic insufficiency at index LVAD procedure

The decision of whether and/or how to intervene on pre-existing aortic insufficiency at the time of LVAD implant is influenced by a variety of factors. Chief among them is the severity of aortic pre-existing insufficiency. Traditionally, moderate or greater AI has prompted intervention while mild AI at the time of LVAD implant has often been managed without procedural intervention (6). However, as will be discussed in greater detail later on, it is now well appreciated that AI is likely to worsen with time following LVAD support. Therefore, particularly in the DT population where duration of LVAD support may be anticipated to be relatively longer in comparison to bridge to transplant patients, there may be consideration for correction of even mild degree of AI at the time of LVAD implant.

Once the decision to intervene on the aortic valve at the time of LVAD implant has been made, a variety of surgical approaches to deal with aortic valve pathology during LVAD implantation have been described including aortic valve closure (21, 22), repair (23, 24), and replacement (11, 25). In the presence of previous mechanical aortic valve replacement, closure techniques with a sandwich plug or patch (22, 26) have been described although most groups prefer converting these valves to bio-prostheses. With in situ bio-prostheses perioperative

assessment will dictate the requirement of replacement if there is evident structural deterioration. In native aortic stenosis the degree of preexisting AI in the case of mixed disease will guide the need for intervention.

Robertson et al. (15) demonstrated that aortic valve closure was associated with increased mortality in comparison to aortic valve repair/replacement analyzing INTERMACS data from 305 patients who underwent concomitant aortic valve procedures during LVAD implantation; an increased incidence of postoperative AI was the pathophysiologic trade-off observed with aortic valve repair. The main concerns with aortic outflow tract closure are the potential catastrophic outcome in the setting of sudden pump failure as well as the limitations that will be encountered in the event of myocardial recovery and consideration of LVAD decommission. Many groups have implemented central oversewing to approximate the fibrous nodules of Arantius (Park's stitch) (27) to deal with preoperative AI with variable mid- and long-term outcomes in regards to AI recurrence (28–30). The decision-making in this paradigm is heavily influenced by an attempt to limit aortic cross-clamp time; operative experience, quality of aortic leaflet tissue, as well as projected time of support are all factors to be considered by the operating surgical team.

Aortic insufficiency after LVAD implantation

Multiple studies have demonstrated that AI during continuous flow LVAD support is a progressive disease (9, 17). Reviewing INTERMACS data from 1,399 patients who developed moderate to severe AI during follow-up, Truby et al. (17) reported a temporal increase in the prevalence of significant AI with predictors of worsening AI including older age, female sex, smaller body mass index, mild pre-implantation AI, and DT. Recent data has shown the impact of uncorrected mild AI at the index implantation with 44% developing moderate or greater AI within 2 years follow-up (18); interestingly 9% of patients with no AI at the original implantation were seen to develop *de novo* AI. Failing conventional medical treatment strategies for AI, including blood pressure control (goal mean of 60–80 mmHg), diuretic therapy, and pump speed optimization with concomitant right heart catheterization (31), more definitive treatment will be required.

Conventional surgical approaches to ameliorate post-LVAD AI have been carried out with good results, accepting the risks of redo sternotomy and right ventricular injury as well as failure (32). In order to reduce procedural risk in this cohort of comorbid patients, percutaneous transcatheter approaches including transcatheter aortic valve replacement (TAVR) and percutaneous occlude devices of native or bioprosthetic prostheses have been developed (33–36). In a systematic review and meta-analysis of percutaneous transcatheter interventions for AI in continuous flow LVAD, TAVR and occlude devices demonstrated similar efficacy in significantly reducing severe AI (37).

Although variable device success has been demonstrated with TAVR for native pure AI (38), encouraging data has been produced from second-generation transcatheter heart valves that incorporate leaflet-clasping mechanisms to anchor themselves in the absence of valvular apparatus calcification (39). Such devices may become an important part of the armamentarium to address post-LVAD AI.

Preventative measures

In a meta-analysis of eight studies with a total of 548 patients, Gasparovic et al. (40) reported a pooled incidence of *de novo* AI of 37%, with predictors of development and progression being older age, persistent aortic valve closure, female sex, and duration of LVAD support. Furthermore, Patil et al. (41) reported systolic blood pressure at 3 months, aortic valve closure and longer support duration being independent predictors of *de novo* AI following LVAD implantation. It is therefore pertinent that pump speed optimization takes place under hemodynamic and echocardiographic guidance prior to discharge, especially in patients fitting the above criteria. Strict blood pressure control during follow-up in combination with continuous outpatient hemodynamic and echocardiography-directed pump speed optimization allowing for at least intermittent AV opening is thought to potentially reduce the development and progression of AI after LVAD implant. By allowing intermittent aortic valve opening there is putatively less aortic commissural fusion and aortic root dilation, both of which are mechanisms for the development of AI post LVAD implant. Pulsatility or intermittent low-speed algorithms that may facilitate aortic valve opening may also prove of clinical significance in the future (42).

As commencement of LVAD support will instantly decrease left ventricular end-diastolic pressure and increase proximal ascending aortic pressure, the resulting increase in transvalvular gradient may unveil clinically significant AI that was "masked" by severe heart failure (15). This is probably even more applicable to patients with pre-existing increased proximal ascending aortic dimensions (43). Intraoperative assessment of the aortic valve pre- as well as post- LVAD implantation is therefore recommended in the context of DT.

Regarding intraoperative procedural modifications, the field of computational fluid dynamics (CFD) has offered a great degree of translational insight. Callington et al. (44) demonstrated that a lower outflow graft anastomosis location with appropriate angulation (inclination angle $\geq 90^{\circ}$, azimuthal angle of 60° or 120°) might reduce blood flow stagnation in the aortic root and produce normal wall shear stress and

moderate pressure values in the region. Part of the authors' hypothesis was that a high root pressure due to the jet flow might contribute to *de novo* development of AI post LVAD implantation. Furthermore, an LVAD management strategy that allows intermittent AV opening has been shown with CFD simulations of blood flow, including platelet-surrogate dynamics, to improve biocompatibility by promoting platelet washout, reducing stasis, and decreasing thrombogenicity (45). More recently, Kasinpila et al. (46) also have shown that development of AI is associated with increased flow recirculation and turbulent eddies at the aortic root region; the distance from aortic root to the outflow graft was smaller in patients who developed AI.

Mitral valve

Mitral regurgitation (MR) affects up to 10% of the general population, making it the most common heart valve disorder (47). In patients admitted with decompensated heart failure, between 36 and 53% of patients have MR of at least moderate severity, and its presence is associated with a poorer prognosis (48–50). The mitral valve and its apparatus forms a complex structure, and its function is intrinsically linked to left ventricular size and function. Amongst patients with heart failure the most common etiology is functional MR. Adverse ventricular remodeling leads to annular dilation and papillary muscle displacement, resulting in leaflet tethering and failure of coaptation. Impaired systolic function and ventricular dyssynchrony reduce the valve closing forces and further contribute to leaflet tethering. MR itself leads to increased volume loading of the left ventricle (LV), resulting in further LV dilation and creating a vicious cycle. MR may be secondary to other conditions, such as rheumatic heart disease or congenital abnormalities, and may be the primary cause of heart failure, or exacerbate cardiac insufficiency in a patient with co-existing heart failure. Gene expression analysis of myocardium from patients with significant MR undergoing left ventricular assist device (LVAD) implantation show increased expression of genes associated with inflammation, and reduced expression of cell energetics and proliferation genes, suggesting that these patients are a distinct subset of patients with cardiomyopathy, which may impact on response to therapies (51).

Conventional heart failure pharmacological treatments and cardiac resynchronization therapy have been shown to reduce the severity of MR through positive remodeling and reduction in the degree of ventricular dyssynchrony (52, 53). Prospective trials of percutaneous mitral valve edge to edge repair in patients with functional MR have provided mixed results. However, there may be benefit in a subset of patients with severe MR and LV systolic impairment on optimal medical therapy (54, 55). Functional MR can also be treated with conventional mitral valve repair or replacement, either alone or at the time of other surgical procedures such as coronary artery bypass grafting. Repair is associated with high rates of recurrent MR, and the benefits in terms of long term clinical outcomes has not been established (56). A prospective study of percutaneous mitral valve repair in patients listed for heart transplantation reported a procedural success rate of 87.5%, with low complication rates. Almost one quarter of patients were taken off the transplant list at 1 year due to clinical improvement, suggesting that this is viable therapy in patients with advanced heart failure (57). There have been concerns regarding the effect of percutaneous mitral valve repair on subsequent LVAD placement, as the functional mitral stenosis may affect left ventricular filling. However, a propensity matched study of 27 patients with prior percutaneous valve repair demonstrated similar 2-year outcomes to a matched group with untreated functional MR with pulmonary artery and wedge pressures being lower in patients with prior valve repair (58).

In patients with end stage heart failure that has proven refractory to conventional heart failure therapies, approximately one third have at least moderate to severe MR (59). Effective LVAD therapy leads to mechanical unloading of the LV and a reduction in pulmonary artery pressures. This leads to changes at the myocyte and biochemical level, resulting in positive ventricular remodeling, and reduction in left ventricular volumes (60, 61). The marked early improvement in MR severity in most patients following LVAD implantation alone means that concomitant mitral valve surgery is rarely required. In the pivotal MOMENTUM 3 study, which compared a third generation centrifugal LVAD, the HeartMate 3 (Abbott, Abbott Park, IL), with a second-generation axial flow pump, the HeartMate II, 43.5% of patients had at least moderate MR or greater prior to implantation and did not undergo concomitant mitral valve intervention (62). At 1 month following implantation, 6.2% of patients treated with the HeartMate 3 device had residual MR, as compared to 14.3% in the HeartMate II arm. After 2 years of LVAD support, the proportion of patients with clinically significant MR remained low, 9.4% in the HeartMate 3 group vs 15.4% in the HeartMate II arm.

In an INTERMACS analysis that examined all LVAD implantations between 2008 and 2014, 263/4930 adults with moderate to severe MR underwent a concomitant mitral valve procedure, of whom 96% received a mitral valve repair (63). Patients undergoing mitral valve intervention had higher pulmonary artery pressures, more severe MR, and were more likely to have had prior mitral valve intervention. No difference in short- or long-term survival was seen in patients undergoing mitral valve procedures, although there was a reduction in re-hospitalization, predominantly due to a reduction in right heart failure. A systematic review of 8 studies examining the role of mitral valve intervention at the time of LVAD implantation failed to show a survival benefit as compared to LVAD implant alone (64). Consensus guidelines supported by the ISHLT and

American Association for Thoracic Surgery state that routine repair or replacement for severe MR is not recommended. Routine replacement of a properly functioning mechanical mitral valve is also not recommended.

Data on long term outcomes in patients with residual MR is conflicting. A recent INTERMACS analysis of patients receiving implants between 2006 and 2017 revealed that 18.8% of patients had at least moderate MR at 3 months post LVAD implant (65). Incidence of late right heart failure and renal failure were higher post-operatively, and there was a trend toward increased longer term mortality. Similar findings were also seen in a single center, which revealed that in the 20% of patients with residual MR, right ventricular function was worse and dimensions larger. Time to first hospitalization was significantly shorter amongst those with significant MR (66). However a more contemporary analysis incorporating data from the MOMENTUM 3 study and continued access protocol showed no difference in survival, rehospitalization rates or incidence of right heart failure in patients with residual MR (67).

There is limited data examining the impact of residual MR specifically in patients receiving an LVAD as DT. In one study that included 91 patients, 68% had moderate or severe MR. The presence of at least moderate MR was an independent predictor of reduced survival at 30 days and 2 years (68). In the previously discussed INTERMACS analysis of concomitant mitral valve procedures, there was no overall benefit from intervention. However, in the subgroup of patients implanted as an initial DT strategy, there was a trend for higher 2-year survival for patients that underwent mitral valve intervention (73% vs 64%, $p = 0.09$) (63). This data would suggest a potential benefit of mitral valve intervention in the subset of LVAD patients implanted as DT, although the numbers analyzed are too small to draw definitive conclusions.

Predicting which patients are likely to be left with residual MR is challenging. Those at increased risk appear to be younger, more likely to be female, non-Caucasian, with non-ischemic etiology of heart failure (65). They also typically have worse right ventricular function, more tricuspid regurgitation (TR) and higher pulmonary artery pressures (66). More severe MR at baseline, and larger LV end diastolic diameter are consistent risk factors across different cohorts (69). A single center study identified that patients with persistent atrial fibrillation and larger left atrial dimensions were less likely to achieve a significant reduction in MR severity, and had worse long term survival (70). This suggests that LVAD therapy is less effective at left atrial remodeling and may have limited impact on MR severity if left atrium enlargement is a significant contributor to mitral annular dilation. Posterior displacement of the mitral coaptation point also predicts residual MR risk (71). While those with predominantly Carpentier type 1 MR due to annular dilation are likely to improve following LVAD implantation, type IIIb valve dysfunction due leaflet and chordae restriction may be less likely to improve, as LVAD unloading will reduce closing forces and may further limit coaptation (72).

Perioperative measures may reduce the risk of residual MR. Appropriate inflow cannula alignment, as determined by a combined assessment of anterior and lateral angulation was associated with greater improvement in MR severity at 1 month (73). Use of centrifugal flow LVAD pumps is also associated with a greater reduction in MR, as compared to axial flow pumps (62). Hemodynamic optimization of LVADs is a key component of long-term care. Selection of the most appropriate pump speed through ramp testing and right heart catheterization have been shown to reduce pulmonary capillary wedge pressures, through improved mechanical unloading (74). Whether this translates to a reduction in MR severity has not been assessed. Institution of guideline directed heart failure therapies in patients with long term LVADs has been shown to improve survival and quality of life (75). One small prospective study demonstrated that medical therapies in LVAD supported patients aids remodeling through a reduction in left ventricular dimensions and mass more than LVAD alone, however there was no impact on the degree of MR (76). A comprehensive list of representative studies regarding the interplay of MR during LVAD implantation is provided in Table 2.

Mitral stenosis and prosthetic mitral valves

Mitral stenosis impairs left ventricular filling that leads to reduced flows in an LVAD supported patient. Therefore, mitral valve repair or replacement is recommended in patients with moderate or severe mitral stenosis of any cause. The presence of a prosthetic mitral valve is not a contraindication to LVAD implantation. Trans mitral flow typically improves following LVAD implantation, therefore the risk of thrombus formation is low. The 2019 European Association of Cardiothoracic Surgeons Expert Consensus recommend that 'Exchange of a functional mitral mechanical or biological prosthesis at the time of long-term mechanical circulatory support device implantation is not recommended (84).

Tricuspid valve

Moderate or severe tricuspid regurgitation (TR) is seen in around 20% of patients with chronic heart failure, and around a third of patients presenting with acute heart failure (85). Its prevalence increases as heart failure severity worsens and is associated with higher morbidity and mortality (86).

Right ventricular remodeling is a common consequence of left ventricular systolic impairment and/or left sided valve dysfunction, because of pulmonary arterial hypertension. This

TABLE 2 Key studies in chronological order of publication reporting on the interaction of MR and LVAD implantation.

References	Design	Year	Study groups	*N*	Main outcome
Taghavi et al. (77)	Retrospective Multi-institutional	2013	LVAD (HM II) with -MV intervention -No MV intervention	 21 36	No difference in survival at 1 year. MV intervention was associated with a decrease in pulmonary vascular resistance
Goodwin et al. (78)	Retrospective Single institutional	2017	LVAD (HM II/HVAD) with <moderate-severe MR ≥ moderate-severe MR	 195 43	Resolution of MR was sustained at 180 days post LVAD implantation. No difference in survival was seen between two groups
Kassis et al. (66)	Retrospective Single institutional	2017	LVAD (CfLVADs)	69	Significant residual MR post-LVAD implantation was associated with persistent pulmonary hypertension, worse RV function, and significantly shorter time to hospitalization and death
Fukuhara et al. (79)	Retrospective Single institutional	2017	LVAD (HM II/HVAD/VentracorVentaAssist/DuraHeart/DeBakey VAD) with >moderate MR and -MV repair -no MV repair	 52 63	Concomitant MV repair was associated with less frequent late right heart failure
Dobrovie et al. (80)	Retrospective Single institutional	2018	LVAD (HM II/HVAD) with None to moderate MR Severe MR	 63 65	Preoperative severe MR resolves in most patients early on after LVAD implantation and is not associated with worse clinical outcomes or intermediate-term survival
Robertson et al. (63)	Retrospective Registry (INTERMACS)	2018	LVAD (LVADs) and -MV repair -MV replacement -No MV procedures	 252 11 4,667	Concomitant MV procedure was not shown to improve survival, but a trend toward increased survival was seen in DT patients with moderate to severe MR who underwent MV procedure
Kawabori et al. (81)	Retrospective Single institutional	2019	LVAD (HM II/HVAD) with severe MR and -MV procedure -no MV procedure	 26 82	Investigators did not identify any advantage in outcomes for patients who underwent MV procedure
Okoh et al. (68)	Retrospective Single institutional	2019	DT LVAD (HM II) with baseline MR < moderate MR ≥ moderate MR	 29 62	≥ moderate MR was seen to be associated with worse survival at both short and midterm follow-up
Pawale et al. (82)	Retrospective Single institutional	2019	LVAD (HM II/HM 3/HVAD) with severe MR and -MV procedure -no MV procedure	 78 28	Concomitant MV repair can be carried out safely during LVAD implantation. Investigators suggest a better reduction in MR severity and reduced rate of readmission for heart failure
Kanwar et al. (62)	Retrospective Registry (MOMENTUM 3 trial)	2020	LVAD with >moderate MR -HM II -HM 3	 206 197	HeartMate 3 was seen to improve clinically significant MR earlier, sustainably, and to a greater degree than HeartMate 2. Outcomes following LVAD implantation were not influenced by baseline or residual MR
Cruz Rodriguez et al. (83)	Retrospective Single institutional	2021	LVAD (HM II/HVAD)	111	Residual moderate to severe MR was found to be present in 1/4 of patients. An association was found with increased incidence of right heart failure, higher mean pulmonary pressure, and pulmonary capillary wedge pressure with no effect on 1 year survival
Jain et al. (65)	Retrospective Registry (INTERMACS)	2022	LVAD (CfLVADs)	8,364	18.8% of patients were found to have residual MR with concomitant mitral valve procedures appear to reduce this risk. Residual MR was associated with worse clinical outcomes

MR, mitral regurgitation; MV, mitral valve; DT, destination therapy; LVAD, left ventricular assist device; HM2, heartmate 2; HM3, heartmate 3, HVAD, heartware ventricular assist device.

causes tricuspid annular dilation and leaflet tethering, leading to functional TR. High right ventricular preload due to venous congestion also leads to volume loading of the right ventricle, increasing the degree of TR. A significant proportion of patients with chronic heart failure have cardiac implantable electronic devices and leads crossing into the right ventricle can also impair tricuspid valve closing. The right ventricle is sensitive to volume loading conditions, relief of venous congestion through effective diuresis can lead to favorable right ventricular remodeling and reduce the degree of TR (87). Targeted pulmonary vasodilator therapies in patients with left sided heart failure have not shown to be of significant clinic benefit and may be harmful (88).

Right ventricular failure remains a common early complication following LVAD implantation, and is associated with prolonged intensive care stays and increased mortality (89). Right heart failure following LVAD arises from a multitude of factors. Higher left sided output provided by the LVAD increases the preload delivered to a deconditioned right ventricle. Furthermore, displacement of the interventricular septum to the left side alters RV geometry and may further exacerbate TR. Perioperative transfusion of blood products, and hypoxia can place additional stress on the right ventricle. Nevertheless, predicting which patients will develop right heart failure remains a challenge, and requires a multi-modality assessment, combining clinical factors, cardiac imaging, and hemodynamic assessment. Severe TR was shown to be an independent risk factor for the requirement of mechanical right ventricular support in one study and was incorporated into a risk scoring system (90). However, larger retrospective analyses have failed to show that TR severity is an independent marker of risk for right heart failure (91–93).

TR typically improves in the first month following LVAD implantation, as the reduction in pulmonary artery pressures aids right ventricular remodeling. A EUROMACS registry study demonstrated that 65% of patients with moderate to severe TR pre implant have no to mild TR at 30 days post-implant (94). Patients with idiopathic dilated cardiomyopathies were more likely to improve as compared to other etiologies.

Despite the natural improvement in tricuspid valve competence post-LVAD in the short-medium term, the presence of at least moderate TR appears to complicate the early post-operative course, with a higher need for mechanical right ventricular support, prolonged inotrope use and intensive care stay (95). Whether TR is itself the cause, or whether it is simply a marker of severity of pre-operative right ventricular dysfunction remains debatable. Surgical correction of TR increases right ventricular afterload, which in turn may further compromise the function of a deconditioned right ventricle.

Concerns regarding early right ventricular recovery likely explains why tricuspid valve repair is the most frequent concomitant valve intervention performed at the time of LVAD implantation (96). However, there is wide variability in practice amongst different centers, with around one quarter of patients with moderate to severe TR undergoing tricuspid valve procedures, most commonly tricuspid annuloplasty (97).

Single center retrospective studies have suggested a reduction in rates of early right heart failure, improved postoperative outcomes, and reduced early rehospitalization in patients undergoing concomitant TV repair, without a clear survival benefit (98–100). A systematic review of eight retrospective studies showed no difference in rates of right heart failure, renal failure, early or late mortality (101). However, the group undergoing tricuspid intervention were sicker at baseline, with higher bilirubin levels and central venous pressure, which commonly portend a poorer prognosis. As these patients had similar post-operative outcomes, the authors suggested that tricuspid valve intervention may ameliorate this excess risk. Tricuspid valve intervention increased cardiopulmonary bypass time by an average of 35 min in this meta-analysis.

Larger registry database analyses have consistently failed to show a benefit from concomitant tricuspid valve intervention. A stratified INTERMACS registry analysis of 8,263 patients revealed an increased risk of adverse events, including bleeding, arrhythmia and stroke, and higher mortality in patients with moderate to severe TR undergoing valve intervention (102). Similarly, a Society of Thoracic Surgeons database analysis revealed an excess of adverse events in patients with significant TR undergoing concomitant tricuspid valve intervention, including higher rates of renal dysfunction, reoperation, and blood transfusion, as well as prolonged intensive care stay (103).

A prospective randomized controlled trial of tricuspid valve intervention (annuloplasty or replacement) vs no intervention was recently presented at the 2022 American Association of Thoracic Surgeons meeting (TVVAD trial) (104). The primary endpoint was incidence of right heart failure at 6 months. The trial was stopped early due to futility after enrolment of 60 patients. No differences were seen in any of the secondary endpoints, including all-cause mortality.

The durability of tricuspid valve repair at the time of LVAD implant is questionable, with between 21 and 37.8% of patients developing at least moderate TR at follow up (97, 105, 106). This was associated with higher rates of late right heart failure.

The European Association of Cardiothoracic Surgeons Expert Consensus on long term mechanical circulatory support recommend "Re-evaluation of patients with moderate to severe TR after treatment with diuretic therapy, if condition permits" (class 1C) and "In carefully selected patients, tricuspid valve repair for moderate to severe TR at the time of long-term mechanical circulatory support implantation may be considered" (Class IIb C) (84). This consensus document was published prior to the large INTERMACS analysis described earlier and the recently concluded TVVAD randomized trial. Furthermore, no studies have identified a specific subgroup of patients who may benefit from a concomitant TV procedure. Therefore, it is difficult to know which parameters to use in clinical decision making when selecting patients for

TABLE 3 Key studies in chronological order of publication reporting on the interaction of TR and LVAD implantation.

References	Design	Year	Study groups	*N*	Main outcome
Piacentino et al. (99)	Retrospective Single institutional	2011	LVAD with severe TR -TV procedure -no TV procedure	 34 81	Concomitant TV procedure was associated with improved early clinical outcomes. Furthermore, a trend toward improved overall survival was documented for the TV procedure cohort
Robertson et al. (103)	Retrospective Registry (STS Database)	2014	LVAD (CfLVADs) with >moderate TR -TV procedure -no TV procedure	 588 1,608	Concomitant TV procedure during LVAD implantation for moderate to severe TR did not reduce early death or right VAD requirement. Investigators documented overall worse early postoperative outcomes
Song et al. (97)	Retrospective Registry (INTERMACS)	2016	LVAD (CfLVADs as DT) with >moderate TR -TV procedure -no TV procedure	 215 757	Concomitant TV procedure did not result in improved survival with 21%−27% of patients undergoing TV procedure developing recurrent late TR
Critsinelis et al. (100)	Retrospective Single institutional	2018	LVAD (HM II/HVAD) with severe TR	59	Concomitant TV procedure did not impact patient outcomes but did reduce the incidents of 30-day readmission
Barac et al. (105)	Retrospective Single institutional	2020	LVAD (Durable) and TV procedure	156	37.8% of patients undergoing TV ring annuloplasty at the time of LVAD implantation had recurrent TR at intermediate follow-up. This was independently associated with late right heart failure
Veen et al. (94)	Retrospective Registry (EUROMACS)	2021	LVAD (uncorrected TR) -mild to moderate -moderate to severe	 1,690 806	Uncorrected TR was associated with increased early as well as late mortality. On average TR was seen to diminish progressively following LVAD implantation. Investigators suggested TR grade should not be the sole criterion for patient selection for TV procedure

TR, tricuspid regurgitation; TV, tricuspid valve; LVAD, left ventricular assist device: HM2, heartmate 2; HM3, heartmate 3; HVAD, heartware ventricular assist device.

concurrent TV repair, if this should be done at all. Future prospective studies should assess the impact of baseline factors, such as hemodynamic measures of right ventricular performance, echocardiographic measures such as TV annular diameter, TR severity (moderate vs severe), and clinical factors including INTERMACS status and inotrope score, to develop a personalized approach to assessing need for concomitant tricuspid valve intervention. A comprehensive list of representative studies regarding the interplay of TR during LVAD implantation is provided in Table 3.

Multiple valve pathology

Some degree of pathology involving multiple valves is commonly encountered in the advanced heart failure population undergoing LVAD implant. When there is significant pathology involving multiple valves, concomitant multiple valve intervention with LVAD implant may need to be considered. There is limited empirical data to guide clinicians in prognostication around LVAD implant with multiple concomitant valve intervention (summarized in Table 4), but it is intuitive that the longer cross-clamp and cardiopulmonary bypass that are associated with multiple valve intervention may predispose the patient to greater risk at that the time of LVAD implant. In general, the principles outlined above for individual valve pathologies may form a starting point decision making, but clearly the ultimate the decision over whether to move forward with LVAD implant surgical plan will need to be individualized based on patient-specific factors when confronting concomitant multiple valve pathology. Nevertheless, contemporary data does suggest that LVAD implant with concomitant multiple valve intervention can be undertaken with acceptable outcomes (107–110). In a single-center experience of concomitant valve procedures during LVAD implantation, Sugiura et al. (109) elegantly demonstrated no association with mortality; investigators reported on a cohort of 91 patients including 29 double valve procedures. Patients undergoing concurrent valve procedures did, however, have significantly higher risk of right heart failure as well as stroke that may be partially attributed to the longer cardiopulmonary bypass and cross-clamp times. The largest to date cohort of patients undergoing multiple valve procedures during LAVD implantation stems from analysis of the MOMENTUM 3 trial, which included

TABLE 4 Key studies in chronological order of publication reporting on the outcomes of concurrent multiple valve procedures during LVAD implantation.

References	Design	Year	Study groups	*N*	Main outcome
John et al. (107)	Retrospective Multi-institutional	2014	LVAD (HM II)		Multiple valve procedures were associated with a higher 30-day ($p = 0.04$), as well as 2-year ($p = 0.046$) mortality
			-No valve procedure	641	
			-Single valve procedure	205	
			-Multiple valve procedure	37	
Maltais et al. (108)	Retrospective Multi-institutional	2016	LVAD (HM II/HVAD)		Investigators concluded that survival was comparable between groups with no influence from concomitant procedures
			-No valve procedure	398	
			-Single valve procedure	190	
			-Multiple valve procedure	26	
Sugiura et al. (109)	Retrospective Single institutional	2019	LVAD (HM II/HVAD)		Concomitant procedures were not associated with increased mortality
			-No valve procedure	435	
			-Single valve procedure	62	
			-Multiple valve procedure	29	
John et al. (110)	Retrospective Registry (MOMENTUM 3)	2022	LVAD (HM3)		Adjusted analysis did not identify any difference in survival at 2 years between single and multiple valve procedures
			-No valve procedure	1,380	
			-Single valve procedure	325	
			-Multiple valve procedure	85	

LVAD, left ventricular assist device: HM2, heartmate 2; HM3, heartmate 3; HVAD, heartware ventricular assist device.

85 patients who underwent multiple valve intervention (110). An adjusted analysis performed by the investigators did not identify any difference in survival at 1 or 2 years between single and multiple valve procedures. These findings suggest that in selected patients undergoing LVAD implant concomitant valve intervention does not pose prohibitive risk.

Discussion

There appears to be a signal for temporal reduction in mortality risk associated with concomitant valve procedures during index LVAD implantation. Earlier studies have reported 30-day mortality rates ∼25% with combined aortic valve procedures, a nearly 5-fold increase relative to isolated implants (111). In contrast, in the more contemporary landscape, there is a growing body of literature that supports that concomitant valve surgery during LVAD implantation can be delivered without impacting survival, in selected patients (98, 108, 112). Although LVAD clinicians' knowledge and ability to manage concomitant valve disease in LVAD patients has likely improved over time, it is also true that LVAD technology has significantly evolved. This becomes evident from published outcomes of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), a multicenter, 1:1 randomized, pivotal study comparing the treatment efficacy of the HeartMate 3 LVAD with the HeartMate II LVAD in patients with advanced-stage HF (62, 113). The HeartMate 3 was shown to be more efficient at hemodynamic unloading of clinically significant MR early, sustainably, and to a greater extent. Furthermore, uncorrected baseline as well as residual MR had no influence on outcomes after LVAD implantation at 2-year follow-up (62). Further data from the MOMENTUM 3 trial portfolio that includes 2,200 patients, investigated the outcomes of 466 patients who underwent a concomitant valve procedure at the index LVAD implantation (110). Carrying out concomitant valve procedures exposed patients to early postoperative morbidity including stroke, bleeding, and right heart failure, but there was no detectable difference in 30-day mortality and 2-year survival. Furthermore, no difference in outcomes amongst patients with significant mitral or tricuspid regurgitation irrespective of corrective surgery was demonstrated. Based on their findings, investigators suggested that sufficient equipoise exists to consider a randomized trial assessing the benefit of commonly performed valve interventions during LVAD implantation. In conjunction with growing transcatheter-based procedural arsenal for the amelioration of valve disease, findings such as these imply decisions and strategies around the management of concomitant valve pathology are likely going to continue to evolve as the field moves forward.

The impact of valvular pathology on outcome measures in critically ill patients is well described (114). "Surgical acumen" instinctively dictates anatomical correction of all cardiac pathology to allow for best chance of myocardial recovery or remodeling. Despite many institutional as well as registry studies describing improved outcomes for some valvular pathology correction during LVAD implantation, the jury remains out for several individual pathologies. The question that comes to mind is: are patients being exposed to higher

risk implantations with increased perioperative morbidity and no detectable difference in outcomes? Individualized evidence-based medicine may answer partly this question; for example, smaller females undergoing LVAD implantation with pre-existing mild AI is probably a cohort that requires concomitant aortic valve intervention (19). As the majority of the relevant studies do not report long-term outcomes that are particularly pertinent in DT implant population, the necessity for additional prospective and longer-term follow up studies is evident. In the meantime, management strategies that include maintaining euvolemia, blood pressure control, and optimized hemodynamics allowing for intermittent aortic valve opening are imperative at reducing complications.

Author contributions

ID, PC, and JK performed literature review, manuscript preparation, and critical revision. MK, JP, CB, and CM performed critical revision. All authors approved of the final version of the manuscript prior to submission.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Concomitant or late aortic valve intervention and its efficacy for aortic insufficiency associated with continuous-flow left ventricular assist device implantation

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Moderate to severe aortic insufficiency (AI) in patients who underwent continuous-flow left ventricular assist device (CF-LVAD) implantation is a significant complication. According to the INTERMACS registry analysis, at least mild AI occurs in 55% of patients at 6 months after CF-LVAD implantation and moderate to severe AI is significantly associated with higher rates of re-hospitalization and mortality. The clinical implications of these data may underscore consideration of prophylactic aortic valve replacement, or repair, at the time of CF-LVAD implantation, particularly with expected longer duration of support and in patients with preexisting AI that is more than mild. More crucially, even if a native aortic valve is seemingly competent at the time of VAD implantation, we frequently find *de novo* AI as time goes by, potentially due to commissural fusion in the setting of inconsistent aortic valve opening or persistent valve closure caused by CF-LVAD support, that alters morphological and functional properties of innately competent aortic valves. Therefore, close monitoring of AI is mandatory, as the prognostic nature of its longitudinal progression is still unclear. Clearly, significant AI during VAD support warrants surgical intervention at the appropriate timing, especially in patients of destination therapy. Nonetheless, such an uncertainty in the progression of AI translates to a lack of consensus regarding the management of this untoward complication. In practice, proposed surgical options are aortic valve replacement, repair, closure, and more recently transcatheter aortic valve implantation or closure. Transcatheter approach is of course less invasive, however, its efficacy in terms of long-term outcome is limited. In this review, we summarize the recent evidence related to the pathophysiology and surgical treatment of AI associated with CF-LVAD implantation.

KEYWORDS

left ventricular assist device (LVAD), aortic insufficiency (AI), aortic valve replacement (AVR), aortic valve repair (AV repair), heart transplant (HTx)

Introduction

Moderate to severe aortic insufficiency (AI) in patients who underwent continuous-flow left ventricular assist device (CF-LVAD) implantation is a significant complication affecting long-term outcomes (1–7). According to the INTERMACS registry analysis, at least mild AI occurs in 55% of patients at 6 months after CF-LVAD implantation and moderate to severe AI is significantly associated with higher rates of re-hospitalization and mortality (1). The clinical implications of these data may underscore consideration of prophylactic aortic valve replacement (AVR), or repair, at the time of CF-LVAD implantation, particularly with expected longer duration of support and in patients with preexisting AI that is more than mild (8). More crucially, even if a native aortic valve (AV) is seemingly competent at the time of VAD implantation, we frequently find *de novo* AI as time goes by, potentially due to commissural fusion in the setting of inconsistent aortic valve opening or persistent valve closure caused by CF-LVAD support, that alters morphological and functional properties of innately competent aortic valves (9–13). Therefore, close monitoring of AI is mandatory, as the prognostic nature of its longitudinal progression is still unclear. Clearly, significant AI during CF-LVAD support warrants surgical or percutaneous intervention at the appropriate timing (14–18), especially in patients of destination therapy. Nonetheless, such an uncertainty in the progression of AI translates to a lack of consensus regarding the management of this untoward complication. Additionally, before facing to the evaluation of AI during CF-LVAD support, even today, we have not yet established a reliable, or reproducible, method of quantifying the grade of AI in those patients. In the patients under CF-LVAD support, color doppler method might not be enough to measure the amount of actual AI regurgitant flow, as in most circumstances, significant CF-LVAD-associated AI is a continuous one, not a diastolic one, due to continuous suction by the devices. Such another uncertainty, or variability, in the evaluation of AI might have partly contributed to a current lack of consensus in this topic.

In practice, proposed surgical options are AVR (19, 20), AV repair (21–28), AV closure (29), and more recently transcatheter aortic valve implantation (TAVI) (30–33) or transcatheter device closure (34, 35). Briefly, AVR with bioprosthetic valve could be a gold standard treatment for AI in CF-LVAD patients, especially when the native AV contains structural problems. However, it necessitates longer ischemic time, posing a concern of further deterioration of biventricular function in these VAD patients particularly with reduced right ventricular function at baseline. AV repair, or what we call central AV closure (CAVC) or Park's stitch (21, 22), is more simple and technically possible with shorter ischemic time under limited AV exposure. The drawback of CAVC is a durability specifically when the patients' expected support duration is long, such as destination therapy. AV closure could be a last option to consider, as the clinical outcome is not satisfactory (29). Finally, transcatheter approach is of course less invasive, however, its efficacy in terms of long-term outcome is limited. In this review, we summarize the recent evidence related to the pathophysiology and surgical treatment of AI late after CF-LVAD implantation.

Abbreviations: ISHLT, international society for heart and lung transplantation; INTERMACS, interagency registry for mechanically assisted circulatory support; AV, aortic valve; AVR, aortic valve replacement; HR, hazard ratio; OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association; CHF, congestive heart failure; CAVC, central aortic valve closure.

Pathophysiology of AI associated with CF-LVAD support

Although the true mechanisms of *de novo* AI under CF-LVAD support remain controversial, following three factors are likely to be associated with *de novo* AI: (1) continuous or intermittent AV closure due to the constant increase of aortic diastolic pressure with the decrease in LV end-diastolic pressure, (2) increased transvalvular gradient due to decompression of the LV, leading to stretching or partial prolapse of AV leaflets, and (3) pathologic changes or dilatations in the aortic sinus due to turbulent backflow with high blood velocity from a CF-LVAD outflow (11, 12). These factors could interact with one another, eventually yielding AV disorganization and/or commissural fusion, with a time-related manner. Historically, as diagnostic modalities were quite limited, the effect of CF-LVAD on aortic blood flow dynamics and kinetics as well as on AV physiology had not been fully elucidated. Today, computational fluid dynamic (CFD) studies have demonstrated that the blood stream from LVAD outflow could increase the shear stress on the aortic root and AV. Kasinpila et al. conducted a CFD study in 10 patients with *de novo* AI and 20 patients without AI after CF-LVAD implantation, and concluded that those who developed *de novo* AI had greater wall shear stress on the aortic root and their outflow grafts were placed closer to the aortic root than those patients without *de novo* AI (13). Similar CFD studies were reported by Yoshida et al. (9). They investigated the impact of non-physiological retrograde blood flow in the aortic root on *de novo* AI after CF-LVAD implantation by CFD analysis. Yoshida et al. demonstrated that those with *de novo* AI had a perpendicular outflow anastomosis at the ascending aorta, concluding the angle and position of LVAD outflow anastomosis might impact retrograde blood flow and *de novo* AI after CF-LVAD implantation (9). While higher wall shear stress on the aortic root could be associated with root or annular dilatation, eventually leading to AI progression, lower wall shear stress, as compared to physiological one, is known to be a cause of atherosclerosis (36). Based on the idea, Kainuma

et al. proposed a different explanation on the AV degeneration during CF-LVAD support (10). They used an intraoperative epi-aortic echocardiography and calculated wall shear stress by vector flow mapping technology. This *in-vivo* study, not a computational simulation, demonstrated peak wall shear stress on the ascending aorta, aortic root, and ventricularis of AV was significantly reduced by CF-LVAD support, as compared to baseline (before LVAD). Kainuma et al. suggested such an altered mechanical stress on the AV could be associated with the structural, functional, and histological changes of the aorta and AV (10). Thus, we need more prospective studies to fully clarify the true mechanism of LVAD-induced AI.

Incidence and clinical significance of late AI during CF-LVAD support

In contrast to the pathophysiology, the incidence of late AI during CF-LVAD support has been well-documented (1, 37). A recent analysis on the INTERMACS registry revealed late AI as a progressive disease that develops during CF-LVAD support with well-over 50% developing mild disease at 6 months of support and 15% developing moderate to severe within 2 years (1). Predictors of worsening AI included older age, female sex, smaller body mass index, mild pre-implantation AI, and destination therapy. Significant AI was associated with higher rates of rehospitalization (32.1 vs. 26.6%, $p = 0.015$) and lower rates of survival (77.2 vs. 71.4%, $p = 0.005$) (1). There are a few other recent single-institutional studies focused on detrimental effects of AI after CF-LVAD (2–6). Auvil et al. reported that they found moderate or greater AI in 8.5% of patients who underwent CF-LVAD implantation, at 6 months after the implant, and demonstrated that moderate AI was significantly associated with 2-year mortality after the implant [Odds ratio (OR) 4.32, 95% CI 1.21–15.4, $p = 0.024$] (4). Imamura et al. reported that worsening of AI was observed 53.7% of CF-LVAD patients at 3 months after the implantation, which was significantly associated with higher hazard of death or heart-failure readmission (HR 3.24, 95% CI 1.02–18.5, $p = 0.038$) (2). Kagawa et al. reported that 13.3% of CF-LVAD patients progressed to significant AI during median follow-up of 469 days, and mortality during the follow-up was significantly higher in the significant AI group (59.5 vs. 37.2%, $p = 0.006$) (5).

In contrast, there are several studies proposing that the influence of late AI on mortality during CF-LVAD support is not significant. Patil et al. reported that mild AI developed in 51.6% of CF-LVAD patients over a median duration of 126 days and moderate one developed in 14.0% over a median duration of 493 days (37). Like other studies, independent predictors of AI were duration of support and persistently closed aortic valve, although they did not find any association between AI progression and survival outcomes. Holley et al. showed that significant *de novo* AI occurred in 15.2% of patients after CF-LVAD implantation and such a *de novo* AI was not significantly associated with mortality (38). Compatible to the prior studies, they concluded that the independent predictors of late AI were older age, female gender, longer duration of LVAD support, and destination therapy.

As for the predictors of late AI, the effect of device type is a matter of much account and still controversial (18, 37, 39, 40). Historically, the development of intermittent low-speed (ILS) algorithm, or its analog, to avoid persistent closure of the AV, was expected to decrease the rate of late *de novo* AI (41–45). However, the favorable evidence of its efficacy on late AI is still limited. Patil et al. compared 58 HeartMate II (Axial pump, Abbott, MN, USA) cases with 35 HeartWare HVAD (Centrifugal pump, Medtronic, MN, USA) cases, and reported that the incidence of mild or greater AI was 43.1% in HeartMate II vs. 65.7% in HeartWare HVAD ($p = 0.035$, without baseline adjustment), during median follow-up of 527 days (37). Malic et al. compared 270 HeartMate II cases with 121 HeartMate 3 (Abbott, MN, USA), and reported that the cumulative incidence of mild or greater AI was 11.3% in HeartMate II vs. 8.4% in HeartMate 3 ($p = 0.68$, with baseline adjustment), at 1 year after VAD implantation (39). Finally, Jimenez Contreras et al. compared 562 HeartMate II cases with 300 HeartMate 3 cases, and reported that the incidence of moderate or severe AI was 17.0% in HeartMate II vs. 9.9% in HeartMate 3 at 6 months after VAD implantation. The multivariable Cox regression analysis demonstrated that the adjusted HRs of moderate or severe AI in HeartMate 3, as compared to HeartMate II, was 0.624 ($p = 0.0537$, 95% CI 0.386–1.008) (40). More recently, Uriel et al. presented based on MOMENTUM 3 pivotal trial (42), that the incidence of moderate or severe AI was 11.5% in HeartMate II vs. 5.6% in HeartMate 3 at 2 years after VAD implantation and the HRs of moderate or severe AI in HeartMate 3, as compared to HeartMate II, was 0.35 ($p = 0 < 0.01$, 95% CI 0.20–0.59) in their randomized study (46), which could be promising.

Thus, there are several conflicting studies to each other, regarding the risk factors of significant AI and its effect on mortality. However, given the results shown in the registry analysis (1), it would be reasonable to consider AV intervention at the time of CF-LVAD implantation in a patient with significant, or greater than mild, AI.

Concomitant intervention on the aortic valve at CF-LVAD implantation

Should we intervene on the AV with mild AI at CF-LVAD implantation?

Given these clinical impacts of late AI on the prognosis, some clinicians would advocate concomitant intervention on the AV at the time of CF-LVAD implantation, especially in

patients of destination therapy. According to the recent ISHLT guideline, greater than mild AI (assessed by echocardiography with appropriate afterload) should be addressed with either valve closure, repair, or replacement (8) (Class of recommendations: I, Level of evidence: B). However, there is no definite consensus on whether we should preventively intervene on a competent AV with mild or less AI at CF-LVAD implantation. The recent reports on the efficacy of concomitant AV interventions at the time of continuous-flow LVAD implantation were summarized in Table 1. Based on the IMACS registry analysis, Veenis et al. reported that, even after adjustment for other significant predictors, concomitant AVR remained an independent predictor for early (HR 1.23, 95% CI 1.04–1.45) and late (HR 1.48, 95% CI 1.15–1.89) mortality (47). It should be noted, however, that when they focused just on the patients with moderate to severe AI, concomitant AV intervention was not an independent predictor of mortality, indicating that this result would not preclude concomitant AVR or repair when the patient has significant AI at CF-LVAD implantation. Likewise, based on the IMACS registry analysis, Yalcin et al. demonstrated that concomitant AV surgery at CF-LVAD implantation was associated with increased risk of bleeding events (HR 1.158, 95% CI 1.018–1.317, $p = 0.026$), but not thromboembolic events (48). These findings may indicate that stringent criteria for a concomitant AV procedure at the time of VAD surgery may be warranted, especially in patients with only mild AI (47).

On the contrary, while there are several concerns for concomitant AV procedures, Tanaka et al. reported the detrimental impact of uncorrected mild AI at the time of CF-LVAD implantation on the non-survival outcomes (49). Although their analysis was a single-center one and did not demonstrate significant survival differences, after propensity-score matching, uncorrected mild AI was significantly associated with a higher risk of progression to moderate or greater AI (43.6% with the mean follow-up period of 2.3 ± 1.8 years) and worse NYHA functional class ($p < 0.01$). Notably, more CHF-related readmissions were observed in the mild AI group, as compared with no or trace AI (HR: 2.62, 95% CI 1.42–4.69) (49). Their results shed light on the need for proactive intervention on the mild AI at CF-LVAD implantation to improve the patients' quality of life in the future.

As for the surgical management of mild AI, Fukuhara et al. reported the efficacy of concomitant AV repair, or central AV closure as described later, at CF-LVAD implantation on the progression of AI (24). This study by Fukuhara is unique and worthwhile, in that they specifically focused on those with mild AI, to reveal whether we should intervene on the AV with mild AI simultaneously at VAD implant or not. In the AV repair group, freedom from AI greater than moderate at 2 years was 81.8% as compared to 45.0% in the AV non-repair group ($p = 0.031$), leading to no survival difference (24). Interestingly, their decision to perform a repair was made on the selected candidates with anticipated prolonged device support, such as destination therapy, bridge-to-transplant patients with large body size (body mass index >35) and bridge-to-transplant patients with blood type O (50). Given the recent refinements in surgical technique and expected longer waiting period in heart transplant candidates, the threshold of intervening on the AV would be gradually getting lower, especially in these selected candidates.

What is a desirable concomitant AV intervention at CF-LVAD implantation, AVR or AV repair?

An ideal AV procedure to treat AI, simultaneously with CF-LVAD implantation, is still controversial. Potential options could be AVR, AV repair, and AV closure. Based on the INTERMACS registry analysis, Robertson et al. reported that actuarial 1-year survival after CF-LVAD implantation was significantly worse in those who underwent concomitant AV closure (AV closure vs. AV repair vs. AVR, 63.2 vs. 76.8 vs. 71.8%, $p = 0.0003$) (51). As for the efficacy of AI treatment, they also demonstrated that AI recurrence rate (moderate to severe) at 6 to 12 months after the implantation was the highest in the AV repair group (AV closure vs. AV repair vs. AVR vs. No intervention, 5 vs. 19 vs. 9 vs. 10%, $p < 0.0001$) (51). Although Kurihara et al. reported the feasibility of AV (or left ventricular outlet) closure as a concomitant first-line procedure at CF-LVAD implantation, a disadvantage to close AV is that the patient will not be able to maintain hemodynamic stability if the device fails, and that bridge to recovery is no longer an option, as they admit (29). From these results, it would be reasonably safe to avoid AV closure from the first-line modalities.

While AVR with bioprosthetic valve contains a few issues, such as longer ischemic time, valve thrombosis, or commissural fusion (52), AV repair would be advantageous in terms of these issues, at the expense of potential recurrent AI in the future. As there are several other different techniques of AV repair in VAD-associated AI, for example aortic ring annuloplasty (25, 26), one of the most typical techniques among AV repair is a central AV closure (CAVC), or what we call Park's stitch, which was originally reported by Park et al. for a pulsatile LVAD in 2004 (21). This is basically a technique for central AI without any structural problems on the AV, by putting a simple coaptation stitch with a pledged supported 4-0 polypropylene sutures to approximate the fibrous nodules of Arantius. As compared to AV closure, the benefit of CAVC is that AV is still able to open for ejection, even though the effective orifice area is diminished. CAVC has the potential to be the ideal technique because it is inexpensive, quick, and simple to perform, and might not have the same degenerative potential as biologic valve prostheses. In 2014, Park's group first published its efficacy in CF-LVADs (22). They conducted a concomitant CAVC at

TABLE 1 Efficacy of concomitant aortic valve interventions at the time of continuous-flow LVAD implantation.

Study and design	*N*	Grade of AI	Results	Potential central messages
Veenis et al. (47) and retrospective, IMACS	AVR ($n = 457$) AV repair ($n = 328$) No AV surgery ($n = 14,482$)	Overall Severe (0.7%) Moderate (3.8%) Mild (31.2%)	Concomitant AVR remained an independent predictor for early (HR 1.226, 95% CI 1.037–1.449) and late (HR 1.477, 95% CI 1.154–1.890) mortality. Patients undergoing AVR or repair for moderate/severe AI had survival similar to those without AV interventions.	Resolution of mild AI may not outweigh the risks associated with AV surgery, whereas resolution of moderate/severe AI may improve LVAD management.
Yalcin et al. (48) and retrospective, IMACS	AVR ($n = 457$) AV repair ($n = 328$) No AV surgery ($n = 14,482$)	Overall Severe (0.7%) Moderate (3.8%) Mild (31.2%)	Thromboembolic rate was 8% in AV surgery group and 9% in no AV surgery group. Concomitant AV surgery was an independent predictor for bleeding events.	Stringent criteria for a concomitant AV surgery at the time of CF-LVAD implantation may be warranted.
Fukuhara et al. (24) and retrospective, single-center	AV repair ($n = 41$) No AV surgery ($n = 15$)	Overall Mild (100%)	Freedom from AI >moderate at 2 years was 81.8% in AV repair group and 45.0% in No AV surgery group ($p = 0.031$). In No AV surgery group, 83.3% of patients with large body surface area-indexed aortic diameter developed >moderate AI, while none of the individuals with smaller aortic root did. In AV repair group, patients with large indexed aortic root have all been free of AI at 2 years.	While it is recommended that the AV be intervened on when the AI is more than mild, this study suggests that a subset of patients even with mild AI degree may benefit from an AV repair at the time of CF-LVAD insertion.
Fukuhara et al. (23) and retrospective, single-center	AV repair ($n = 57$) No AV surgery ($n = 283$)	Moderate/severe AI by group AV repair (24.6%) No AV surgery (0%)	Kaplan-Meier analysis revealed that Freedom from significant AI was 66.7% in AV repair group and 59.9% in No AV surgery group at 2 years ($p = 0.77$). A generalized mixed-effects model demonstrated a 57% decrease in the odds of significant AI progression in AV repair group, after adjusting for time effect and degree of baseline AI.	Concomitant AV repair may be an effective strategy in addressing pre-existing AI for patients support by CF-LVAD.
Robertson et al. (51) and retrospective, INTERMACS	AVR ($n = 85$) AV repair ($n = 95$) AV closure ($n = 125$) No AV surgery ($n = 5,039$)	Moderate/severe AI by group AVR (47.8%) AV repair (38.8%) AV closure (35.7%) No AV surgery (2.0%)	After adjustment, AV closure was an independent predictor of mortality (HR 1.87, 95%CI 1.39–2.53, $p < 0.0001$). At 6–12 months post-operatively, moderate to severe AI developed in 19, 5, 9, and 10% of patients who underwent AV repair, AV closure, and AVR and No AV surgery ($p < 0.0001$).	Concomitant AV repairs maybe performed during CF-LVAD implantation with results comparable to those for patients who did not undergo AV repair. AV closure is associated with significant reductions in both short- and long-term mortality. The durability of an AV repair, however, is worse than for other approaches.
McKellar et al. (22) and retrospective, single-center	AV repair ($n = 18$) No AV surgery ($n = 105$)	Greater than mild AI by group AV repair (100%) No AV surgery (0%) AI score (0–5) AV repair (1.8 ± 1.4) No AV surgery (0.15 ± 0.43)	At median follow-up of 312 days, the mean AI score remained lower for AV repair group (0.27 ± 0.46) than that for No AV surgery group (0.78 ± 0.89, $p = 0.02$). The proportion of patients with more than mild AI was significantly less in AV repair group (0 vs. 18%, $p = 0.05$) The patients in AV repair group were significantly older and had a greater incidence of renal failure at baseline.	AV repair using a central coaptation stitch is effective in reducing AI in patients with native valve AI at CF-LVAD implantation. Longer term follow-up is required to determine whether its use is warranted prophylactically in patients of destination therapy.

(Continued)

TABLE 1 (Continued)

Study and design	*N*	Grade of AI	Results	Potential central messages
			The 30-day mortality was greater in AV repair group, but the late survival was similar between the two groups. No reoperations were required for recurrent AI.	
Tang et al. (28) and retrospective, single-center	AV repair ($n = 40$) AVR ($n = 6$)	Moderate/Severe AI by group AV repair (70.0%) AVR (66.7%)	In AV repair group, AI severity was decreased by 2.1 ± 1.0 grades ($p < 0.001$), but 7.5% had recurrence of at least moderate AI by 3 years. Success of AV repair in downgrading AI severity was associated with a smaller aortic root diameter ($p = 0.011$) and sinotubular junction diameter ($p = 0.003$). Duration of cardiopulmonary bypass was 32 min longer and duration of aortic cross-clamp time was 38 min longer for AVR vs. AV repair group. No difference in 30-day or overall survival between AV repair and AVR group was seen.	AV repair at CF-LVAD implantation is efficacious and durable. AI recurrence rate of 7.5% at 3 years represents a reasonable compromise between its simplicity and expediency vs. durability. Alternatively, a bioprosthetic AVR can be performed.
Kurihara et al. (29) and retrospective, single-center	LVOT closure ($n = 16$) No LVOT closure ($n = 510$)	Severe AI by group LVOT closure (68.8%) No LVOT closure (0%)	Survival at 30 days, 6 months, 1 year, and 2 years was similar for No LVOT closure group (90.4, 80.6, 74.3, and 67.5%) and LVOT closure group (81.3, 81.3, 75.0, and 68.8%, $p = 0.59$). There were no deaths related to LVOT closure.	For select patients with AI who are undergoing CF-LVAD implantation, LVOT closure produces acceptable outcomes and, therefore, is a viable option. Longer-term studies are necessary to determine whether aortic root thrombus and subsequent thromboembolic complications eventually become an issue in these patients.

N, Number of patients; AI, Aortic insufficiency; AV, Aortic valve; AVR, Aortic valve replacement; HR, Hazard ratio; CI, Confidence interval.

the time of CF-LVAD implantation in 18 patients, those with greater than mild AI at baseline. Amazingly, among all the 18 patients, the grades of AI were mild or less at 2 years after CF-LVAD implantation (22).

A largest single-center experience of AV repair by central AV closure at VAD implantation is reported by Fukuhara and colleagues (23). They conducted concomitant central AV closures in 57 patients at the time of CF-LVAD implantation and its efficacy was compared with 283 patients those who underwent CF-LVAD implantation without central AV closures. Although Fukuhara et al. did not find any significant survival differences between the groups, their generalized mixed-effects model demonstrated a 57% decrease in the odds of significant AI progression among those who underwent the central AV closure as a concomitant procedure, after adjusting for time effect and degree of baseline pre-existing AI (23).

Thus, while CAVC could potentially be a first-line treatment of AI at the time of CF-LVAD implantation, one of its major drawbacks is a recurrence of AI during follow-up. Although there are few studies directly comparing CAVC with AVR, Tang et al. conducted a retrospective analysis on the concomitant CAVCs ($n = 40$) and AVRs ($n = 6$) (28). The CAVC group yielded shorter ischemic and cardiopulmonary bypass time, however, 7.5% of CAVC patients had recurrence of at least moderate AI by 3 years. Although they did not find any survival difference between the groups, such a decision of CAVC or AVR, as a concomitant procedure at CF-LVAD implantation, should depend on each clinical context.

The effect of impella—Another indispensable consideration

In 2018, the new United Network for Organ Sharing (UNOS) donor heart allocation system commenced giving a priority to patients supported with non-dischargeable mechanical circulatory support (MCS) devices while awaiting heart transplantation, prompting temporary MCS devices in heart transplant centers being more frequently used in the United States (US) (53). The Impella device (Abiomed Inc,

TABLE 2 Summary of suggested medical and surgical interventions to treat aortic insufficiency in patients support by continuous-flow LVAD.

Timing	Interventions	Benefits	Risks
Timing 1: At CF-LVAD implantation Better to intervene if greater than mild AI is seen For mild AI, it depends on the expected support duration or AV morphology.	AV repair	Shorter ischemic time	Potential recurrence of AI
	Bioprosthetic AVR	Longer durability	Longer ischemic time
	AV closure	Shorter ischemic time Longer durability (potentially)	Potentially thrombogenic Difficulty in LVAD weaning
Timing 2: During CF-LVAD support Medical managements to avoid worsening of AI Significant AI often requires high pump speed for compensation.	Speed optimization (right heart catheter or echo guided)	Avoid continuous closure of AV	Inappropriate speed may cause under-supported condition
	Afterload adjustment (vasodilator)	Reverse flow to left ventricle may decrease	Hypotension
	Volume optimization (intake restriction or diuretics)	Reverse flow to left ventricle may decrease	Low output syndrome
Timing 3: When significant AI refractory to medical managements is seen	AV repair	Shorter ischemic time	Potential recurrence of AI
	Bioprosthetic AVR	Longer durability	Longer ischemic time
	TAVI	Less invasive	Valve migration Paravalvular residual AI
	Transcatheter AV closure	Less invasive	Potentially thrombogenic Difficulty in LVAD weaning

CF, continuous-flow; AV, Aortic valve; AVR, Aortic valve replacement; TAVI, Transcatheter aortic valve implantation.

Danvers, MA, USA) is an axial-flow percutaneous ventricular assist device used in cases in cardiogenic shock (54), and the use of Impella is gradually increasing especially in the US, reflecting the forementioned updates in the UNOS criteria. As for those who are eligible for heart transplantation, recently they could be directly bridged to transplant with the Impella in the US, as a new status 2 category. However, those who are ineligible for transplant might need to undergo CF-LVAD implantation as destination therapy to survive, and there are several reports on the adverse impact of the Impella on the AV in such patients (55–58). In fact, just on the Impella support, an increase in AI grade was observed in 17.2% of patients with an event per support days of 0.03 (55). Such a potentially iatrogenic damage on the AV could be associated with AI development even after VAD implants. Rao et al. compared the development of *de novo* AI after CF-LVAD implantation between those who were on the Impella support and those not, concluding that mild or moderate *de novo* AI was observed in 82% of patients in the Impella group, as compared 43% in the non-Impella group ($p = 0.038$) (56). The pathophysiology of AI due to the Impella support is still unclear. Oishi et al. reported two cases of *de novo* moderate AI due to the Impella, both of which required concomitant CAVCs at the VAD implantation (57). They speculated, like CF-LVAD support, that the AV is not opening by the Impella support, making the pressure load on the AV greater and causing disorganization and remodeling of the valve (57). Thus, especially when the Impella was placed before CF-LVAD implantation, careful intraoperative observation of the AV is mandatory at VAD implant, of course after the Impella removal, to avoid future progression of Impella-induced *de novo* AI.

Preventive strategies of *de novo* AI after CF-LVAD implantation

Up to this point, we summarized the current updates of AI associated with CF-LVAD, regarding its pathophysiology, incidence, clinical significance, and its concomitant surgical treatment at the time of CF-LVAD implantation. Henceforth, we moved on to the preventive strategies of *de novo* AI after VAD implants (14), followed by the options of late intervention on the AV.

Since continuous closure of the AV is reported as one of the major risk factors of *de novo* AI (17, 37, 59, 60), pump speed optimization to maintain AV opening would be one of the key aspects in the prevention of *de novo* AI (16). Jorde et al. demonstrated the efficacy of speed optimization study, or right heart catheter pressure study with transthoracic echocardiography with different pump speed before discharge, on the prevention of *de novo* AI (59). They conducted this optimization in 29 patients, and they found only 1 patient developed greater than mild AI during a median follow-up time of 205 days (59). In contrast, without this optimization study, 20 out of 62 patients developed greater than mild AI during a median follow-up time of 265 days. Jorde et al. concluded that

their speed optimization study before discharge was significantly associated with reduced risk of *de novo* AI after CF-LVAD implantation (HR 11.2, 95% CI 4.6–27.4, $p = 0.003$) (59). Based on their report, such a speed optimization study is now routinely performed before discharge in some VAD-implant centers.

Another key aspect in the prevention of *de novo* AI could be afterload optimization. In fact, in non-VAD general populations, elevated systolic pressure is known to be associated with increased risk of valvular heart disease including AI (61, 62). Mechanistic evidence for the potential causal role of high blood pressure on *de novo* AI is unclear, although some speculate that high blood pressure causes abnormally high tensile stress on the AV, which can lead to endothelial injury or disruption (62). Like general populations, blood pressure management is an essential part of the routine care of CF-LVAD patients, especially for the prevention of thromboembolic events and *de novo* AI. Patil et al. reported that systolic blood pressure at 3 months after CF-LVAD implantation was an independent predictor of more than mild *de novo* AI, as well as aortic valve closure and longer support durations (60). However, in other studies, such a significant association between blood pressure in CF-LVAD patients and AI development was not observed (17, 59). Table 2 shows the summary of suggested medical and surgical interventions to treat AI in the patients support by CF-LVAD. Thus, so far there is no established strategies that can perfectly prevent the progression of AI. Once *de novo* AI in CF-LVAD patients becomes significant, next we need to consider when to intervene.

Late intervention on the aortic valve

Even today, there is no definite consensus on when to intervene significant *de novo* AI after CF-LVAD implantation (16). Clinically, severe AI does not necessarily result in heart failure or elevated filling pressures. First-line medical treatment of *de novo* AI could be diuretics and vasodilators to decrease congestion and control blood pressure. However, once the patient becomes symptomatic because of significant AI, he or she surely needs to undergo right heart catheter study with simultaneous echocardiography for speed optimization (63). An increase in pump speed might be considered to improve cardiac output and end-organ perfusion, but this is at the expense of worsening AI. In general, this speed optimization for significant AI is only palliative and effective in the short term. Even today, there is no clear recommendation regarding the most pertinent surgical or interventional options to treat such patients. If the patient is eligible for heart transplantation, upgrading on the waiting list could be considered in some countries. Other potential treatment modalities are like the ones mentioned previously at the concomitant procedures with CF-LVAD implantation (15). Those are bioprosthetic AVR, CAVC, and surgical AV closure. In the future, total artificial heart could be another choice (64). Since these options requires redo-sternotomy in such a high-risk patient with elevated filling pressures due to significant AI, TAVI or trans-catheter device closure of AV can also be a reasonable select for *de novo* AI.

What is a desirable secondary AV intervention for late *de novo* AI during CF-LVAD support, AVR, AV repair, or else?

To the best of our knowledge, prospective studies on the efficacy of bioprosthetic AVR or AV repair for late *de novo* AI is quite limited, probably because of the following three reasons: (1) we currently tend to intervene on the AV more aggressively at the time of CF-LVAD implantation and the need of late AV intervention is decreasing, (2) for late *de novo* AI, less invasive procedures, such as TAVI or percutaneous closure, are more likely to be conducted instead of surgical interventions, and (3) In some countries, urgent heart transplantation is now becoming a feasible option to deal with *de novo* significant AI. For these reasons, there is no definite agreement on an ideal secondary AV intervention, and the decision should depend on each clinical scenario.

Nonetheless, AVR with bioprosthetic valve could be a gold standard therapy of *de novo* AI in VAD patients, especially when significant morphological change in the AV is observed. However, this procedure necessitates longer ischemic time and decent exposure of the aortic root, as compared to AV repair, which may raise a concern for postoperative right ventricular dysfunction in these high-risk candidates (19). We found two case series reports on the secondary AVR for late *de novo* AI (19, 20). Firstly, Atkins et al. reported that 6 out of 225 CF-LVAD patients developed *de novo* severe AI accompanied by heart failure, and for these 6 patients, they conducted 1 AVR with bioprosthetic valve, 1 Dacron patch closure, 2 aortic valve repair, and 2 TAVIs, one of which required revision by open surgery for AVR (20). Among these 6 patients, while 5 patients experienced significant improvement in functional capacity and symptom, 1 patient who underwent AVR unfortunately passed away postoperatively secondary to multiorgan failure and sepsis (20). Secondly, Gyoten et al. reported the similar case series of late AVR for *de novo* AI (19). They performed a total of 792 CF-LVAD implantations during the study period, and among them, 6 AVRs were performed for late severe AI, all of which were successfully done. However, 4 patients required temporary right ventricular assist devices, and 3 of them necessitated urgent heart transplantation to survive right heart failure. Judging from these two reports by Atkins and Gyoten (19, 20), secondary AVR for *de novo* AI in CF-LVAD patients is surely a procedure with considerable surgical risks.

A next question here would be whether AV repair can be a satisfactory alternative of AVR, with less risks and comparable outcomes. As far as our investigation, unfortunately, there is few reports on the efficacy of AV repair for late *de novo* AI. Our group previously published one case report of AV repair, or CAVC, for late *de novo* AI in a CF-LVAD patient, which was quite successful (27). Certainly, AV repair is less invasive as compared to AVR, in that it merely needs shorter ischemic time and less dissection around the aortic root, at the expense of potential AI recurrence in the future. Although we do not find the evidence on long-term outcomes after secondary AV repair for late *de novo* AI, based on the AI recurrence rate after concomitant AV repair at CF-LVAD implantation (23, 24, 51), clinical utility of AV repair could be similar to AVR.

Apart from the clinical case series above, there is a registry database analysis on the risk of AVR in CF-LVAD patients. Zaidi et al. reported the survival outcomes of AVR and TAVI late after CF-LVAD implantations, using the Nationwide Readmission Database in the US (7). Although they did not refer to the efficacy of AVR or TAVI in terms of controlling AI grade, they demonstrated in-hospital mortality was significantly higher in the AVR group than the TAVI group (42.3 vs. 6.4%, adjusted OR 10.4, 95% CI 1.37–79.5, $p = 0.02$), warranting a prudent judgement on the indication of surgical AVR for late *de novo* AI. Additionally, Doi et al. reported a case of commissural fusion after bioprosthetic AVR after CF-LVAD implantation, casting doubt on bioprosthetic AVR as a desirable option, as compared to AV repair (52). Right ventricular failure due to longer ischemic time is another non-negligible concern, as Gyoten et al. reported (19). Based on these data, the decision of AVR, AV repair, or other AV interventions should be tailored by case-by-case basis, considering surgical risks, right ventricular functions, AV morphologies, and expected support time.

TAVI is less invasive, but still not a promising option

Another option for treating AI could be TAVI. Although TAVI is not used routinely as a treatment option for severe AI, as of the year 2022, an international multicenter registry data already demonstrated its feasibility and efficacy in non-VAD patients, especially with new-generation devices (65). However, when it comes to the AI on CF-LVAD patients, only a few case series with very limited sample size (30, 32, 33, 66) or single case reports (67–72) are found. Yehya et al. conducted a TAVI in 9 CF-LVAD patients for severe AI (30). They reported all the 9 patients were discharged home and 8 patients were alive at 6 months. Five procedural complications were found, which are two valve migrations, one retroperitoneal hematoma, one groin hematoma, and one femoral pseudoaneurysm (30). As for two cases complicated with valve migrations, they used CoreValve 31 mm (Medtronic, MN, USA), one of the prior generation devices. Technically, most of TAVI devices are not initially designed to place on the dilated annulus in such AI patients. As Yehya et al. admits, in AI cases the lack of significant annular calcification to serve as an anchor for the valve can pose a technical challenge while increasing the risk of valve migration and lack of stability (30). In fact, even in the centers of excellence with new-generation devices, the second valve implantations were required in 12.7% of pure AI patients who underwent TAVI (65). Additionally, suction from the *in-situ* CF-LVAD may disturb prosthesis deployment and increase the risk of prosthesis migration and still there is no consensus on how to optimize pump speed to prevent valve migration while deploying the device (69). Hopefully, these issues may be partly addressed by the devices technically designed to place on the annulus without significant calcification (31, 73), such as JenaValve (JenaValve Technology, Munich, Germany) (70)and J-valve (JC Medical, Suzhou, China).

There are three other case series regarding TAVI for AI in CF-LVAD patients. First one is by Belkin et al., reporting 7 patients underwent 9 attempted TAVI procedures (33). Unfortunately, two patients expired within the first day for cardiogenic shock due to inadequate valve fixation and severe paravalvular leakage. Five patients out of 7 (71%) survived over median follow-up of 9 months. It is noteworthy that they demonstrated significant improvements in the right ventricular function, as well as the degree of AI (33). Second one is by Gondi et al., reporting 11 patients underwent TAVI. Like the report by Belkin et al., one died during the procedure from ventricular fibrillation associated with valve migration and one died 19 days after the procedure for persistent shock. Eight patients out of 11 (73%) were alive at 12 months, and all survivors had improvement in the grade of AI and NYHA class (66). Third one is by Dhillon et al., reporting 4 patients underwent TAVI (32). One valve migration occurred out of 4 cases, which required a rescue valve-in-valve procedure. Although all the 4 patients were once successfully discharged home, 3 patients (75%) expired at 10 days, 2 months, and 3 months after the procedure, by congestive heart failure, septic shock, and LVAD thrombosis, respectively (32). These data might indicate that their TAVI candidates could have been ineligible for redo surgical intervention, just because too sick at baseline, and accordingly their outcomes after TAVI, possibly a palliative option, was still quite poor. Thus, TAVI could be a reasonable option for the treatment of AI in selected CF-LVAD cases, however, prospective studies with larger sample size are needed to assess the durability and long-term efficacy of this procedure, in addition to its technical refinements.

Trans-catheter closure of the aortic valve; is a last option to consider?

As mentioned previously, concomitant AV closure at CF-LVAD implantation was associated with increased risk of mortality (51). Moreover, it also contains ineluctable drawbacks, such as risk of sudden death if the device fails, and difficulty in CF-LVAD weaning even when recovery is an option (29). In this sense, AV closure, surgical or trans-catheter one, could be a last option to consider. However, same as TAVI, for those who cannot tolerate invasive open surgery, such as old CF-LVAD patients of destination therapy, trans-catheter closure of the AV might be a palliative option to treat AI under selected circumstances. Retzer et al. reported the efficacy of trans-catheter AV closure using an Amplatzer Multi-Fenestrated Septal Occluder "Cribriform" device to close the AV of CF-LVAD patients (34). Notably, technical success was accomplished in 100% of patients. However, 6-month survival rate was only 30%, reflecting pre-procedural co-morbidities such as right ventricular failure. Phan et al. conducted a systematic review and meta-analysis on the outcomes after percutaneous trans-catheter interventions for AI in CF-LVAD patients (35). They included 8 cases of TAVI and 21 cases of trans-catheter AV closure, concluding that both procedures were effective in reducing the AI grade. Nonetheless, while 20 months survival was ∼35% in the TAVI group, it was zero in the trans-catheter AV closure group. These data might indicate that survival outcomes after trans-catheter AV closure are unsatisfactory. Therefore, this option might not be the first-line treatment of VAD-associated AI, especially in young and healthy candidates. Furthermore, the ethical dilemma of AV closure with considerations of CF-LVAD withdrawal is another important consideration. Even on the appropriate level of sedation, sudden termination of pump rotation may lead to immediate death associated with acute pulmonary congestion in the patients with AV closure. In view of comfort care at terminal stage, we cannot overlook such an ethical drawback of AV closure.

Conclusions

The present review summarized current updates on CF-LVAD associated AI, in terms of its pathophysiology, incidence, clinical impacts on outcomes, prevention, and surgical or trans-catheter interventions. As a concomitant procedure with CF-LVAD implantation, current guidelines are recommending AV repair or AVR for greater than mild AI, which is well-supported (15). For mild or less AI at VAD implants, the decision to intervene on the AV should be tailored by case-by-case basis, considering patients' co-morbidities, surgical risks, right ventricular functions, AV morphologies, and expected support time. Correcting mild AI during CF-LVAD implantation may be reasonable in destination therapy patients. As for the managements of late *de novo* AI, still there is no clear consensus on the timing of intervention or the choice of treatment modality. Clearly, symptomatic severe AI in a CF-LVAD patient needs to be addressed, either surgically or percutaneously. Hopefully in the future, TAVI would become a first-line treatment of late *de novo* AI in CF-LVAD patients, after technical refinements and device improvements. Despite the scarcity of established evidence so far, our continuing efforts are imperative to develop new insights in the future, overcoming this scabrous clinical entity during CF-LVAD support.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Tricuspid surgery at the time of LVAD implant: A critique

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Tricuspid regurgitation (TR) is a common finding in patients with end stage heart failure referred for implantation of left ventricular assist devices. While functional TR frequently resolves after left ventricular unloading, patients with residual and progressive TR demonstrate increased rates of RV dysfunction and poor survival. Criteria for intervention on the tricuspid valve have focused on the degree of tricuspid annular dilatation and the severity of tricuspid regurgitant volume. The surgical decision making regarding intervention on the tricuspid valve remains obscure and historical cohort data cannot distinguish cause from effect.

> *"Even if the degree of regurgitation is determined, the clinical significance and optimal therapeutic intervention (medical management vs. surgical correction) remain difficult to determine, primarily because tricuspid regurgitation is most often secondary to, or accompanied by, another disease process. The relative contribution of the regurgitant blood flow to the clinical situation may be difficult to assess in the face of right ventricular failure or elevated pulmonary arterial pressure." (1).*

KEYWORDS

tricuspid valve, left ventricular assist device (LVAD), annuloplasty, right ventricular dysfunction, heart failure

Introduction

The role of surgical intervention in the pathophysiology of functional tricuspid regurgitation (TR) is obscure. While moderate to severe tricuspid regurgitation is associated with high mortality (2), indications and optimal timing of operative intervention are not well-established. Significant TR is most often secondary and related to tricuspid annular dilation and leaflet tethering in the setting of RV remodeling because of pressure or volume overload (e.g., primary pulmonary hypertension or PH secondary to left-sided heart disease). Current recommendations for surgical intervention identify populations with severe TR undergoing left-sided valve surgery or patients with tricuspid annular dilatation in the absence of pulmonary hypertension and dilated cardiomyopathy (3). Recommendations for concomitant tricuspid surgery

at the time of LVAD implantation are not supported by prospective clinical trials and largely reflect surgical intuition. Consensus statements consider tricuspid intervention as "generally accepted" if not recommended (4) and suggest that TV repair be considered in "carefully selected patients" (5). However, given that significant TR in the post LVAD population is associated with increased mortality (6), it is reasonable to ask whether an objective and replicable standard for tricuspid valve intervention can be identified and made operational.

The current supposition of TR and LVAD

Tricuspid regurgitation secondary to left sided heart failure is a consequence of RV dilatation (mid-ventricular anterolateral wall), caudal displacement of the anterior papillary muscle, leaflet tethering, and valvular deformation. While there is minimal annular dilatation early in the natural history of the pressure loaded right ventricle, increasing right ventricular (RV) diastolic volume worsens the coaptation defect as the tricuspid annulus dilates along the anterolateral axis. Progressive interventricular septal shift toward the left ventricle increases LV diastolic pressure with increased RV afterload and "TR begets more TR." Chronic volume overload results in right ventricular remodeling, variously defined by the changes in ventricular geometry and compliance which describe RV dysfunction.

Despite the reduction in RV pressure overload that accompanies implantation of a left ventricular assist device, residual TR can persist. Fixed pulmonary vascular resistance, residual mitral regurgitation, and inadequate decompression of the left ventricle (pump position, pump speed, and afterload) can all contribute to right sided atrioventricular incompetence. Acute unloading of the dilated LV causes a leftward shit of the interventricular septum, decreasing the septal contribution to RV contraction and altering RV geometry with exacerbation of antero-septal tricuspid leaflet tethering. Early RV failure after LVAD is defined by an inability to separate from cardiopulmonary bypass (e.g., inadequate LVAD filling requiring right ventricular assist device) and is likely a distinct physiology from the progressive RV failure seen in postoperative LVAD patients. Tricuspid regurgitation is common to the distorted geometry of both acute and chronic RV failure after LVAD implantation.

What if we do nothing? The natural history of TR after LVAD

Nakanishi et al. (7) examined the prevalence and prognostic significance of residual TR in patients with more than 1 year of LVAD support. Significant residual TR—defined as a regurgitant jet $>$ 20% of the right atrial area—was observed in ∼25% of patients. While residual TR was significantly associated with mortality, there was no significant survival difference in patients with and without preoperative TR. Right ventricular fractional area change (RVFAC) and tethering distance (e.g., the distance from atrial surface of the tricuspid leaflet to the tricuspid annular plane) were improved only in patients without residual TR. Preoperative TV annular diameter, but not TV tethering, was significantly associated with residual TR. Interestingly, TV annulus diameter increased in all patients after 1 year of LVAD support, from 41.7 to 44 mm ($p = 0.033$) among patients with residual TR and from 38.7 to 41.1 mm ($p = 0.017$) among patients without residual TR. Most importantly, multivariate logistic regression identified residual MR as the most significant predictor of residual TR (OR 4.5).

In an analysis of the EUROMACS database, Veen et al. (8) observed an immediate decrease in significant TR to non-significant TR in two-thirds of patients after isolated LVAD implantation. The odds of moderate to severe TR after an LVAD decreased even further over time, becoming comparable after ∼1.4 years in patients with preoperative moderate to severe TR vs. patients with none to mild TR pre-LVAD. There were also notable differences in disease etiology: post LVAD TR decreased faster in patients with idiopathic dilated cardiomyopathy compared to other diagnoses suggesting that biological differences in ventricular biology impact the efficacy of left ventricular support. While residual TR was associated with both early and late mortality, patients with significant preoperative RV dysfunction and severe TR had post implant survival and hazard ratios comparable to those patients with significant preoperative RV dysfunction and minimal TR. In a sensitivity analysis, pre-LVAD right ventricular dysfunction was identified as the driving factor on mortality regardless of the severity of pre-LVAD TR. Sensitivity analysis is an attempt to avoid the confounding effect of tricuspid regurgitation, as TR is both a consequence of and a contributor to right ventricular dysfunction.

In a single institution study, Zadok et al. (9) found that among patients with significant TR pre-LVAD, more than half (55%) ameliorated their TR severity by 6 months. Among patients with residual TR (e.g., persistence of significant regurgitant fraction) after implantation, right ventricular stroke work index (RVSWI) was significantly lower in comparison to patients whose TR resolved (242 vs. 432). A similar relationship was demonstrated for the pulmonary artery pulsatility index (PAPI) with residual TR patients having significantly less contractile reserve. In short, patients who failed to improve their TR severity grade post-surgery demonstrated worse RV systolic function as assessed by hemodynamic parameters. Other than atrial fibrillation, there were no hemodynamic or clinical markers among the pre-LVAD patients with significant TR to predict post implant residual tricuspid regurgitant disease. Interestingly, 13% of patients without significant TR at the time of LVAD implant progressed to significant TR over the course

of the study (1 year followup). Again, significant post-LVAD TR was associated with mortality.

The evidence: Bias, confounding, and questions of study design

Confounding is the situation in which the epidemiologic difference in the risk of the outcome between exposed (tricuspid valve intervention) and unexposed (no tricuspid surgery) can be explained by other differences in the contrasted groups (10). The vast majority of published studies on the impact of tricuspid valve repair at the time of LVAD implantation are retrospective and observational and nearly all are historical cohort studies comparing outcomes between LVAD patients with and without tricuspid valve intervention (11–15). There is statistical *confounding by indication*. "Treatment" (e.g., tricuspid intervention) is preferentially prescribed to groups of patients based on their underlying risk profile (e.g., severity of TR or annular dilatation). Consequently, patients exposed or not exposed to intervention might not be comparable, precluding any causal inference between tricuspid valve repair and outcome. This is *selection bias*, best described as a potential fundamental difference among the patients in the treatment arm (tricuspid intervention) due to the way in which patients were allocated to the treatment group.

Far more important is the question of *misclassification bias* in the published observational studies. Significant TR can—and frequently does—resolve after isolated LVAD implantation. Tricuspid valve repair in a patient with significant preoperative TR that would have resolved after isolated left ventricular unloading is *misclassified* as the tricuspid intervention is redundant, valvular intervention did not impact TR. Differential misclassification bias skews the data toward the null hypothesis (e.g., tricuspid intervention has no impact on the primary outcome), making historical cohort studies an unlikely source of information for surgical decision making.

Another confounder is the relationship between tricuspid regurgitation and RV failure. Significant tricuspid regurgitation is well-tolerated in LVAD patients without RV dysfunction (16) and RV dysfunction is found among patients with and without significant TR. While TR is treatment variable under study, RV dysfunction is the clinical variable associated with outcome.

Propensity scoring, wherein the likelihood of being exposed to the intervention (e.g., tricuspid valve surgery) is used to match patients can account for confounding. Veen et al. (17) in an examination of the EUROMACS registry used retrospective propensity scoring to compare nearly 500 patients who underwent LVAD implantation with or without tricuspid valve surgery. While hospital deaths, days on inotropic support, use of temporary RVAD support, and cumulative incidence of right heart failure were comparable in both groups, patients with tricuspid surgery had significantly longer stays in the ICU ($P = 0.026$). Despite significantly less moderate to severe TR immediately after surgery in the tricuspid intervention group, differences in the probability of TR disappeared during the follow up period suggesting that concomitant TV surgery is not associated with improved clinical outcome.

To avoid the confounding relationship between TR and ventricular function, the TVVAD trial (NCT03775759) stratified patients by pre-operative right ventricular dysfunction (none/mild vs. moderate vs. severe) at the time of randomization. Sixty patients with moderate or severe TR on pre-operative echocardiography were randomized to either LVAD implantation alone (no TVR, $n = 28$) or LVAD implantation with concomitant tricuspid valve surgery (TVR, $n = 32$). At 6 months there was no difference in the incidence of moderate or severe right heart failure (46% in the LVAD only group and 44% in the group with LVAD and concomitant tricuspid intervention).

Despite the clinical value of observational cohort studies, they provide the weakest epidemiologic evidence for causation and efficacy of intervention, as the risk of uncontrolled bias and confounding are potentially lethal flaws. Greenwood's (18) adage that he should like to shame surgeons out of "the comic opera performances which they suppose are statistics of operations" may be hyperbole, but the criticism is valid. The ecological fallacy has merit in surgical epidemiology and one cannot infer the properties of an individual from the average response of the group (19). Even if the appropriate level of aggregated data were identified, surgeon specific differences significantly impact the validity of retrospective observational studies (20) and it is unlikely that historical cohort data could inform patient—specific surgical decision making.

Is it the tricuspid valve… are we measuring the wrong thing?

The goal of valve surgery is the preservation of ventricular function and intervention on the tricuspid valve is premised upon the impact a reduction in TR will have on progressive RV dysfunction and subsequent RV failure. But, in the absence of structural valve disease, is it reasonable to expect intervention on the tricuspid annulus to impact ventricular biology? Does unrepaired TR drive ventricular remodeling and subsequent RV dysfunction? Is functional TR a consequence of RV failure, a mechanism of RV failure, or both? The short answer is we do not know.

The role of tricuspid annular dilatation, tricuspid regurgitation, and RV dysfunction is problematic for surgeons. Annular pathology seems such a correctable target for surgical intervention, particularly given the association between tricuspid annular diameter (>40 mm) and late right heart failure (21). However, recent studies of patients undergoing guideline—directed repair of functional TR (annular diameter >

40 mm independent of TR severity) at the time of mitral surgery demonstrate no differences in survival and the incidence of "late TR" is low in patients with unrepaired mild TR (22). While Gammie et al. (23) recently demonstrated a lower incidence of progression to TR in patients who underwent tricuspid annuloplasty at the time of mitral valve repair, preliminary data do not address the role of recurrent mitral regurgitation on the subsequent evolution of tricuspid insufficiency. Importantly, tricuspid annular dilatation was not a predictor of progressive TR in the absence of baseline regurgitation suggesting that annular dilatation alone is not a viable criterion for surgical decision-making. In the absence of tricuspid repair, moderate to severe TR after MVR did not predict clinical outcomes or performance standards at 2 years.

There are strong theoretical arguments for the surgical correction of TR, but the physiological studies upon which the intervention is premised also demonstrate the over-riding importance of preload and afterload in determining RV stroke volume and ventricular performance. Nearly one fourth of our patients have moderate to severe MR after isolated cfLVAD and this persistent RV afterload is associated with an increased incidence of right heart failure (RAP > 14 mmHg, cardiac index <2.2 L/min/m^2, and need for inotropic support at 6 months), higher mean pulmonary artery pressures, and elevated pulmonary capillary wedge pressure (24). There were no differences in LVAD parameters between the MR severity groups and significant residual MR did not predict functional TR after isolated LVAD despite the MR severity dependent association with progressive RV dysfunction. Similar findings have been reported by the Michigan group (25) where postoperative cfLVAD MR severity independently correlated with the incidence of RV failure. Here, however, MR severity had a positive correlation with TR severity and TV repair to improve valve competence was associated with worsened RV function.

While persistent MR after LVAD is a consistent marker of progressive RV failure (26), residual TR is not (27). In our experience the prevalence of significant residual MR after LVAD is similar between the groups with insignificant and significant TR, suggesting residual left sided failure is not the only etiology. Patients with significant residual TR after LVAD implantation frequently demonstrate decreased right ventricular stroke work index (RVSWI) and pulmonary artery pulsatility (PAPI)—both specific measures of RV function. If the rationale for tricuspid repair is the preservation of RV function, then functional metrics of RV performance should correlate with the severity of tricuspid regurgitation. While there is no clearly defined and broadly accepted definition of RV dysfunction or RV failure, we have found pulmonary artery pulsatility index (PAPi) a useful predictor of presumed intrinsic RV dysfunction (28). PAPi is the only measure of right heart physiology that is known to correlate with RV specific myocyte dysfunction as measured by calcium sensitivity and contractile reserve (29). A lower pulmonary artery pulsatility score was associated with more severe TR in a *post-hoc* analysis of the ESCAPE trial and PAPi—but not RAP:PCWP ratio or RVSWI—was a significant predictor of mortality by multivariable Cox regression analysis (30). Pulmonary artery pulsatility index (PAPi < 1.8) is associated with various measures of right heart failure after LVAD implantation (31) and pre implantation PAPi score is a predictor of subsequent RVF after LVAD (32). Even in patients without pulmonary hypertension, significant TR is associated with lower PAPi scores (right ventricular dysfunction) and worse survival (33). PAPi scores might provide a more consistent marker for RV reverse remodeling and allow clinical trial design that is focused on the mechanisms that result from surgical intervention (annuloplasty) rather than the degree of improvement in clinical outcome.

What we think we know

Residual or recurrent TR after LVAD implantation—particularly that associated with progressive RV dysfunction—is a poor prognosticator and a consistent marker of patient mortality (6). Numerous studies suggest that concomitant TV intervention is not associated with freedom from RV dysfunction and there is no consensus on the indication for TV intervention at the time of LVAD implant (annular dilatation of >40 mm or severity of regurgitation). The significant pre-operative TR common to end stage heart failure improves (and frequently resolves) in the majority of patients after LVAD implantation independent of intervention on the tricuspid valve (7–9). Intervention on the tricuspid valve at the time of LVAD has never demonstrated a survival advantage and concomitant TV procedures are associated with increased morbidity and mortality in a stratified analysis of the INTERMACS database (12). While concomitant TV surgery has been demonstrated to improve LVAD filling and hemodynamics (15), tricuspid annuloplasty does not impact the incidence or progression of late RV failure (27). Concomitant tricuspid surgery has a significant fail rate (14) and a small but persistent subset of patients (10–15%) without pre-operative TR develop TR over time (8).

Atrial fibrillation associated TR is a distinct group of LVAD patients in which concomitant tricuspid valve surgery may be warranted. The Michigan group has recently demonstrated that functional MR related to atrial fibrillation and characterized by a dilated left atrium had excellent survival and low recurrence after annuloplasty (34). Importantly, patients with "atrial MR" had preserved left ventricular end-diastolic volumes (LVEDV < 5 cm). Answer et al. (35) have argued for including atrial fibrillation in the surgical decision making on tricuspid procedures during LVAD implantation.

Unanswered questions: Is there a rationale for concomitant tricuspid repair?

The role of surgery in patients with a dilated annulus and minimal TR remain controversial, as does the role for intervention in patients with significant TR and preserved annular dimensions. Annuloplasty of the dilated annulus with severe TR may reduce the physiologic impact of RV dysfunction but demonstrates no consistent relationship to a documented reversal of right ventricular remodeling that is thought to impact long-term survival. At present, we cannot identify an LVAD patient "at risk" for severe post-implant TR and there is no reason to believe that "prophylactic" reduction annuloplasty might impact the incidence of progressive disease. (e.g., downsizing mitral annuloplasty does reduce left ventricular end diastolic volume and improve LV ejection fraction but demonstrates no improvement in survival when compared to optimized medical therapy) (36).

Given the high incidence of recurrent TR after annuloplasty, is repair the wrong approach? Would valve replacement alter the mechanics of RV dysfunction and subsequent RV failure? AICD leads and biventricular pacing wires are nearly ubiquitous in the end stage heart population and "pinning" of tricuspid leaflets by trans-annular EP device leads is a common observation (25% in our patient population). Annuloplasty is unlikely to significantly impact the tethered leaflet. Is reduction annuloplasty with a flexible band or remodeling annuloplasty with a rigid ring relevant to the conversation regarding concomitant surgery and TV repair? Does annuloplasty ring size impact durability and ventricular pathophysiology, or does a "one size 28 mm reduction annuloplasty fit all"? Given the importance of RV geometry and the impact of pump speed on septal and posterior leaflet displacement, is preservation of the pericardium and passive ventricular constraint more important than preservation of annular dimensions? Many of us embrace the reduction in RV failure seen with the thoracotomy approach as more than case selection bias (37). Are the known gender differences in the incidence of TR significant to surgical decision making (38)? Most importantly, does intervention on the tricuspid valve impact RV function and contribute to reverse remodeling?

Any conclusions?

Surgeons looking to the aggregate data of historical population studies for surgical decision making will be frustrated by differences in study design, variable definitions and descriptions of RV dysfunction, and most significantly by the remarkable complexity of right ventricular failure. Despite enormous amounts of data, there is little information, and even less knowledge as to the "correct" surgical decision. What is clear is that no "once size fits all" approach to TR at the time of LVAD implantation will be effective therapy for all patients. While there may be patients who would benefit from TV procedures at the time of LVAD implant, defining a population cohort for whom evidence based data can recommend intervention seems unlikely given the dynamic complexity of functional TR. It is more likely that biomarker and functional imaging data will define a patient cohort in which TV intervention is ill advised and unlikely to contribute to reverse remodeling. As noted by McGee (39), effective heart failure surgery is being able to discriminate the patients that will improve from those that will not benefit or be potentially harmed from the surgical procedure. Perhaps the question of concomitant surgery is itself superfluous. Transcatheter approaches to the tricuspid valve are rapidly evolving and it is likely that percutaneous intervention prior to or after LVAD implantation will allow more nuanced and temporally appropriate patient specific therapies (40). In the interim, we are left with imaging, statistical inference, and the too often disregarded judgement that comes with clinical experience.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Key questions about aortic insufficiency in patients with durable left ventricular assist devices

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The development of the latest generation of durable left ventricular assist devices (LVAD) drastically decreased adverse events such as pump thrombosis or disabling strokes. However, time-related complications such as aortic insufficiency (AI) continue to impair outcomes following durable LVAD implantation, especially in the context of long-term therapy. Up to one-quarter of patients with durable LVAD develop moderate or severe AI at 1 year and its incidence increases with the duration of support. The continuous regurgitant flow within the left ventricle can compromise left ventricular unloading, increase filling pressures, decrease forward flow and can thus lead to organ hypoperfusion and heart failure. This review aims to give an overview of the epidemiology, pathophysiology, and clinical consequences of AI in patients with durable LVAD.

KEYWORDS

durable left ventricular assist devices, aortic insufficiency, valvular heart disease, pathophysiology, heart failure, mechanical circulatory support (MCS)

Introduction

Durable left ventricular assist device (LVAD) therapy is indicated in selected patients with advanced heart failure refractory to guideline-directed medical treatment to improve survival and quality of life. Improvement of the technology with the latest generation of pump (continuous-flow, fully magnetic) and the modifications in the cardiac allocation system in the United States contributed to significantly change the landscape of indications and outcomes in patients with durable LVAD (1). Most patients are now implanted as destination therapy or bridge to candidacy (2). Survival following LVAD implantation has reached 90% (3) and 58.4% at 1 and 5 years (4). Although a significant reduction in adverse events such as pump thrombosis or stroke is observed, time-related adverse events such as aortic insufficiency

(AI) remain an area of concern in the context of increased support duration (5). The presence of significant AI in patients with durable LVAD can compromise the functional and survival benefit of the therapy. Understanding the pathophysiology and the hemodynamic consequence of AI is critical to improve patient's management and to optimize outcomes following LVAD implantation. The purpose of this comprehensive review is to describe the pathophysiology, hemodynamic and clinical consequences of AI in patients with durable LVAD.

Epidemiology of aortic insufficiency in patients with durable left ventricular assist devices

What is the prevalence of aortic valve disease before durable left ventricular assist device implantation?

Approximately 5% of patients who were evaluated for a LVAD or heart transplantation suffered from moderate or severe AI (**Table 1**) (6–8). In a sub-analysis of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate-3 (MOMENTUM-3) trial portfolio, 27% of the 1,790 patients who received a HeartMate-3 exhibited some degree of AI, with 2.3% having moderate or severe AI; amongst this group, 95% underwent an aortic valve procedure at the time of LVAD implantation (8).

Progression of AI severity, in patients with pre-existing AI at the time of LVAD implant, has been reported in several publications (9–13). Patients with mild AI before LVAD implantation progress to significant AI at a higher rate than those who had trace or no AI. In a study by Kagawa et al. 94.5% of patients with no AI pre-operatively were free from significant (more than mild) AI at 1 year in comparison to only 62.4% in the group with mild AI pre-operatively (13).

What is the prevalence of aortic insufficiency during left ventricular assist device support?

Between 11 and 52% of patients develop *de novo* AI on LVAD support (**Table 1**) (9, 14–19). The frequency of AI progressively increases with time. In a cohort of 78 patients implanted with a HeartMate-XVE (n = 25) or a HeartMate-II (n = 53) between 2004 and 2008, Cowger et al. found that 11% of these patients presented with moderate to severe AI at 6 months, 26% at 1 year and 51% at 18 months (14). Noteworthy, these numbers represent the data of both pulsatile (HeartMate-XVE) and continuous flow (HeartMate-II) devices. Patients receiving a HeartMate-II had more progressive AI than those receiving the HeartMate-XVE (14). Another more contemporary study of patients implanted only with non-pulsatile devices showed a lower rate of AI, where the freedom from moderate or severe AI at 1,3 and 5 years was 94%, 76%, and 65%, respectively in a cohort of 237 patients (20).

What are the risk factors associated with *de novo* aortic insufficiency in patients with durable left ventricular assist devices?

The most important risk factors associated with development or progression of AI in LVAD patients include older age, sex (female), absence of aortic valve opening, smaller body surface area and longer LVAD support duration (9, 12, 14, 19, 21). A correlation between a smaller aortic root diameter and development of AI has also been shown and might explain the higher incidence *de novo* AI in females (22). Surgical factors, such the location and the angulation between the outflow graft and the ascending aorta also play a role (22). It has been observed that the most desirable anastomosis site should be 2 cm above the sinotubular junction at an angle $\geq$90° transversally and between 60° and 120° in the coronal plane (23, 24). Because AI develops with time, the destination therapy strategy is associated with a higher rate of AI compared to the bridge to transplant strategy. Finally, continuous flow pumps seem to generate more AI than pulsatile pumps (14, 19). Tanaka et al. have demonstrated that pre-implant mild or greater AI and longer LVAD support were risk factors for moderate or greater AI post-LVAD (9). Other pre-operative characteristics such as hypertension, diabetes, dyslipidemia, and the left ventricular (LV) ejection fraction have not been associated with AI (21).

Pathophysiology of aortic insufficiency in patients with durable left ventricular assist devices

What are the histopathological findings in the aortic valve in left ventricular assist device supported patients with aortic insufficiency?

Left ventricular assist device support can lead to AV fusion (25). The precise cause of aortic valve commissural fusion is still unknown. Some authors describe leaflet thickening on the aortic side while others have noted a thinning and shortening of leaflets

TABLE 1 Summary of aortic insufficiency (AI) prevalence pre-left ventricular assist device (LVAD) implant, during left ventricular assist device (LVAD) support and clinical impact.

Study (Year of cohort)	Study type	*N*	Prevalence	AI severity	Clinical impact AI vs. no AI groups
Prevalence before LVAD					
Pal et al. (6) (2005–2007)	Retrospective analysis of HMII BTT trial (multicentre prospective cohort)	251	4.8%	Severe	–
Robertson et al. (7) (2006–2012)	Observational, retrospective/prospective	5,344	3.9%	Moderate or severe	–
John et al. (8) (2014–2016)	Sub-analysis of prospective, multicentre, randomized clinical trial	1,790	2.3% 26.8%	Moderate or severe Any AI	–
Tanaka et al. (9) (2006–2018)	Observational, retrospective	604	18.4%	Mild or greater	No survival difference Higher readmissions in AI group (<0.01)
Prevalence of AI during LVAD support					
Hiraoka et al. (11) (2005–2012)	Observational, retrospective	82	52%	More than mild	–
Truby et al. (12) (2006–2016)	Retrospective analysis of INTERMACS study	10,603	13.2%	Moderate to severe	Higher mortality ($p < 0.005$) and readmissions ($p < 0.015$) in moderate-severe AI group
Kagawa et al. (13) (2004–2018)	Observational, retrospective	316	No AI: 5.5% Trace AI: 13.9% Mild AI: 37.6%	More than mild, at 1 year	Higher mortality in significant AI group ($p = 0.06$)
Pak et al. (15) (2004–2009)	Observational, retrospective	HMI 93HMII 73	HMI: 11.1% HMII: 24.8%	Mild to moderate or greater, at 1 year	–
Aggarwal et al. (16) (2005–2011)	Observational, retrospective	79	52%	Mild or greater, at a median follow-up of 187 days	Higher mortality in AI group ($p = 0.03$). No difference in readmissions
Jorde et al. (17) (2004–2013)	Observational, prospective, and retrospective	224	22.4%	Mild or greater, at 1 year	–
Cowger et al. (18) (2000–2011)	Observational, prospective	166	36%	Mild to moderate or greater, at 1 year	No difference in 2 year survival
Rajagopal et al. (10) (2004–2011)	Observational, retrospective	184	11.4%	Moderate or greater	No difference in survival
Deo et al. (19)	Systematic review	657	25%	- Support period 412 days	No difference in survival
Holley et al. (20) (2005–2013)	Observational, retrospective	237	15.2%	Moderate or severe	No difference in overall survival at 1 year

(26–28). It is speculated that fusion is caused by extended time of leaflet coaptation due to the little to no antegrade flow through the valve (25, 29). Possible mechanisms include morphological changes in valvular endothelial cells under different shear strains or an environment that is completely static and encourages local fibrosis (25, 29). When the valve is closed, strong transvalvular pressures (TVP) cause the valve leaflets to stretch. As the leaflets open, they loosen up. Because higher TVP are applied to the leaflets with LVAD use, in a constant fashion as opposed to intermittently, collagen synthesis and remodeling are stimulated (25, 30).

Stasis develops on the ventricular surface of the valve when the AV remains closed and thus promotes thrombus formation and organization, which furthers leaflet fusion (14, 25, 29, 30). Wang et al. state that the leaflet fusion can be responsible for the retraction of the leaflet tips and the generation of a central orifice that becomes fixed in the absence of intermittent AV opening, causing AI (25).

How can a durable left ventricular assist device induce aortic insufficiency?

The mechanisms of AI are multifactorial. The absence of aortic valve (AV) opening is one of the strongest factors

associated with AI. Durable LVAD promote LV unloading by pumping the blood from the LV directly into the aorta, which decreases LV pressures. The transvalvular gradient is defined as the difference in pressure between the aortic root and the LV. With an LVAD, the transvalvular gradient is increased due to the unloaded LV and the elevation of the pressure in the aorta by the continuous flow from the outflow graft (30). This contributes to the closure of the AV (30). The increased load on the AV causes valve deterioration and remodeling, which results in AI (30).

How does a left ventricular assist device change the aortic root biomechanics?

As described by John et al., normal valve biomechanics are dependent on the distensibility of the sinus tissue and the pressure cycle in the aortic root, pressure pulsatility and vortex generation (30). The retrograde flow from the LVAD prevents vortices from forming, resulting in early valve closure and a shortened systole. Thrombus formation can be found more frequently in the non-coronary sinus despite the wash out provided by the retrograde flow, due to increased blood stagnation secondary to the absence of coronary arteries draining that particular sinus (30).

Left ventricular assist device support can also contribute to the development of aortic root dilation and can thus participate to AI. The underlying mechanism used for aortic root dilation in LVAD patients seems to be the increased aortic wall sheer stress caused by the turbulence induced by the device (14, 31, 32). This leads to thinning of the aortic wall by apoptosis of smooth muscle cells and by a decrease in elastin content (14, 31, 32). In fact, aortic root diameters tend to be larger at baseline and at follow-up for patients who develop AI during LVAD support as opposed to those without AI (15). Fine et al. noted a small increase in aortic root diameter in the first 6 months post-LVAD implant which was associated with AI development, but aortic diameters remained stable thereafter (31). On the contrary, some authors have found an increase in aortic wall thickness, collagen, or smooth muscle content (33).

How to assess aortic insufficiency severity in left ventricular assist device patients?

First, it is important to evaluate whether there is opening of the AV or not, using the M-mode in the parasternal long axis view, over 10 cardiac cycles (34). Then, Color Flow Doppler is added to semi-quantify the severity of the AI and its timing during the cardiac cycle. Of note, the echocardiographic evaluation and quantification with conventional methods (i.e., vena contracta, jet width/left ventricular outflow tract diameter, pressure half-time, and proximal iso-velocity surface area) is more difficult in LVAD patients with AI due to the presence of multiple eccentric jets and acoustic shadow caused by the device (35). The volumetric assumptions used to derive those formulas are incorrect in this clinical setting, as AI on LVAD occurs throughout the cardiac cycle, both in systole and diastole (5).

Therefore, new methods have been described for the evaluation of AI in LVAD patients: diastolic flow acceleration and the systolic-to-diastolic (S/D) velocity ratio of the outflow cannula (35).

A detailed description of all the available methods is beyond the scope of this review and can be found elsewhere (5). Briefly, from a modified right parasternal view, a Pulse Wave Doppler is placed in the outflow cannula, <1 cm proximal to its anastomosis to the ascending aorta. Diastolic acceleration is calculated by measuring the diastolic slope, from the beginning to the end of diastole; the S/D ratio is obtained by dividing the peak systolic velocity by the peak end-diastolic velocity (35). This S/D velocity ratio is inversely proportional to the severity of AI, and the diastolic acceleration of the outflow cannula is directly proportional with the severity of AI (34, 35). Moderate or greater severity AI, defined as a regurgitant fraction >30%, will exhibit a S/D ratio of <5.0 or a diastolic acceleration of >49.0 cm/s^2 (5, 35).

By using these methods, Grinstein et al. reclassified approximately 30% of patients with trace/mild AI as evaluated by conventional methods to at least moderate AI (34). Patients who were diagnosed with more than moderate AI using these new TTE parameters had a higher PCWP than patients who had less severe AI. Additionally, there was a non-significant trend toward declining right ventricular (RV) function in patients with moderate or higher levels of AI as determined by these updated TTE criterias (34). However, there was no such difference when AI was evaluated using conventional TTE parameters (34).

Hemodynamic consequences of aortic insufficiency in patients with durable left ventricular assist devices

What are the hemodynamic changes in patients with durable left ventricular assist devices and aortic insufficiency?

When AI is hemodynamically significant, the blood circulates in a "closed loop" between the pump, the aortic root, and the LV (**Figure 1**). As the proportion of retrograde flow increases, sub-optimal LV unloading occurs, resulting in increased left-sided filling pressures and volume overload to the LV. These hemodynamic changes associated with AI result in an

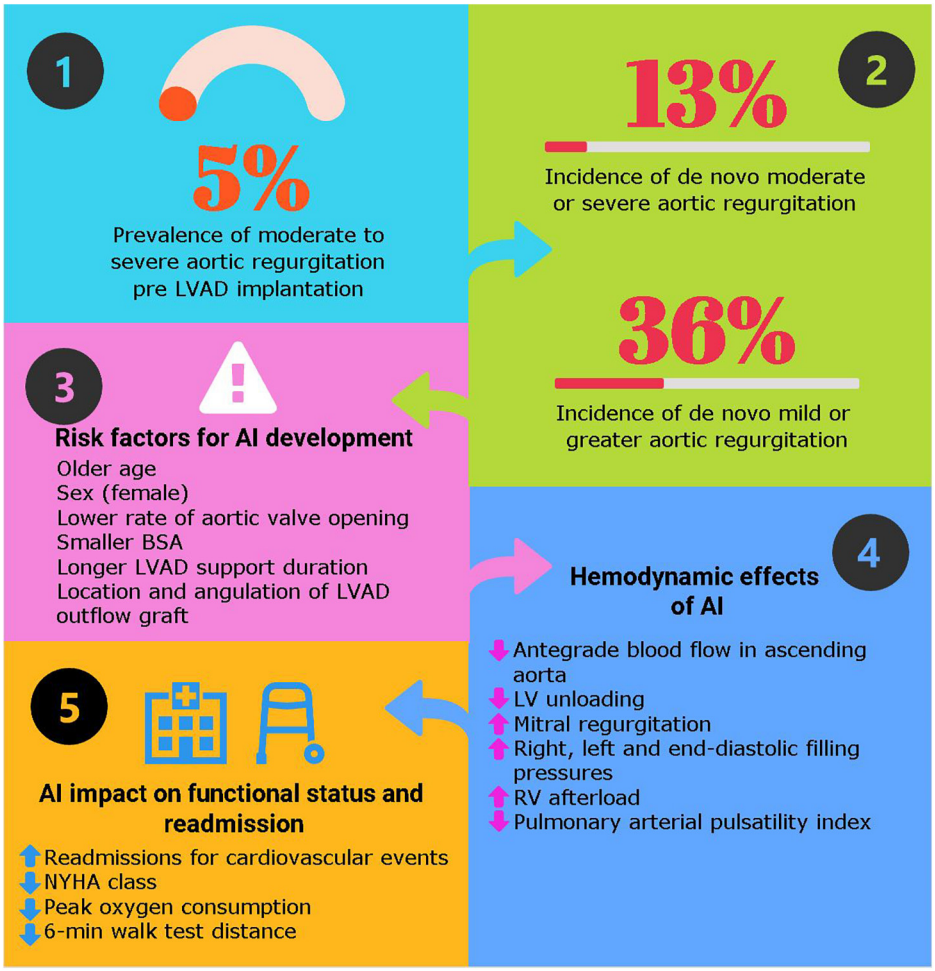

FIGURE 1
Key answers about aortic insufficiency in patients with durable left ventricular assist device. Hemodynamic effects of left ventricular assist devices (LVAD) with aortic insufficiency. Adapted with permission from Noly et al. (53).

increase of the left ventricular end-diastolic diameter, reduced systolic blood pressures, cardiac output and elevations in brain natriuretic peptide levels, when compared with patients with no/mild AI (12, 36).

This has been nicely demonstrated by Sayer et al., where AI initially causes increased biventricular filling pressures [central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP)] while maintaining the same cardiac index (CI) (36). With time, if the PCWP remains elevated, pulmonary hypertension develops causing additional strain on the RV (36).

What are the consequences of aortic insufficiency on right ventricular function?

The right ventricle (RV) remains the Achilles heel of this technology. Right-sided failure can occur after LVAD implantation, when a vulnerable RV faces a sudden rise in cardiac output provided by the LVAD, and is unable to accommodate to this increased preload. In addition, altered RV contractility secondary to the withdrawal of inotropes or to the loss of septal contraction may contribute (37). Aggressive unloading of the LV by the pump may cause an interventricular septal shift toward the LV, altering the RV geometry and its contractility (38).

The presence of AI can further compromise RV function, indirectly through its impact on increased LV filling pressures and reduced effective pre-load. First, higher pulmonary wedge pressures lead to a passive rise in pulmonary artery pressures and consequently higher RV afterload (39). In addition, the closed-loop circuit described above creates a reduction in the effective cardiac output, thus reducing RV pre-load and potentially contributing to RV failure.

In patients with significant pulmonary hypertension before LVAD implantation, it may not totally resolve post-operatively

despite LV unloading by the device, thereby leaving some residual and variable degree of increased RV afterload (40). These patients may be more susceptible to suffer from RV failure in the presence of AI; indeed, Sayer et al. demonstrated the impact of AI on a decreasing pulmonary artery pulsatility index (PAPI) (6).

Clinical implications of aortic insufficiency in patients with durable left ventricular assist devices

Impact of aortic insufficiency on mortality?

The impact of AI on mortality remains controversial. Some authors reported a higher mortality rate in patients with AI (12, 13) while others do not (9, 16, 18–20, 41). Kagawa et al. and Truby et al., reported higher mortality rates amongst patients with significant (≥moderate) AI, 59.5% vs. 37.2% (p = 0.006) and 28.6% vs. 22.8% (p = 0.05), respectively (12, 13). This discrepancy might be explained by the presence of more severe AI in the papers having found a mortality difference as compared to the ones who have not. Another possible explanation is that some studies might be underpowered to detect such a difference due to their small cohorts. In contrast, the study by Truby et al., is one of the largest studies published on the subject, with over 10,000 patients and thus plays a very important role (12).

Functional status, hospital readmission, adverse events?

Aortic insufficiency in LVAD patients leads to worsening functional status and higher readmission rates as opposed to patients with a competent valve (9, 12, 13, 41). When comparing patients without AI and those with mild AI at the time of LVAD implantation, patients with mild AI had a worse NYHA class and more readmissions caused by heart failure (HR 2.62, $p < 0.01$) (9). The survival was similar between groups, over a short follow-up of 3 years (9). Similarly, Imamura et al. found that at 6 months following LVAD implantation, patients with mild AI showed reduced peak oxygen consumption during cardiopulmonary exercise tests compared to those without AI (11.0 ± 3.3 vs. 14.4 ± 3.5 ml/min/kg^{-1}, $p = 0.004$) and a shorter 6-min walk distance (328 ± 84 vs. 407 ± 66 m, $P = 0.001$) (41). During the 2-year LVAD support period, patients with mild or greater AI had a greater readmission rate for cardiovascular events than patients without AI (55% vs. 8%, $p = 0.001$) (41).

The impact of AI on post-transplant outcomes in patients supported with LVAD is not known. Although the duration of LVAD support is not associated with post-transplantation outcomes, it is reasonable to postulate that increased pulmonary pressures might lead to higher rates of primary graft failure secondary to pulmonary hypertension, (42). RVAD or various post-operative complications and end-organ damage (acute kidney injury, hepatic congestion resulting in bleeding, and inflammatory syndrome). This hypothesis remains to be tested.

How could we prevent *de novo* or worsening aortic insufficiency in patients supported with left ventricular assist devices?

Medication optimization

One of the aims of medical management is to relieve congestive symptoms with diuretics and improve filling pressures with vasodilators (18). In addition to blood pressure control, vasodilators decrease aortic wall stress and thus may limit progressive aortic dilation (18). The International Society of Heart and Lung Transplantation guidelines recommend a mean arterial pressure goal <80 mmHg (43). While a combination of many classes of agents may be necessary to achieve adequate blood pressure control, including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics, there are evidences that the Guideline-directed medical therapy should be pursued in LVAD-patients. In cases of refractory heart failure, inotropes may be necessary.

Pump parameters optimization

Targeting pump speeds in the lower range may be helpful to promote AV opening and ultimately reduce the risk of developing AI. This strategy could facilitate intermittent aortic valve opening, reduce AV malcoaptation and fusion and thus prevent AI development (5, 18). This has also been suggested in cases of asymptomatic AI. The benefits of aortic valve opening must be weighed against the risk of organ hypoperfusion, as well as pump thrombosis due to low flows.

On the other hand, when congestive symptoms are present and refractory to medical therapy, patients should undergo an echocardiography guided ramp study, as well as right heart catheterization. Increasing the pump speed will initially promote LV unloading and a decrease in LV end-diastolic pressure (LVEDP). However, this will then start a vicious cycle of complete aortic valve closure leading to increased AI due to a rise in the TVP, ultimately raising the LVEDP (5, 17, 36,

44). An increase in pump speed may acutely improve CI and PCWP (36). For LVAD patients without AI, the increase in pump speed also increases the PAPI as opposed to patients with AI, where no improvement is observed (36). This may be due to the inability of the RV to increase contractility despite improved overall hemodynamics (36).

The ideal rotations per minute (RPM) are the RPM that best achieve hemodynamic optimization, defined as a PCWP <18 mm Hg, CVP <12 mm Hg and a CI >2.2 L/min/m^2, with, ideally, intermittent AV opening and minimal mitral insufficiency (45).

When aggressive medical and pump parameters optimization fails to improve symptoms, surgical and percutaneous aortic valve interventions might be considered. The detailed description of those techniques is addressed in another article of this collection. Improvement in functional status has been observed (46, 47). Survival rates range from 55–89% at 1 year, with higher in-hospital mortality rates in the surgical group in comparison to the percutaneous group (48–52). The outcomes of these patients are based on small series; prospective validation on bigger cohorts is thus necessary. A waiting list status upgrade, for patients who are candidates for heart transplantation, may also be explored.

Conclusion and perspective

In conclusion, the incidence of AI increases with longer support durations. Development of AI in patients supported with a durable LVAD compromises the benefit of the therapy. There is still a lack of consensus on the effect that AI has on mortality, but several studies report that AI increases heart failure related hospitalizations and contributes to the deterioration in functional status. Multiple strategies exist to minimize *de novo* AI development and its hemodynamic impact on the LV and RV during LVAD support. Further research studies are needed to better characterize the severity of AI, to better understand its impact on patients transplanted, and to prevent its development.

Author contributions

EC was responsible for the literature review, drafting the manuscript, and the creation of the figure and table. P-EN supervised the work and provided direction. P-EN, AD, MC, YL, and WB reviewed the manuscript and provided feedback. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Patient-specific, echocardiography compatible flow loop model of aortic valve regurgitation in the setting of a mechanical assist device

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Background: Aortic regurgitation (AR) occurs commonly in patients with continuous-flow left ventricular assist devices (LVAD). No gold standard is available to assess AR severity in this setting. Aim of this study was to create a patient-specific model of AR-LVAD with tailored AR flow assessed by Doppler echocardiography.

Methods: An echo-compatible flow loop incorporating a 3D printed left heart of a Heart Mate II (HMII) recipient with known significant AR was created. Forward flow and LVAD flow at different LVAD speed were directly measured and AR regurgitant volume (RegVol) obtained by subtraction. Doppler parameters of AR were simultaneously measured at each LVAD speed.

Results: We reproduced hemodynamics in a LVAD recipient with AR. AR in the model replicated accurately the AR in the index patient by comparable Color Doppler assessment. Forward flow increased from 4.09 to 5.61 L/min with LVAD speed increasing from 8,800 to 11,000 RPM while RegVol increased by 0.5 L/min (2.01 to 2.5 L/min).

Conclusions: Our circulatory flow loop was able to accurately replicate AR severity and flow hemodynamics in an LVAD recipient. This model can be reliably used to study echo parameters and aid clinical management of patients with LVAD.

KEYWORDS

LVAD, aortic regurgitation, patient specific 3D printed phantoms, Doppler assessment, 3D printing

Introduction

Continuous flow left ventricular assist device (cf-LVAD) technologies for end-stage heart failure patients have become a long-term treatment strategy (1). Development of *de novo* aortic regurgitation (AR) after implantation is a well-recognized complication of long term cf-LVAD support. One quarter to one-third of patients develop at least mild to moderate aortic regurgitation within the 1st year and these patients face reduced device durability, higher rates of hospitalization, and worse survival (2, 3).

Current guidelines recommend surgical correction of more than mild AR at the time of LVAD implant but the treatment strategy of significant AR that develops after LVAD implant is more complex (4, 5). In this scenario, device-management with reduction of LVAD speed may be attempted to reduce the net-negative pressure created by the LVAD inflow cannula. In

practice, it is not clear if decreasing the pump speed does decrease the AR severity or makes it worse. In addition, the accurate quantification of AR severity by Doppler methods is often very challenging in these patients. Guidelines for AR severity assessment in cf-LVAD patients recommend a multi-parametric approach based on traditional transthoracic echocardiography (TTE) parameters including pressure half time (PHT), vena contracta diameter (VC), jet width to left ventricular outflow tract width ratio, and corroboration with hemodynamic findings (6). However, these Doppler parameters have not been validated in this specific patient group with continuous suction from the inflow cannula of the LVAD to unload the LV. This results in continuous blood flow from the inflow cannula to the outflow cannula that is positioned in the proximal aorta (1, 6).

In this setting, the development of an *in vitro*, patient-specific, AR model that incorporates a cf-LVAD could represent a much-needed reference standard for dynamic flow and accurate AR volume quantification. Recently, 3D printing technology has been applied to the LVAD population for pre-implantation planning, but such patient-specific anatomic modeling has not been utilized for functional replication of this continuous flow/AR challenge (7–10).

The aim of the present study was to create a circulatory loop that combines 3D printed patient-specific geometry in order to: (1) replicate the hemodynamic conditions of AR in the presence of a cf-LVAD; (2) directly measure AR volume (RegVol) in an experimental setting to isolate the impact of LVAD speed changes on AR severity; and (3) assess the performance of recommended quantitative echocardiographic parameters for the assessment of AR severity compared to a reference standard of flow.

Methods

Patient-specific 3D printed model

For our study, we selected an 81-year-old male with HM II LVAD and a history of ischemic cardiomyopathy. Appropriate Institutional Review Board approval and consent were obtained from the patient.

From computed tomographic (CT) image data, segmentation of the patient-specific model was performed using Mimics software (Materialize NV, USA) (Figure 1A). The segmentation of the left heart was created based on pixel threshold intensity, including the inner region and the boundaries of the specific anatomic structures to be replicated (blood volume, left atrium, left ventricle, mitral valve, aorta, LVAD coupling connectors, and inflow cannula). The 3D digital model was then saved as a STL file and exported for 3D printing. Each anatomic element was 3D printed, considering the approximate mechanical properties of the biologic tissue and available elastomeric materials (Agilus shore, a Stratasys J750, Stratasys, 7665 Commerce Way Eden Prairie, MN 55344). The inflow cannula was also 3D printed to maintain a fixed inflow cannula position (Figure 1A). The aortic valve was configured to create a fixed regurgitant orifice area (ROA) of approximately 34 mm^2 (Figure 1C inset). The material for the AV was chosen to replicate a stiff structure that would approximate the physiological finding in an elderly patient with calcified aortic leaflets.

We used a previously described process of segmentation to recreate a 3D patient-specific model. This model was outsourced for printing (11). Please see Supplementary Table 1 for details of the materials.

Circulatory flow loop

Our group has previously described an echo-compatible flow loop that, coupled with 3D printing technology, was able to replicate patient-specific hemodynamic conditions in different clinical settings, and provide reference standard flow and pressure measurements (12, 13). The flow loop was designed to achieve up to 7 L/min forward flow and provide variable compliance and resistance. Briefly, the loop consists of a pulsatile pump (Kollmorgen s300 brushless servo drive. Kollmorgen, Radford, V), arterial compliance and resistance elements, and a fluid reservoir (Figure 1B). High fidelity pressure transducers (Mikro-Tip Transducer, model SPR-370s. Millar, Houston, TX) were positioned on either side of the mitral valve and proximal to the aortic valve to record peak chamber pressure in the ventricle and the aorta. The pressure and flow information was recorded continuously (Figure 2). The pulsatile pump consists of a Lexan, hollow cylinder that houses a piston with an adjustable displacement volume up to 200 mL. Platinum cured silicone tubing was used to connect all flow loop elements. Beat-rate and flow conditions are controlled by a custom Labview virtual instrument (National Instruments, Austin, TX) program. For the present study, the flow loop configuration was designed to accommodate a HMII LVAD in the correct anatomical position. The flow loop was filled with a mixture of 30% glycerin, 70% water, and 0.01% cornstarch to simulate blood viscosity and ultrasound scattering behavior, as previously published (14, 15).

Testing protocol and imaging

A fixed beat rate of 60 BPM and a fixed forward flow volume was used for all experimental conditions. With this constant preload, afterload and heart rate, 6 progressively higher LVAD speeds, from a baseline speed of 8,800 RPM to 1,100 RPM (8,800, 9,200, 9,600, 10,000, 10,400, and 11,000) were tested for their impact on aortic and left ventricular pressure, forward systemic flow and regurgitant flow. Doppler echo parameters were assessed at each LVAD pump speed.

For each LVAD speed setting, the systemic flow (L/min), cf-LVAD flow (L/min), aortic pressure (mmHg) and left ventricular pressure (mmHg) were directly captured. Aortic regurgitant volume (RegVol, ml) was calculated as the difference between the forward systemic flow measured directly within the flow loop through high fidelity transducers and cf-LVAD flow. An average of 3 measurements were recorded from the diastolic phase of 3 consecutive *in vitro* pulse cycles and used for statistical analysis.

Echocardiography parameters

Echocardiographic acquisitions were performed using an IE33 machine (Philips, The Netherlands) equipped with a S5 probe for 2-dimensional and Doppler acquisition. Standard echocardiographic parameters for the assessment of AR severity [Continuous Wave Doppler on AR jet with evaluation of peak Velocity (cm/sec), Velocity Time Integral (VTI) and Pressure

FIGURE 1
(A) Patient specific 3D printed model. **(B)** Mock circulatory flow loop setup. **(C)** Reconstruction from CT dataset of the patient specific model coupled with the Hearmate II LVAD and (inset) showing the regurgitate orifice. The yellow arrow indicates a zoom in on aortic regurgitation orifice.

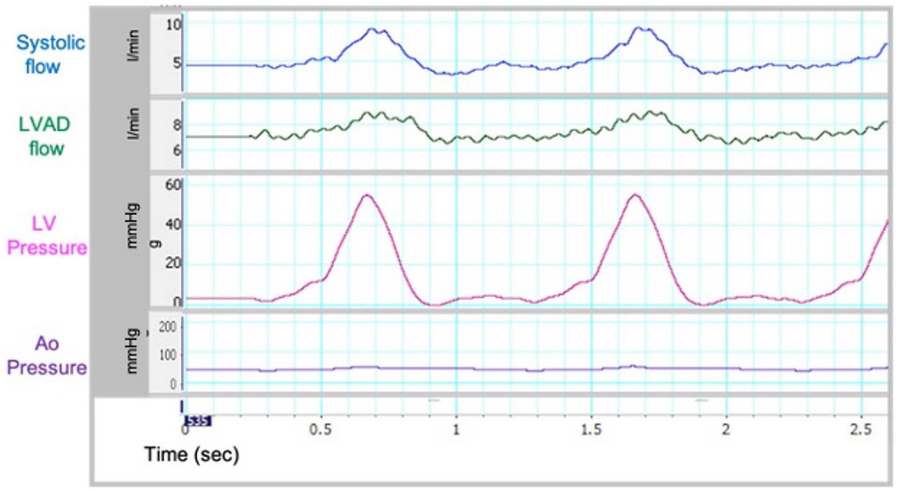

FIGURE 2
Flow and pressure curves from flow loop.

half time (PTH, msec); color Doppler of regurgitant jet width with operator appraisal, measurements of vena contracta (cm) and proximal isovelocity surface area (PISA, cm^2)] and Pulsed Wave Doppler interrogation of inflow and outflow cannula for determination of systolic and diastolic velocities (cm/sec) were recorded for every flow condition. To minimize variability, echocardiographic acquisitions were standardized for gain, filters, compression and rejects settings. TTE parameters describing AR severity and PISA-derived regurgitant Volume (Vol_PISA, cc/beat) were compared to the reference standard represented by the RegVol measured within the flow loop as described above. To enhance image acquisition the left heart model was placed in a water filled bath. A modified apical view was used for all Doppler evaluations.

Statistical analysis

Data were analyzed using STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Continuous variables were evaluated for normality using the Shapiro-Wilk test for normal distribution. To explore the relationship among the different indexes of AR, the Pearson coefficient of correlation was tested with linear regression analysis. Repeatability of hemodynamic data was assessed with repeated measurements on a second set of experiment under the same conditions and quantified by direct Pearson's correlation. Inter-observer variability for echocardiographic data was assessed by repeated measurement by independent readers for all echo parameters and quantified by direct Pearson's correlation.

Results

Reproducing patient-specific hemodynamics

Sample waveforms for systemic and LVAD flow and left ventricular pressures in the flow loop are shown in Figure 2. These were similar to *in vivo* waveforms as reported by Rosenbaum et al. describing a left heart catheterization ramp protocol for hemodynamic optimization and variations in disease states (16). As such, our *in vitro* model was able to replicate the hemodynamic conditions of cf-LVAD recipients. The recorded pressure and flow within the circulatory loop were consistent on repeated measurements, with Pearson's correlation coefficients >0.96 for all analyzed Pressures and Flow variables (Supplementary Table 2).

Hemodynamic parameters

As the LVAD speed increased from 8,800 to 11,000 RPM, forward flow increased from 4.09 to 5.61 L/min, which is in line with expected increased forward flow in the setting of increased left ventricular support provided by the cf-LVAD in clinical practice. Moreover, the mean systemic and aortic flow increased, and the end-diastolic aortic pressure increased, while the LV end-diastolic pressure (LVEDP) decreased, consistent with increased LV "unloading" with higher LVAD speed (Table 1, Figure 3).

Echocardiographic parameters

AR created within the 3D patient-specific model replicated well the AR experienced by the patient with qualitatively similar continuous wave Doppler profile, peak velocities and event timing (Table 2, Figure 4). In addition, the color Doppler velocity map was very similar to the clinical echo depiction of AR severity.

Effect of LVAD speed on AR severity

Increasing the LVAD speed, the RegVol increased only by approximately 0.5 L/min (2.01 to 2.5 L/min) or approximately <10 ml/beat (34.5 to 42.4 ml/beat). As such, the severity remained moderate across all tested flow conditions.

The evaluation of AR by continuous wave Doppler (CWD) demonstrated a trend toward increasing peak velocity (355 to 400 cm/sec) and regurgitant flow VTI (247 to 289) with increasing LVAD speed, pointing to a more significant AR. Moreover, a progressive increase in the systolic component of the flow was noted, that mirrored the pattern seen *in vivo* (the regurgitation tends to become more continuous or "pancyclic", and loses the systolic pause, with regurgitant flow recorded in systole) with the increases of LVAD speed (Figure 5). PHT increased with increasing LVAD speed (700 to 1,180 ms), suggesting a direct correlation ($R^2 = 0.67$) between PHT and RegVol that is inverse to what would be expected with worsening AR severity as suggested by higher peak velocities and AR VTI. Of note a similar pattern was seen in the *in vivo* echocardiographic clinical studies from the model patient (PHT from 1,175 to 1,865 ms with increasing LVAD speed from 8,800 to 10,600 RPM).

Color Doppler analysis revealed that with increasing LVAD speeds there was a progressive increase in vena contracta diameter (0.6 to 1 cm at 8,800 and 11,000 RPM respectively). As such, if the vena contracta diameter only appeared to classify the AR as moderate at 8,800 RPM, it reached measurements consistent with severe AR at higher LVAD speed. Similarly, a progressive increase in the PISA radius (0.4 to 0.94 cm) and thus PISA-derived regurgitation volume (AR_PISA, from 31.6 ml at 8,800 RPM to 141.7 ml at 11,000 RPM) was noted with increasing LVAD speed.

AR_PISA resulted in an overestimation that was progressively more substantial at increased LVAD speeds (+5 to +99 ml/min at 8,800 and 11,000 RPM respectively), and resulted in classifying AR as moderate at low LVAD speed and severe at higher RPM (≥9,600 RPM), even though as described the RegVol only changed by approximately 10 ml.

Peak systolic over peak diastolic velocity ratio (S/D) on pulse wave Doppler as measured at the outflow cannula a was measured for all flow conditions (17). The ratio remained <5.0 (range 1.36–1.24) and progressively decreased at increasing LVAD speeds. S/D inversely correlated with RegVol ($R^2 = 0.81$) and its small range of variation was consistent with the small change in absolute RegVol.

The interobserver variability was good for all tested classic echocardiographic parameters, as showcased by high correlations for PHT, peak velocities, vena contracta diameter and PISA radius ($R^2 = 0.78$, 0.95, 0.84 and 0.97 respectively for PHT peak velocity and vena contracta diameter). For S/D ratio the correlation was somewhat lower ($R^2 = 0.68$).

Supplementary Figure 1 depicts association between echocardiographic parameters and directly measured regurgitant volume.

Discussion

In this study we created a patient-specific flow model that allowed us to (i) accurately replicate AR in the setting of cf-LVAD and (ii) directly measure the regurgitant volume at different LVAD speeds. We present preliminary data demonstrating that changes in LVAD speed change AR severity by only a small fraction as based on directly measured regurgitant volume when other hemodynamic parameters remained constant, and traditional echocardiographic parameters overestimated the severity of AR in the cf-LVAD patient. Our findings support the current clinical guideline recommendations to avoid use of PHT to assess AR severity in LVAD patients and suggest that other Doppler profile elements such as AR duration and systolic flow interruption may be important for AR quantification (16).

In the current era of cf-LVAD, it is clearly established that AR is a common complication of long term LVAD use and is associated with worsening heart failure, poor end-organ perfusion, and decreased survival. Accurate quantification of aortic regurgitation remains difficult for cf-LVAD patients. Indeed, echocardiography lacks validation in this setting, and a reliable gold standard for regurgitant volume quantification is not clinically available. For instance, cardiac MRI cannot be performed due to the presence of a mechanical pump. Methods that combine echocardiography and right heart catheterization data to derive the aortic regurgitation volume have their own significant limitations (18).

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TABLE 1 Directly measured hemodynamic parameters within the flow loop at different LVAD speeds.

	Systemic flow		LVAD flow		Reg volume		LVEDP		Ao EDP	
LVAD SPEED (rpm)	l/min	% change	l/min	% change	l/min	% change	mmHg	% change	mmHg	% change
8,800	4.09	–	6.17	–	2.07	–	13.52	–	36.5	–
9,200	4.29	4.8	6.56	6.37	2.31	11.69	12.66	−6.3	38.56	5.64
9,600	4.39	7.25	6.85	11.08	2.47	19.28	12.25	−9.4	40.7	11.5
10,000	4.79	17.11	7.25	17.45	2.46	18.7	13.48	−0.3	43.69	19.7
10,400	4.94	20.7	7.55	22.42	2.61	26.35	11.8	−12.7	46.16	26.5
11,000	5.61	32.25	8.16	32.25	2.54	22.9	11.35	−16.0	50.64	38.7

LVED, left ventricular end diastolic pressure; AoEDP, Aortic end diastolic pressure.

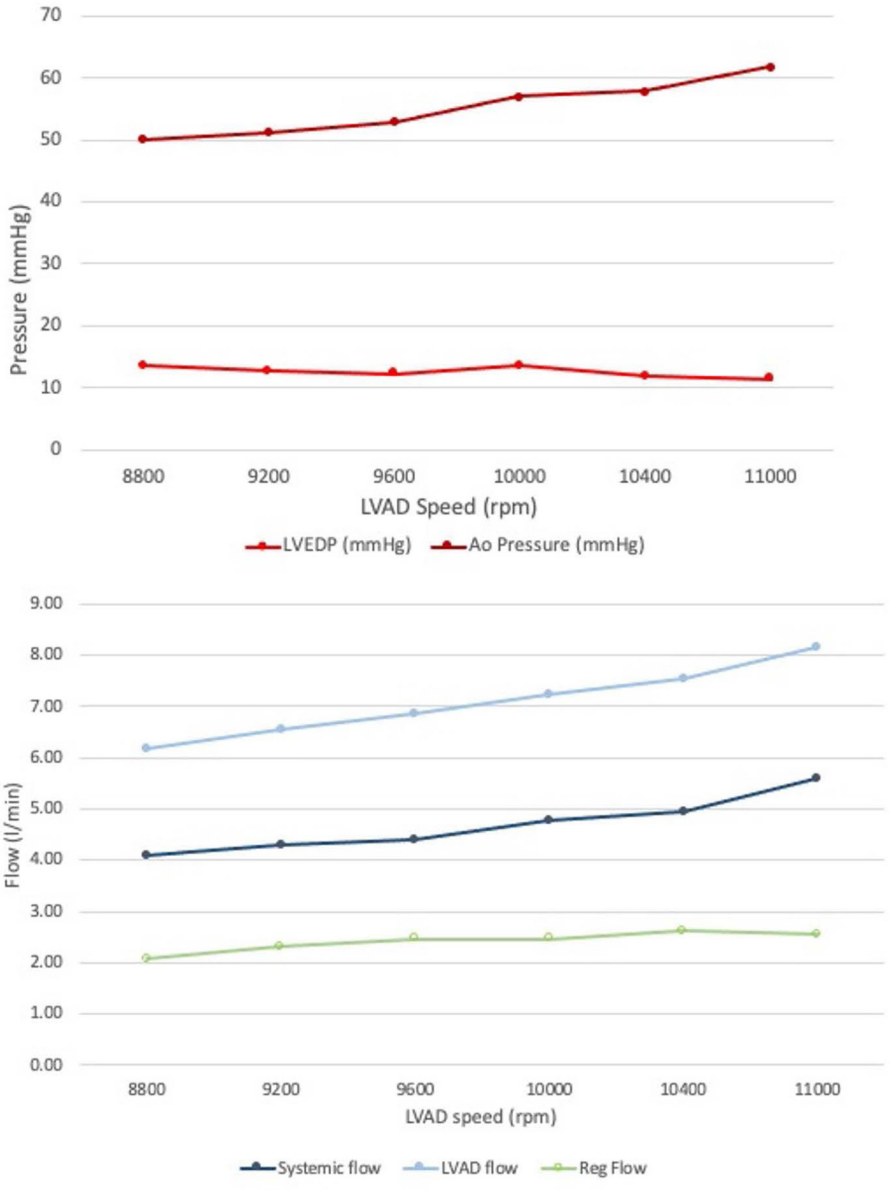

FIGURE 3
Invasive measurements obtained from the mock circulatory flow loop. **(Top)** End diastolic pressures in the Aorta and LV. **(Bottom)** Forward systemic flow and LVAD flow; regurgitant flow form AR obtained by subtraction: note how the regurgitant volume did not significantly change at increased LVAD speed.

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TABLE 2 Impact of LVAD speed on echo parameters describing AR severity and echo based regurgitant volume calculation vs. directly measured AR regurgitant volume—image quality was deemed insufficient by both expert reader to obtain an accurate PISA radius and the subsequent calculations of ERO and RegVeol.

LVAD SPEED	Echo parameters								Direct measurements	
	Vena contracta (cm)	PISA radius (cm)	VTI	Peak V (cm/sec)	PHT (msec)	S/D ratio	ERO (cm^2)	VoL_PISA(cc/beat)	Reg volume (cc/beat)	SD* (cc/beat)
8,800	0.6	—	247	355	700	1.348	—	—	34.53	1.19
9,200	0.75	0.4	248	362	820	1.354	0.12	31.66	37.94	1.13
9,600	0.8	0.7	274	385	870	1.232	0.27	75.77	41.11	0.79
10,000	0.9	0.8	283	387	894	1.251	0.36	101.69	40.94	0.51
10,400	0.92	0.9	287	393	985	1.171	0.45	128.53	43.61	1.18
11,000	1	0.95	289	400	1,180	1.178	0.49	141.68	42.50	0.50

*SD Standard deviation for repeated measures of direct measurements of Regurgitant volume within the flow loop.

In this study we describe an *in vitro* replication of dynamic flow conditions of cf-LVAD patients with AR that served as a gold standard against which standard TTE parameters for AR severity could be evaluated. Models simulating aortic regurgitation in cf-LVAD have previously been described. In a model of various regurgitant lesions by Shehab et al. they were able to successfully re-create the hemodynamic conditions of AR (19, 20). However, their work lacked a 3D patient specific model that was anatomically correct that allowed for accurate measurement of aortic valve area, left ventricular outflow tract and reproduced aortic valve regurgitation that could then be quantified by echocardiography.

Although our model incorporated a fixed-area aortic valve, the model behaves similarly to that of the aortic valve in an LVAD patient with minimal or no contribution to forward flow from the left ventricle. As such, we were able to test in isolation the effect the LVAD speed changes on the regurgitation volume and compare the direct measurements to the echo derived parameters of AR severity. Indeed, our experimental conditions maintained constant heart rate, preload, afterload, and the regurgitant valve area.

The net increase in the total regurgitation volume between a cf-LVAD baseline speed of 8,800 RPM and the maximum speed of 11,000 RPM was trivial in our experimental setting, somewhat surprisingly and in contrast to previous reports and our own echocardiographic findings (17, 21, 22).

This is helpful from a clinical perspective: knowing that the regurgitant volume does not increase significantly with LVAD speed is a significant argument against the common practice of attempting to mitigate AR severity through a reduction in LVAD support. Our experimental data suggests that the risk of inducing an increase in filling pressure and reduced cardiac output is not counterbalanced by a real impact on AR severity.

One change that did occur with increasing LVAD speed was to the time profile of AR on CWD analysis. In both the clinical echocardiogram and in our experimental setting, the CWD demonstrated diastolic AR for lower LVAD speed but pancyclic regurgitant flow with incremental speed. As mentioned however, the directly measured regurgitant volume (RegVol) did not change significantly. It can be therefore extrapolated that the AR is not always continuous but depends on LVAD speed and perhaps loading conditions. Therefore, we suggest that in clinical practice AR severity should be measured through TTE parameters at the lower LVAD speed.

In our study, the traditional parameter for severity, vena contract, and PISA overestimated AR severity. While these findings need further exploration, we have clearly demonstrated that PHT is unreliable for AR severity assessment. Indeed, we found an inverse relationship between PHT on CWD and AR severity. In our model, PHT progressively increased at increased LVAD speed—that is to say, for slightly increased RegVol, a trend that is contrary to what is normally expected in non cf-LVAD related AR. Current guidelines recommend against using PHT alone to grade AR severity, recognizing its dependence on LV preload, afterload and aortic pulse pressure. Of note, all of these are affected by the presence of the cf-LVAD, which creates a continuous flow in the aorta and presence of recirculating blood in the LV, making the PHT likely even less reliable to grade AR severity in this subset of patients.

As for the more recently proposed parameters to assess AR severity in cf-LVAD patients, the outflow cannula Doppler systolic to diastolic velocities ratio (S/D) remained <5.0 for all LVAD speed

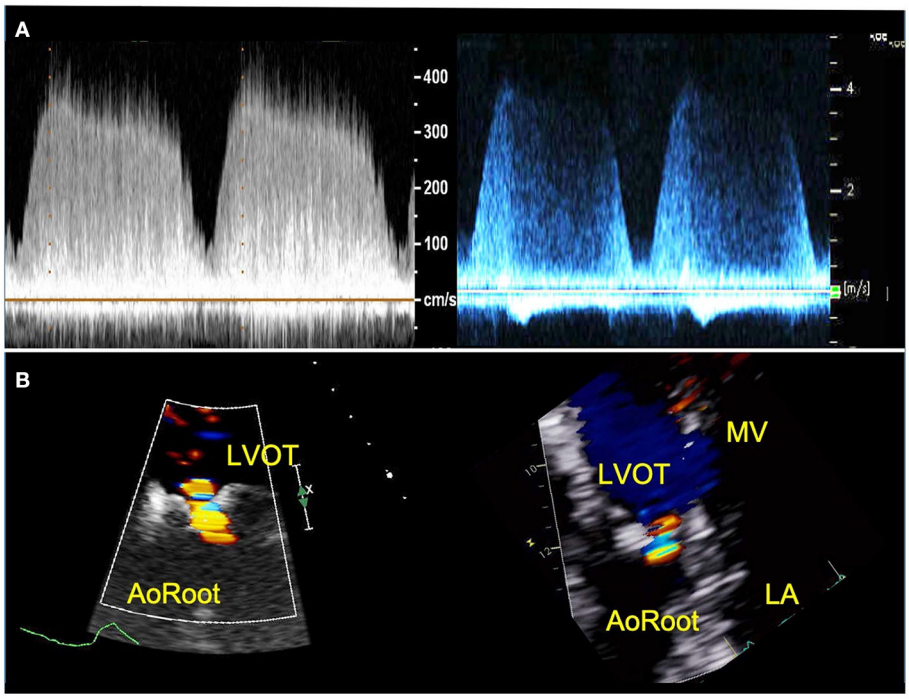

FIGURE 4
TTE images of AR from patient (right) and 3D printed model within the circulatory flow loop (left). **(A)** Continuous wave Doppler of AR flow demonstrating comparable profiles and peak velocities; **(B)** color Doppler images or the regurgitant AR flow, for vena contracta measurement. LVOT, Left ventricle outflow tract; LA, left atrium; MV, mitral valve.

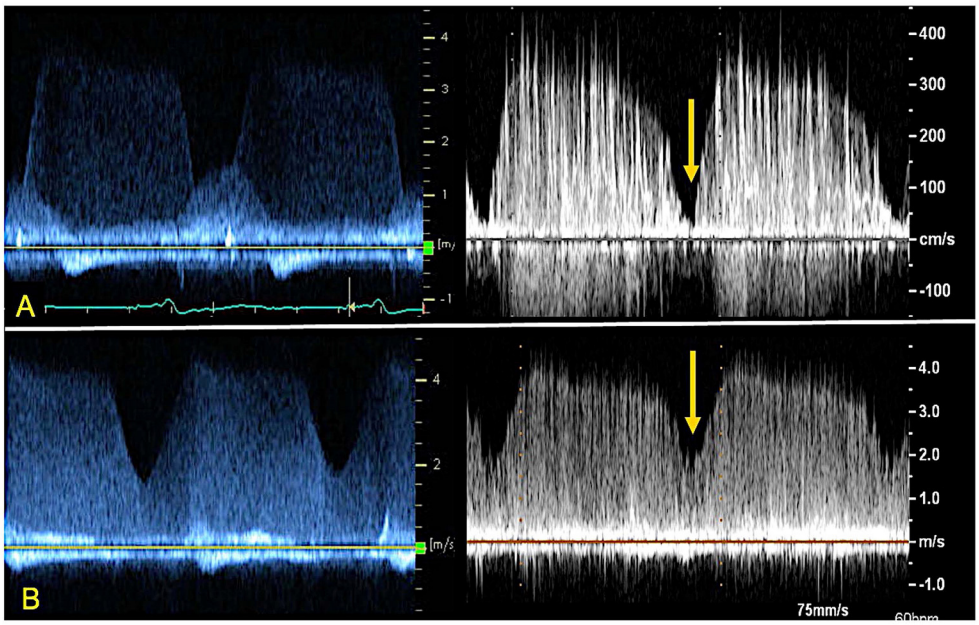

FIGURE 5
CWD from index patient's ramp study (left) and 3D printed model within the circulatory flow loop (right) depicting AR profile at different LVAD speeds. Note the loss of systolic dip in the CWD curve as the AR becomes "pancyclic" going from 8800 RPM **(A)** to 11000 RPM **(B)** of LVAD support. The yellow arrow indicates the "systolic dip".

conditions in our model, correctly classifying AR as at least moderate (regurgitant fraction >30%) (17). The Doppler profile quality in our mock-circulatory flow loop did not allow for reliable measurement of diastolic acceleration, another proposed novel parameter for AR severity assessment, that was thus not tested. These new approaches will need further exploration.

Our preliminary data from this analysis, within the limitation of a 3D printed model, suggests that traditional echo-based approaches

(vena contracta diameter and regurgitant volume by PISA method) significantly overestimate the AR severity and might thus represent a fallacious tool in guiding clinical management of this population especially at higher cf-LVAD speed. This is in stark contrast to common clinical practice and assumptions as well as more recent data that consider AR in cf-LVAD generally underestimated by echo parameters (17, 21, 22). This model can therefore be used in the future to test the echo parameters across a variety of different patient specific models.

Conclusions

Our circulatory flow loop was able to closely replicate the AR flow and hemodynamics of a LVAD recipient, providing a gold standard of direct flow measures against which TTE-derived parameters of AR severity could be evaluated. Preliminary results indicate that with increasing LVAD speed, the increase in AR regurgitant volume is small, and that standard TTE parameters tend to overestimate such increase, more significantly so at higher LVAD support. Combined, these data might indicate the need for a critical rethinking of the application of traditional TTE parameters to guide the device management of *de novo* AR in patients with cf-LVAD. Further analysis will have to consider AR severity grading by other TTE parameters, as well as different patient specific 3D printed models and different LVAD devices.

Limitations

We replicated and tested flow conditions with only one of the available cf-LVAD devices, the HeartMate II (Abbott, Chicago, IL); however, although is currently unclear whether incidence and impact of AR in cf-LVAD is dependent on the type of device, the majority of available data relate to the HMII.

The model replicated a small and constant contribution from the LV—provided in the model by the flow loop pump, that might not be the case for all cf-LVAD recipients but replicates the clinical scenario in which a residual LV function contributes to LVAD performances by augmenting VAD preload and providing some LVOT outflow. The right ventricle and pulmonary vasculature was not accounted for in the model, therefore the LV-RV interdependence as well as the effect on PA pressures could not be assessed. From an echo perspective, the model did not allow for insonation through a standard parasternal long axis view, therefore, a modified apical view was used for Doppler evaluation. Such a modified approach is however not uncommon in clinical practice, given the shadowing artifact produced by the LVAD inflow cannula. The 3D printed LV, although more compliant, still needs modification to simulate true diastolic function of the left ventricle.

The 3D-printing process was outsourced and material properties were not independently tested given the clinical focus of this study.

Finally, our model represents a single patient with heavily stiffened and remodeled aortic valve; further testing and modeling would be needed to confirm our findings on different patient specific modeling before fully being able to generalize our findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

MK, SL, and SF participated in the study design and conception. EA, CA, SF, and SX equally participated in the acquisition, analysis, and interpretation of data for the work. EA, MK, KE-T, and SL participated in the drafting of the work and its critical revision for important intellectual content. All authors provided approval for the final version of this manuscript and for the publication of the content and agreed to be accountable for all aspects of the work here presented.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.994431/full#supplementary-material

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Aortic valve disorders and left ventricular assist devices

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Aortic valve disorders are important considerations in advanced heart failure patients being evaluated for left ventricular assist devices (LVAD) and those on LVAD support. Aortic insufficiency (AI) can be present prior to LVAD implantation or develop *de novo* during LVAD support. It is usually a progressive disorder and can lead to impaired LVAD effectiveness and heart failure symptoms. Severe AI is associated with worsening hemodynamics, increased hospitalizations, and decreased survival in LVAD patients. Diagnosis is made with echocardiographic, device assessment, and/or catheterization studies. Standard echocardiographic criteria for AI are insufficient for accurate diagnosis of AI severity. Management of pre-existing AI includes aortic repair or replacement at the time of LVAD implant. Management of *de novo* AI on LVAD support is challenging with increased risks of repeat surgical intervention, and percutaneous techniques including transcatheter aortic valve replacement are assuming greater importance. In this manuscript, we provide a comprehensive approach to contemporary diagnosis and management of aortic valve disorders in the setting of LVAD therapy.

KEYWORDS

advanced heart failure, left ventricular assist device, aortic valve, aortic insufficiency, transcatheter aortic valve replacement

Introduction

Left ventricular assist device (LVAD) physiology has important effects on aortic valve (AV) structure and function. AV disorders, particularly aortic insufficiency (AI), can impair the efficacy of LVAD support. AI is either present prior to LVAD implantation or develops *de novo* during LVAD support. The management of AI is challenging, and its occurrence can lead to persistent heart failure symptoms after LVAD implantation, with significant morbidity and mortality. We provide a comprehensive review of the epidemiology, pathophysiology, clinical evaluation, prevention, and management of AV disease in patients being considered for LVAD therapy and those on LVAD support.

Aortic insufficiency

Epidemiology of aortic insufficiency in LVAD patients

The importance of AI during LVAD support and the need for appropriate management was understood during the early days of LVAD support with pulsatile flow devices (1, 2). As the

number of patients with durable LVADs for long-term support increased and as continuous-flow (*CF*) durable LVADs became mainstream, the impact of AI on VAD function and clinical outcomes became increasingly recognized (3). AI can be present prior to LVAD implantation or develop in a previously competent AV (*de novo* AI). In an early retrospective single center study, echocardiograms of 78 patients with Heartmate XVE and Heartmate II LVADs without evidence of AI at the time of implant were reviewed. Freedom from moderate to severe AI was 89.4% had 6 months, 74% at 12 months, and 49% at 18 months. Predictors of progression included female sex, smaller body surface area, Heartmate II device, increasing aortic sinus diameter, and AV that remained closed or intermittently opened, and lower ventricular volumes (4). Another single-center study of 232 patients with *CF* LVADs, primarily HMII found that greater than mild *de novo* AI during LVAD support occurred in 22.4% at 1 year and at least moderate AI was expected in 37.5% at 3 years. An AV that did not open was strongly associated with AI with hazard ratio of 11.2 (5).

In an INTERMACS analysis of 10,603 patients who had no or mild AI during device implantation, 55% of patients had at least mild AI at 6 months follow-up and 14% had moderate AI at 2 years. Predictors of progression to moderate–severe AI included age > 60 years, female sex, BSA < 2.0 m2, and mild pre-implantation AI. Of patients with mild pre-implant AI, 18.9% progressed to moderate–severe AI whereas 10.7% of those with no pre-implant AI progressed to moderate–severe AI. Long support on destination therapy devices was associated with higher rates of moderate–severe AI (6).

Aortic insufficiency remains a challenging issue with current generation devices. In a single-center study of 61 patients with Heartmate 3 who had no significant AI at implant, 20% had significant AI at 3 months post-implant. These patients had a higher rate (HR 2.76) of heart failure readmissions or death compared to those without significant AI at 1 year (7) Another single-center report evaluated 121 patients who underwent HeartMate 3 implantation and 270 Heartmate II implantation with no/trace AI at baseline and who did not undergo aortic intervention at the time of LVAD implant. They concluded that at 1 year, 26.26% of the HeartMate II group had mild AI and 15.15% had greater than mild AI whereas 34.55% of the HeartMate 3 group had mild AI and 7.27% had more than mild AI. Multivariable analysis showed no difference in *de novo* AI development between HeartMate II and HeartMate 3 ($p = 0.68$) (8) In a large single-center analysis of 836 LVAD patients with 6 year follow-up, progression to moderate or severe aortic insufficiency was lower in the HeartMate 3 group than HeartMate II groups (9.92 vs. 17.04%, $p = 0.01$). Multivariable analysis showed a signal toward less progression to moderate/severe AI in HeartMate 3 (HR 0.62, $p = 0.053$). The rate of progression was not different in the two groups in year one post implant, with HeartMate 3 having lower rates of AI progression after year 1 (9). Preliminary analysis from the MOMENTUM trial suggested lower rates of clinically significant AI in the HeartMate 3 than HeartMate II group (5.6 vs. 11.5%, $p < 0.01$) at 2 years, with further analysis ongoing (10).

Pathophysiology of aortic insufficiency in LVAD patients

The pathophysiology of AI on LVAD support is complex. The patterns of hemodynamic stress on the AV and root are altered with LVADs. If the total cardiac output is coming predominantly from the LVAD, Left Ventricular (LV) wall stress decreases but the pressure load on the AV increases throughout the cardiac cycle, which leads to leads to valvular endothelial trauma and valvular deterioration (11). In addition, a persistently closed AV may result in commissural fusion (12, 13). There are structural changes in the aorta with continuous flow LVAD support, with an increase in adventitial thickness and intimal/medial collagen intensity associated with downregulation of extracellular matrix-degrading enzymes (14). The altered aortic root biomechanics can lead to aortic cusp remodeling (15). The proximal thoracic aorta can also enlarge during LVAD support, a phenomenon associated with hypertension (16). All these factors contribute to the development of LVAD–AI. The importance of AV opening has been recognized and is factored into contemporary LVAD design with intermittent speed drops to promote pulsatility and AV opening (17).

The hemodynamic consequences of AI are manifold. The cycle of blood from LVAD to the aorta, then retrogradely to the LV leads to inadequate forward cardiac output despite normal or high LVAD flows (Figure 1). LV dimensions can increase from the higher LV volume, which can predispose to mitral regurgitation. Inadequate LV offloading and increased MR can lead to elevated wedge pressure, pulmonary venous hypertension, and persistent RV dysfunction. As a result, patients can develop persistent heart failure symptoms, impaired tissue perfusion, and volume overload. This can lead to a persistent cycle of worsening heart failure and also diminish any likelihood of myocardial recovery.

Clinical evaluation of aortic insufficiency in LVAD patients

History and physical exam

Mild to moderate LVAD AI may be asymptomatic, at least initially. However, with increasing severity of AI, patients may have persistent or recurrent heart failure symptoms, with dyspnea,

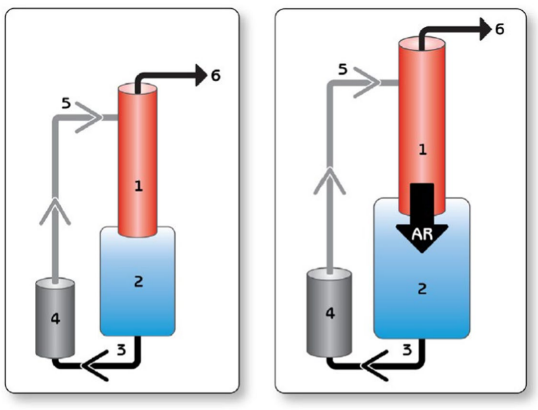


FIGURE 1
Blind circulatory loop in the setting of AR. Left, normal circuit. Right, In the setting of AI, a portion of the LVAD output regurgitates through the AV into the LV and back again through the LVAD, creating a blind loop and decreasing the effective forward flow and, hence, end organ perfusion. 1=aorta; 2=left ventricle; 3=inflow cannula; 4=pump; 5=outflow cannula; and 6=peripheral perfusion. AR, aortic regurgitation. Reproduced with permission from (12).

exertional intolerance, orthopnea, and abdominal or leg swelling. Diuresis may be required, and if the patient is already on diuretics, then dose adjustment might be needed. Both left and right-sided heart failure symptoms may present as significant AI can lead to worsening RV function. Physical exam may reveal JVD, abdominal or peripheral edema. AI murmur may not be heard over LVAD sounds (18). The classical physical exam signs of AI (e.g., Corrigan's pulse, Water hammer pulse etc.) are not present given continuous flow physiology.

LVAD device changes

Aortic insufficiency generally worsen over time with continuous flow LVADs (3). With both the Heartware and HeartMate platforms there is device data that can be trended to give the clinician an insight into the status of the valve.

All *CF* VAD operations are impacted by the change in pressure differential across the pump. This principle of operation has been well documented in the development of the HeartWare waveform or delta P across the pump (19). During periods of worsening AI this pressure differential equalizes (aortic pressure verses left ventricle pressure) and throughout the cardiac cycle there is increased intraventricular volume. This leads to decreased pressure gradients across the pump and reported higher cardiac output. This reported high output is due to the creation of an alternative flow pattern of blood recycling through the AV and not forward flow to the patient (Figure 2). For Heartmate II and HeartMate 3, there is no real time graphical representation of this phenomena, but there are two key values that can be trended over time. These are estimated cardiac output and pulse index. The pulse index calculated as follows:

$$\frac{(PowerMax - PowerMin)}{(PowerAvg)}$$

This change in pump power over time is an attempt to illustrate the power variability during the cardiac cycle (systolic verses diastolic). Just like with Heartware, during AI the pressure gradient narrows, and the trough rises. This will lead to increasing reported values of flow and conversely a reduction in PI values. This reduction in PI is due to the numerator in the equation decreasing with the pressure narrowing throughout the entire cardiac cycle. Therefore, AI should be considered a patient with clinical signs and symptoms of persistent heart failure who has high flow and low PI (20).

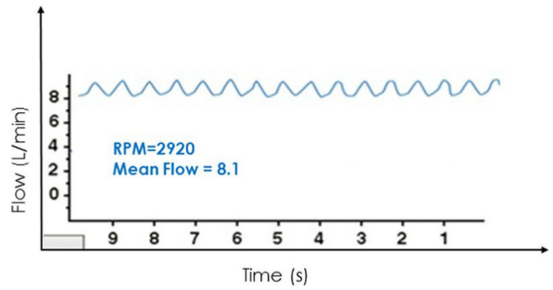


FIGURE 2
Representative heartware tracings of severe aortic insufficiency. Reproduced with permission from (19).

Echocardiogram

Echocardiographic evaluation of the patient before LVAD implantation

Echocardiography is essential in assessing pre-implantation bi-ventricular size and function and ruling out valvular conditions like mitral stenosis and AI, which may reduce LVAD inflow or compromise forward flow by endless loop formation, respectively (21). Gauging pre-implantation AI severity is critical as it typically worsens post LVAD. Parameters like regurgitant jet width to Left Ventricular Outflow Tract (LVOT) diameter ratio, vena contracta, and proximal flow convergence that rely on color Doppler imaging may perform sub-optimally in severe heart failure due to low trans-aortic gradients from low mean arterial pressure and systemic vascular resistance and elevated LV diastolic pressure (21, 22). Pressure half-time can also be shortened by high LV filling pressures (22). A comprehensive evaluation using multiple different parameters is therefore needed. Size and structure of the aortic root and cusps should be carefully reported as aortic root enlargement and leaflet sclerosis/fusion may be clues to incompletely imaged eccentric regurgitation jets. Transesophageal echocardiography (TEE) can sometimes help with better visualization. In cases of doubt, phase-contrast cardiac magnetic resonance (CMR) imaging through the aortic root can provide a more volumetric assessment (22).

Echocardiographic evaluation of the patient after LVAD implantation

Left ventricular assist device reverses trans-aortic pressure gradients. Continuous flow from LV apex to the ascending aorta decreases LV pressure and increased aortic pressures, worsening AI duration, and severity. Remodeling of the aortic apparatus from cusp fusion and aortic root dilatation also contribute to a larger regurgitant orifice area (23, 24).

Surveillance post-LVAD echocardiograms are generally recommended at 2 weeks, 1, 3, 6, and 12 months and subsequently at 6–12-month intervals (21). AI should be evaluated at each exam.

Aortic valve opening should periodically be assessed since a closed AV is more likely to undergo commissural fusion and cusp deterioration. M-mode can be useful for measuring the frequency of valve opening and degree and duration of cusp separation. Five-six cardiac cycles at sweep speeds of 25–50 mm/s should be evaluated. Depending on LV contractility and LVAD pump speed, the AV can open with every beat, intermittently, or not at all. High pump speeds reduce AV opening. Ideally, AV should open at-least intermittently and for >200 ms as measured by M-mode (21).

As with native anatomy, a vena contracta width >3 mm and jet width to LVOT ratio >46% should represent at least moderate AI in the setting of LVAD (21). However, AI from LVAD may extend variably into the systolic phase and can even be present throughout the cardiac cycle. This phenomenon of holo-cyclic AI from LVAD induced reversed aortic gradients may not be fully captured by traditional measures for diastolic AI quantification. Further, the jet width may change between systole and diastole and may increase at higher pump speed. At high pumps speeds, continuous wave Doppler though the AV from a five-chamber view may detect holo-systolic and

holo-diastolic AI with no forward flow. Color M-mode from a parasternal long axis view can also detect the temporality of AI. Due to non-confinement of AI to diastole and due to dependence on loading conditions, neither pressure half time nor aortic flow reversal can be used for AI quantification with LVAD.

These difficulties have led to the evaluation of two novel echocardiographic parameters for grading AI severity with LVAD. Diastolic acceleration (dv/dt) and systolic-to-diastolic peak velocity ratio (S/D) derived from pulse wave Doppler of the LVAD outflow canula have shown better correlation with semi-invasively calculated regurgitant volume and invasive filling pressures when compared to traditional parameters like vena contracta (25) (Figure 3). These measurements are based on the augmentation of outflow cannula flow in diastole due to decreased afterload in the aorta and increased preload in the LV as seen with significant aortic insufficiency. Diastolic acceleration >49 cm/s^2 and S/D ratio of <5.0 correlate with moderate–severe AI. These parameters can reclassify up to a third of patients with mild AI to a moderate–severe range and are able to better predict heart failure hospitalizations, AV intervention, urgent transplant, and death more accurately than vena contracta (26).

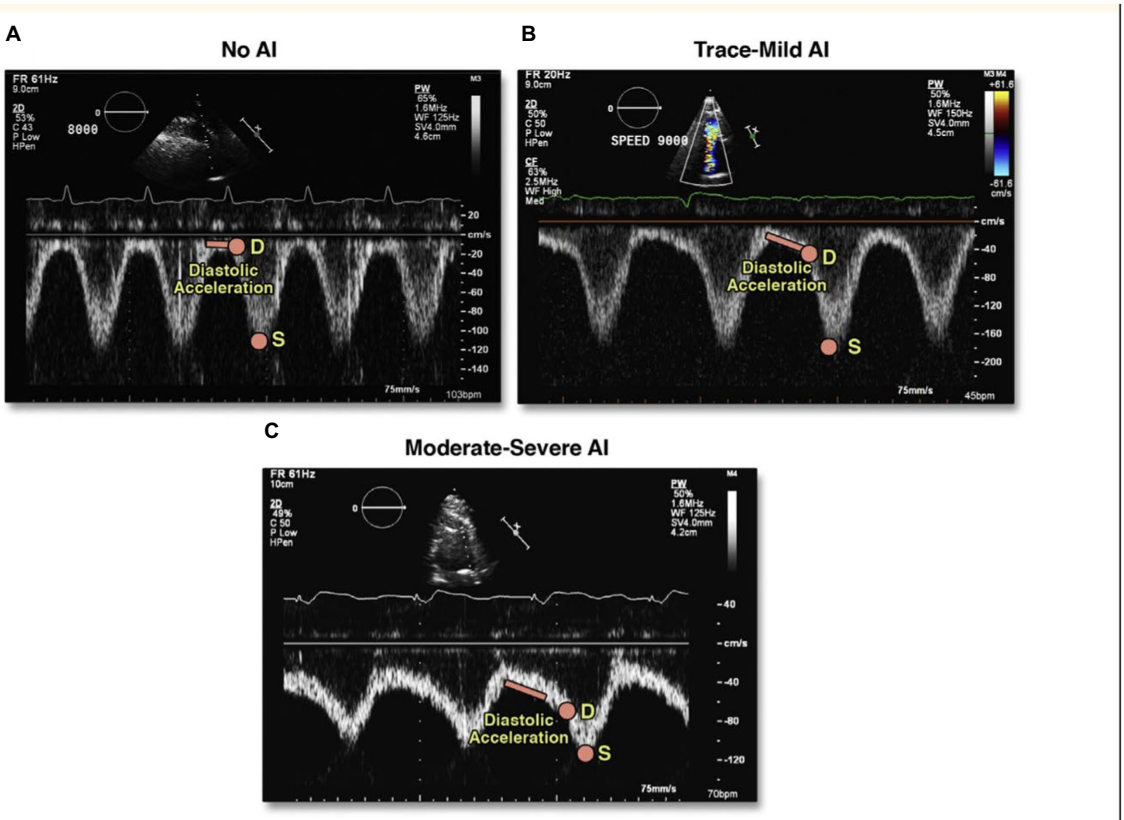
Severe AI can increase LV dimension and shift the interventricular septum to the right. Inflow and outflow cannula flows can be increased due to loop formation while Right Ventricular Outflow Tract Velocity Time Integral (RVOT-VTI) is reduced due to true reduction in cardiac output. AV interventions may typically be needed in such severe cases.

In the absence of a true gold standard for AI quantification with LVAD, a combination of parameters should be used, and interpretations should be made cautiously to avoid underestimation (21).

Cardiac catheterization

Cardiac catheterization has an important role in defining the severity of AI and the consequence of AI on hemodynamics and symptoms. Dynamic studies with LVAD speed adjustment, afterload reducing medications, or during exercise provide additional information (27).

The pulmonary capillary wedge pressure (PCWP) evaluates efficacy of LV offloading. It can be elevated in AI but also with other conditions, such as mitral regurgitation, severe hypertension, and inadequate LVAD speed. The right atrial pressure (RAP) reflects right ventricular (RV) function, and the relation of RAP



Measurement of left ventricular assist device outflow cannula diastolic acceleration and left ventricular assist device outflow cannula systolic-to-diastolic peak velocity ratio (S/D ratio) in a representative patient with **(A)** no aortic insufficiency (AI), **(B)** trace-mild AI, and **(C)** moderate-severe AI. AI severity was graded using vena contracta. D = peak diastolic velocity; S = peak systolic velocity; TTE = transthoracic echocardiography.

FIGURE 3
Novel echocardiographic parameters for assessment of LVAD-AI. Reproduced with permission from (25).

with pulmonary artery pressure (PAP) and PCWP in can be helpful in the determination of the influence of left-sided factors on RV function. In patients with VAD-AI and no native LV ejection, the difference between the LVAD flows and cardiac output measured by right heart catheterization provides an estimate of AI volume.

Hemodynamic ramp studies can be performed during right heart catheterization and sometimes with simultaneous echocardiographic measurements. Increase in LVAD speed leads to increase in LVAD flow. However, with increased LVAD flow, LV systolic pressure can decrease, and the AV to LV gradient can increase, and can worsen AI. In one study of 55 LVAD patients who underwent simultaneous hemodynamic and echocardiographic ramp studies, the cohort with at least mild AI, ramp study with increases in LVAD speed decreased the PCWP and increased the CO, but also led to worsening AI in 78% by echocardiogram (28). This response may vary individually, and other groups have reported persistently high PCWP, lack of decrease in LV dimensions, and persistently low cardiac index despite higher pump speeds (29). Given these patients' generally severe LV dysfunction, decreases in LVAD speed may not always improve hemodynamics and can lead to lower cardiac output and increased mitral regurgitation. Therefore, individualized assessment and adjustment to obtain the most optimal hemodynamics is important, as is recognizing that hemodynamic changes with resting ramp studies may not necessarily translate into improved exercise hemodynamics and functional capacity.

Aortogram, while not commonly performed, can be used to evaluate angiographic AI severity, aortic size, location of outflow graft, AV opening, and presence of aortic root thrombus (30).

Computed tomography

Computed tomography (CT) does not currently have a primary role in the assessment of LVAD AI, but provides important pathophysiological insights into many LVAD complications, including LVAD AI development and progression (31). A larger angle of the outflow graft to the aorta may direct more LVAD flow towards the AV and is correlated with AI (32).

Computational fluid dynamics using CT-derived aorta models have shown increased leaflet tip shear stress but no difference in oscillatory wall stress in those with LVAD AI relative to those without (33). Patients with AI have smaller distance from the aortic root to the outflow graft, and greater regional wall shear stress (34). Patients with AI have a perpendicular ascending aortic anastomosis (35).

Management of aortic insufficiency in LVAD

Surgical management of AI at the time of LVAD implantation

Current guidelines roots for AV intervention at the time of LVAD implantation for any insufficiency greater than mild on TEE (36–38). The modality of intervention, however, continues to be a topic of debate. Concomitant procedures are associated with increased short-term morbidity, and surgeon experience and preference often dictate the surgical plan in the absence of definitive data on superiority of a particular approach (39, 40). Techniques for addressing AI support include AV closure, AV repair, AV replacement, coaptation stitch, and annuloplasty, all of which typically require cardiopulmonary bypass (CPB) and aortic cross clamping (41, 42). Technical aspects of these procedures are discussed first, followed by outcome data.

Aortic valve replacement

Aortic insufficiency can be addressed with a conventional AV replacement with bioprosthetic valve. The bioprosthetic valve leaflets, however, can degenerate over time and develop fuse altogether with the subsequent need for an additional future intervention.

Park's stitch

In this technique, pledgeted 4-0 Prolene sutures approximate the fibrous nodules of Arantius creating a coaptation stitch. This approach allows the AV to still open for ejection, even though the effective orifice area of AV is markedly diminished (1) (Figures 4, 5).

Aortic valve closure

Several methods of AV closure exist. A circular patch of bovine pericardium can be sewn circumferentially to the aortic annulus above the AV, closing the LVOT (Figure 6). If there is a prior aortic bio-prosthesis, running stitches with or without pledgets along three lines of coaptation can be used to close the leaflets. For a bicuspid AV, the thickened edges of the leaflets are sewn together or a central stich in the middle of the leaflets can be placed. If there is a previous mechanical valve, it can be removed and a pericardial patch sewn circumferentially in two layers to the AV annulus (44). In the setting of a previous mechanical AV, the mechanical valve is removed, and the pericardial patch is sewn circumferentially in two layers to the AV annulus with a running 3.0 polypropylene suture (43).

Aortic annuloplasty

Aortic valve repair with an annuloplasty ring sutured under the valve annulus in conjunction with noncoronary leaflet plication has been successfully performed with trivial postoperative AI in a patient with HeartMate 3 intended for destination therapy (45).

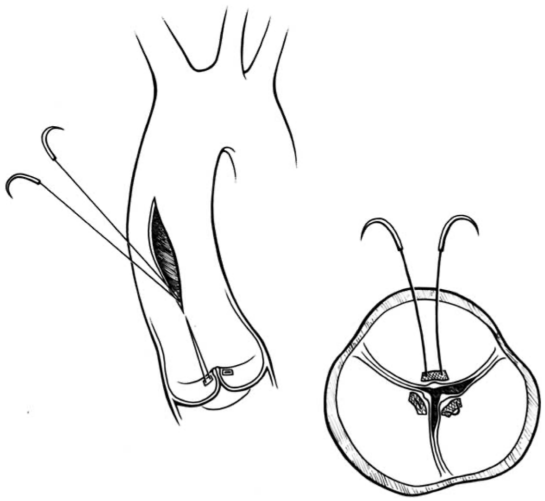


FIGURE 4
Park's stitch. Pledgeted 4-0 Prolene sutures are applied to approximate the fibrous nodules of Arantius to create a coaptation stitch. Reproduced with permission from (1).

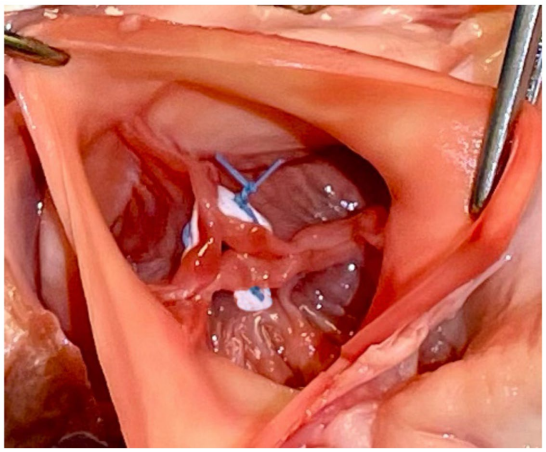


FIGURE 5
Modified park's stitch.

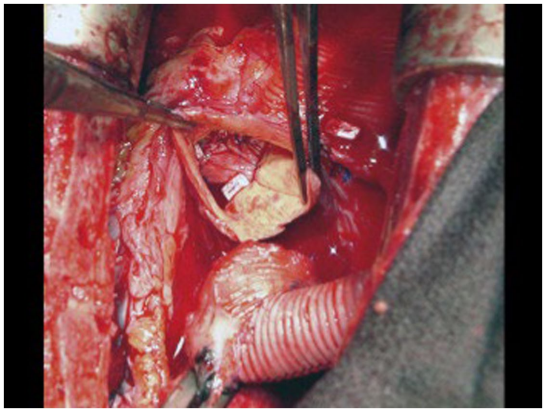


FIGURE 6
A circular patch of bovine pericardium was sutured circumferentially to the aortic annulus above the native aortic valve leaflets. Reproduced with permission from (43).

Outcomes of concomitant AV intervention

Several single-center studies showed conflicting results on outcomes of AV interventions in LVAD candidates (42, 46). In an INTERMACS analysis of 5,344 patients who underwent LVAD implant between 2006 and 2012, 305 underwent concomitant aortic valve intervention, with 125 AV closures, 95 repairs, and 85 replacements. One-year survival was 81% for patients without AV procedure, 79% in the AV repair group, 72% in the AV replacement group, and 64% with AV closure ($p = 0.0003$). Mortality curves diverged in the first 3 months postoperatively. AV closure was independently associated with increased hazard of death in multivariable analysis (HR 1.87, $p < 0.0001$), and the most common causes of death in AV closure groups were bleeding and respiratory failure. Intervention did not guarantee success, and by 6–12 months postoperatively, moderate–severe AI occurred in 18% with AV repair, 9% with AV replacement, and 5% with AV closure.

In a recent analysis of 15,267 patients from the IMACS registry implanted with LVADs from 2013 to 2017, 457 underwent concomitant AV replacement and 328 underwent concomitant AV repair. The specifics of the repair technique were not available. Early (90 day) survival rates were 90.4% in patients without AV procedure, 85% in those with AV replacement, and 87.4% in patients with AV repair ($p < 0.001$). Late survival rates were also different (62.4, 55.5, and 60.9% in the no AV procedure, replacement, and repair respectively, $p < 0.001$). Concomitant AV replacement was an independent predictor for both early and late mortality. Mechanical AV replacement was associated with the worst outcomes.

Interestingly, those who had moderate–severe AI pre-implant, the subset that underwent no AV intervention had similar early, conditional (in 90-day survivors), and late survival to those who underwent AV repair or replacement. This led the authors to advise caution and use stringent criteria for repair/replacement, particularly for those with mild AI, and consider transcatheter AV therapies in selected cases (47).

Best practices concerning cases of mild AI at the time of LVAD need further study. With regard to surgical decision making, AV repair may be reasonable in cases of degenerative disease (cusp prolapse or malcoaptation), while bioprosthetic AV replacement could be of more value in calcific leaflet pathologies. Importantly, AV closure leaves patients completely dependent on the LVAD outflow and is, therefore, contraindicated when recovery is anticipated; furthermore, it may have catastrophic consequences in cases of pump thrombosis or malfunction. At this point, surgical intervention for mild AI may be of value if the patient has risk factors for developing *de novo* AI, such as nonischemic cardiomyopathy, an expected long duration of LVAD support (more than 1 year), and a small body surface area.

The 2013 ISHLT guidelines have no specific recommendation on preferred modality. The 2019 EACTS guidelines provide a IIa recommendation for bioprosthetic AV replacement, IIb recommendation for central coaptation stitch, and recommend against (Class III) closure of the AV (38). The 2020 AATS/ISHLT recommendations provide a Class I recommendation for addressing greater than mild AI with valve closure, repair, or replacement (37).

How to prevent *de novo* AI at the time of initial LVAD implantation

A computational fluid dynamics study demonstrated that a closer position of the LVAD outflow graft in relation to the aortic root and angulation of outflow graft (perpendicular anastomosis to ascending aorta are risk factors for the development of *de novo* AI) (34, 35) Performing the outflow graft-ascending aortic anastomosis at a 45% angle should be considered to reduce the risk of late AI (38).

De novo AI

As previously discussed, AI can develop or progress during LVAD support, with higher likelihood with longer durations of support. Therapies with some value in preventing *de novo* AI include adequate hypertension management, optimizing LVAD speeds to avoid excessive flow and persistently closed AV, and technical advancements such as intermittent pulsatility algorithms (12). Some patients with severe symptomatic AI can also be managed with intravenous inotropic therapy to enhance native contractility (48).

Most centers will consider AV intervention if patients remain symptomatic with moderate–severe AI despite medical therapy including diuretics, afterload reduction, and device optimization. The decision regarding either a surgical intervention or a percutaneous approach is made depending on the patient's general status. Surgical intervention can be in the form of AV closure (Dacron patch), AV repair (Park stitch), AV replacement, or heart transplant (8, 49). Even though redo sternotomy on LVAD represents an invasive route with risks for RV damage, dysfunction, and significant bleeding, it remains an option in selected patients. Transcatheter therapies should also be considered alongside surgical approaches as part of an interdisciplinary approach to management. The EACTS guidelines have strong preference for heart transplant when feasible (Class I) over open valve replacement/surgical closure (Class III) for moderate AI, with transcatheter AV replacement (Class IIa) and interventional closure of AV (Class IIb) receiving intermediate recommendations. For severe AI, high urgency listing for transplantation in those who are candidates is a Class I recommendation, Transcatheter Aortic Valve Implantation (TAVI) is a Class IIa recommendation, and open valve replacement or closure and interventional closure have Class IIb recommendation (38) (Figure 7).

Medical therapies for prevention or treatment of AI in LVAD patients

Medical therapies in LVAD patients for AI prevention or management in the current era focus on hypertension management and re-initiation of guideline-directed heart failure therapies. After normalization of cardiac output by LVAD, blood pressure, particularly diastolic BP, may increase. This may increase hemodynamic stress on the aortic root and valve and contribute to AI development. In a single-center study of 90 patients undergoing HMII and HVAD, those who developed AI had higher SBP, DPB, and MAP at three and higher DBP and MAP at 6 months than those who did not develop AI, and 3-month SBP was an independent predictor of post-LVAD AR (50). Another study of 85 patients did not find an association of BP with *de novo* AI (5). Others have shown trends implicating hypertension in AI development or progression (51). Goal MAP in society guidelines are ≤80–85 mmHg. Medications recommended are those that are standard for heart failure, i.e., ACEI/ARB/ARNI, BB, and MRAs, with the logic that these are already known to the patients, may have beneficial effects on right ventricular and renal function, afterload reduction improves LVAD functioning, the ability to use higher doses post LVAD may enhance ventricular remodeling and potential recovery (52), and the ensuing pulsatility may be helpful in AI prevention and management. The impact of SGLT2i in LVAD patients is currently not well understood but is undergoing investigation.

Transcatheter management of AI in LVAD patients

Surgical approaches for AI management at a time later than the LVAD implant entails a reoperation in a higher-risk cohort of surgical patients and can lead to morbidity and mortality. Therefore,

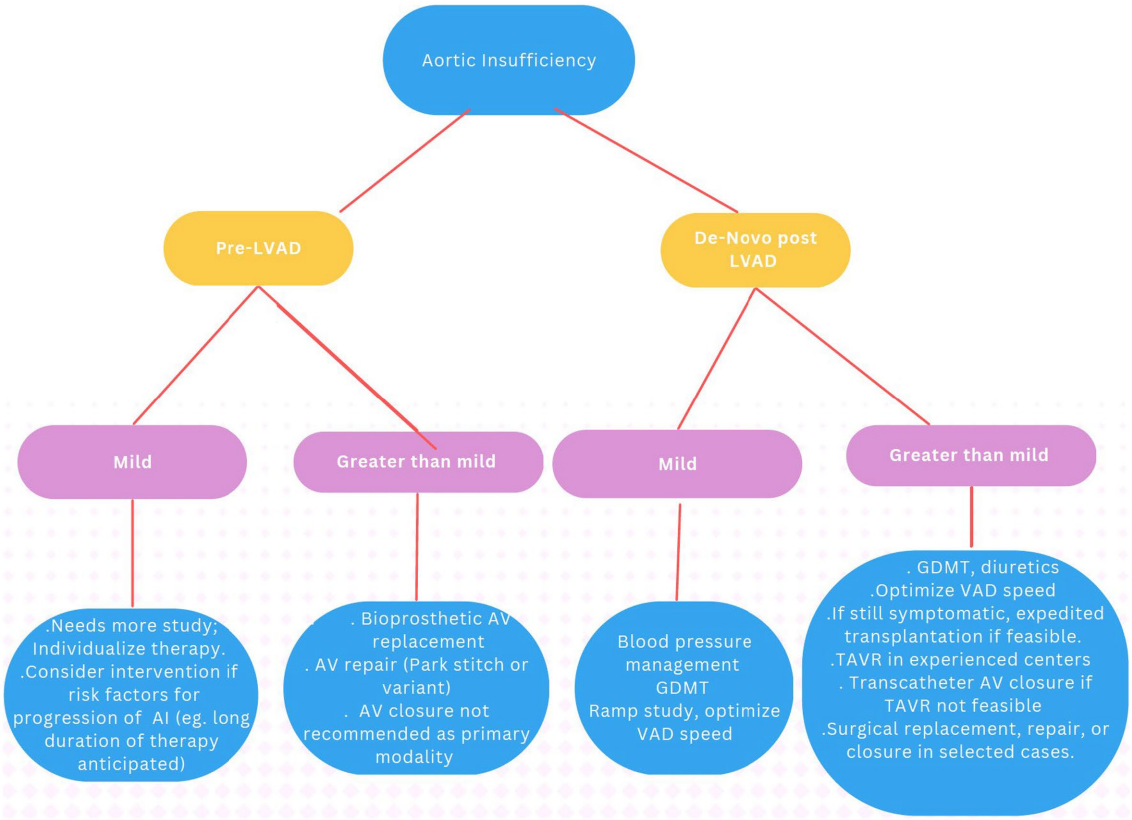


FIGURE 7
Recommendations for management of aortic insufficiency.

transcatheter therapies have assumed greater importance in recent years.

Aortic valve closure

Aortic valve closure *via* a transcatheter approach was first reported in 2011 (53). Over the next few years, multiple reports of transcatheter AV closure were published (54–57).

The procedure is attractive because of its simplicity.

The procedural details are as follows: the AV is crossed in retrograde fashion from usually a femoral access point. Usually, a Multipurpose/Amplatz left 1/Judkins Right 4 catheter is used to cross the valve with a straight tip wire. Next, a stiff wire (Amplatz Extra stiff or a pre-formed helical tip wire, e.g., Safari or Confida wire) is placed in the LV. Over this wire, a Torqvue 45° delivery sheath is advanced across the native AV. Since the length of the Torqvue sheath is limited at 80 cm, it might be necessary in tall patients to consider alternate access or consider a longer 8F/9F sheath (Flexor). Sizing of the device is done *via* TEE or with gated multidimensional CT. Care is taken not to oversize the device beyond the size of the aortic annulus to decrease the chances of interaction with the anterior mitral leaflet or with the coronary ostia. The Amplatzer Cribriform septal occluder (CSO) is almost universally used, however the initial report used an Amplatzer post infarct muscular ventricular septal defect occluder. Post deployment, aortogram is used to ensure no coronary compromise. It is common to see unresolved AI for a short period of time until the device pores start to thrombose (Figure 8).

The patient in the first report by Grohmann et al. improved, although with hemolysis requiring transfusions for up to 6 weeks which caused renal dysfunction—this necessitated stopping anticoagulation to try and promote thrombosis of the device. The patient only survived a few more weeks although the death was related to an accident with battery exchange. At autopsy, the device was well seated and did not cause any coronary compromise (53). Parikh et al. have published the first case series of five patients (54). Amplatzer Cribriform septal occluders were used successfully in all patients. Hemodynamic improvement was noted in all patients acutely. However, there was embolization of the device to the aortic arch in one patient and two other patients did not survive to the 30-day mark despite a stable device. The embolization was thought to be a result of interaction with the struts of a pre-existing bioprosthetic mitral valve. In a systematic review with data on 21 patients, two out of 21 AV closure devices embolized, although not all series included reported on procedural complications (58). Sauer et al.'s patient survived 10 months without major complications and successfully had a transplant—the CSO device appeared to be well seated and endothelialized at explant (55). In a later analysis likely including the patients included in the series by Parikh et al., Retzer et al. compare the characteristics of 10 patients who underwent percutaneous AV closure—three survived to discharge and subsequently were alive at 6 months (59). Non-survivors were more likely to have worse kidney function and have higher pulmonary artery systolic pressure. They were also likely to have higher lactate dehydrogenase levels post implant and develop worsening RV dilation. An interesting point raised is the size of the device used compared to the aortic annulus, and patients who got smaller devices (device to annulus ratio < 0.9) were more likely to survive, suggesting a role for interaction with other cardiac structures. The major criticism of using this technique is that it renders the patient pump dependent.

Transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) has become mainstream therapy for aortic stenosis and is used off label for patients with AI in selected patients with suitable anatomy (60, 61). TAVR in AI has its challenges primarily because of lack of calcification of the AV leaflets and annulus. Annuli in AI patients often are dilated and may be beyond the specifications of valve systems. Both self-expanding and balloon expandable valves have been used for aortic insufficiency in patients with LVADs.

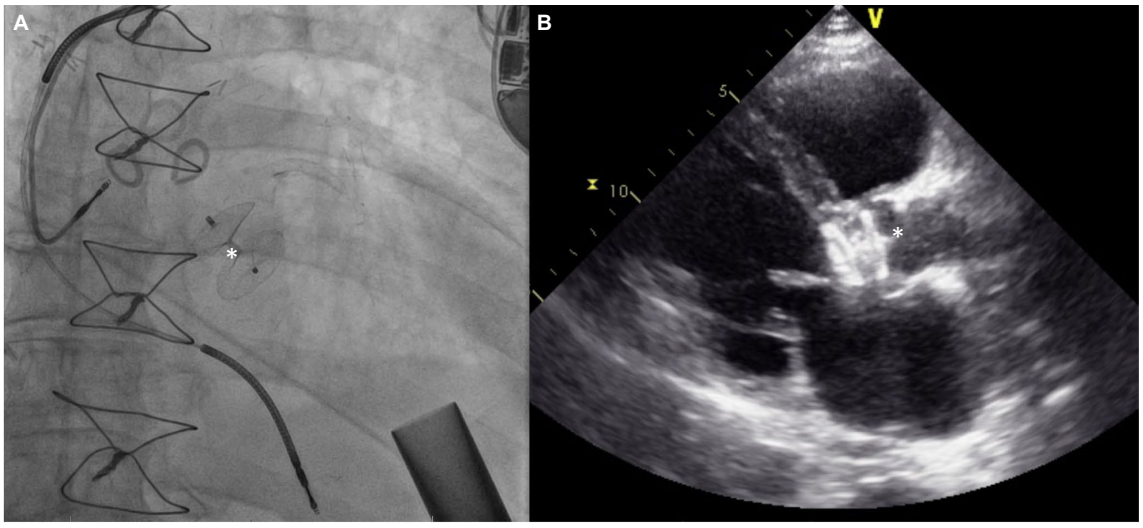


FIGURE 8
(A) Amplatzer device (*) implant for severe AI 3 years after HMII implantation. **(B)** Echocardiograpic appearance of device.

The procedural details are as follows: planning for TAVR in LVAD patients is approached in the usual fashion with CT to measure the annular/LVOT parameters and surrounding anatomy. Transfemoral access is most commonly used, although subclavian/axillary artery approach has also been reported.

More cases have been reported with use of self-expanding valves, with the older generation as well as more current valve iterations. Use of a stiff wire for delivery is generally recommended with the Lunderquist double curve wire being commonly used. Oversizing with a range close or slightly over 30% is essential. The theoretical benefit of using a self-expanding platform is being able to recapture and test the valve in a 75–80% deployed state for longer durations of time to test stability. Longer pacing runs to allow the valve to expand more and stabilize are recommended. Still, valve migrations are common, hence being prepared to stabilize/pull up the valve with a single/double snare technique is required (62). Additional 6F accesses are required for this purpose and a double snare theoretically has a greater chance of successfully repositioning the valve and reduce the risk of aortic injury since the valve frame is compressed by pulling forces on the tabs from either side. The other approach is to place a second valve, usually a balloon expandable Sapien valve using the Corevalve/Evolut as a scaffold (Figure 9). However, this does not work for valve frames that are extremely deep.

Less often, balloon expandable valves of the Sapien family have also been used to treat AI in LVAD patients. Oversizing is of paramount importance here as well and oversizing in excess of 20% is better tolerated than in aortic stenosis patients. Postdilation is often required, and deployment with additional volume is reported anecdotally, based on reports of ability to over-expand the Sapien 3 family of valves without losing competency (63).

The first report of TAVR to treat LVAD associated AI was made by Santini et al. in 2012 (64). In what has been seen in other series that followed, the first Core valve that was deployed was not stable and had at least moderate perivalvular leak. A second Core valve was deployed inside the first one leading to an improved outcome, albeit still with mild peri-valvular leak. More reports of TAVR for LVAD AI have used self-expanding valves. Yehya et al. have reported the largest series with 6 months follow up (65). In two of the nine patients, there was acute valve migration into the LV necessitating snaring of the valve to correct the position and deployment of a second valve (one Sapien 3, one Core valve). One patient died 4 months after TAVR. There was no significant AI in the remaining eight patients at 6 months. Four of these TAVR valves appeared completely closed. There was improvement in RV function and tricuspid regurgitation and a median NYHA II functional class was maintained. This and other early reports include TAVR with first generation of self-expanding valves. The newer iteration of the Evolut platform including a 34 mm valve is a more intuitive choice in order to achieve greater oversizing and more radial force on the non-calcified annulus. Dhillon et al. report a series of four such cases using the 34 mm Evolut valve (66). Three of their cases were uncomplicated, however the fourth had significant ventricular migration which was managed with implantation of a 29 mm Edwards Sapien 3 valve in the waist to try and post dilate/stabilize the valve. The patient continued to have mild–moderate perivalvular leak, eventually had fusion of the valve leaflets and was not able to be rescued. Two of the other three

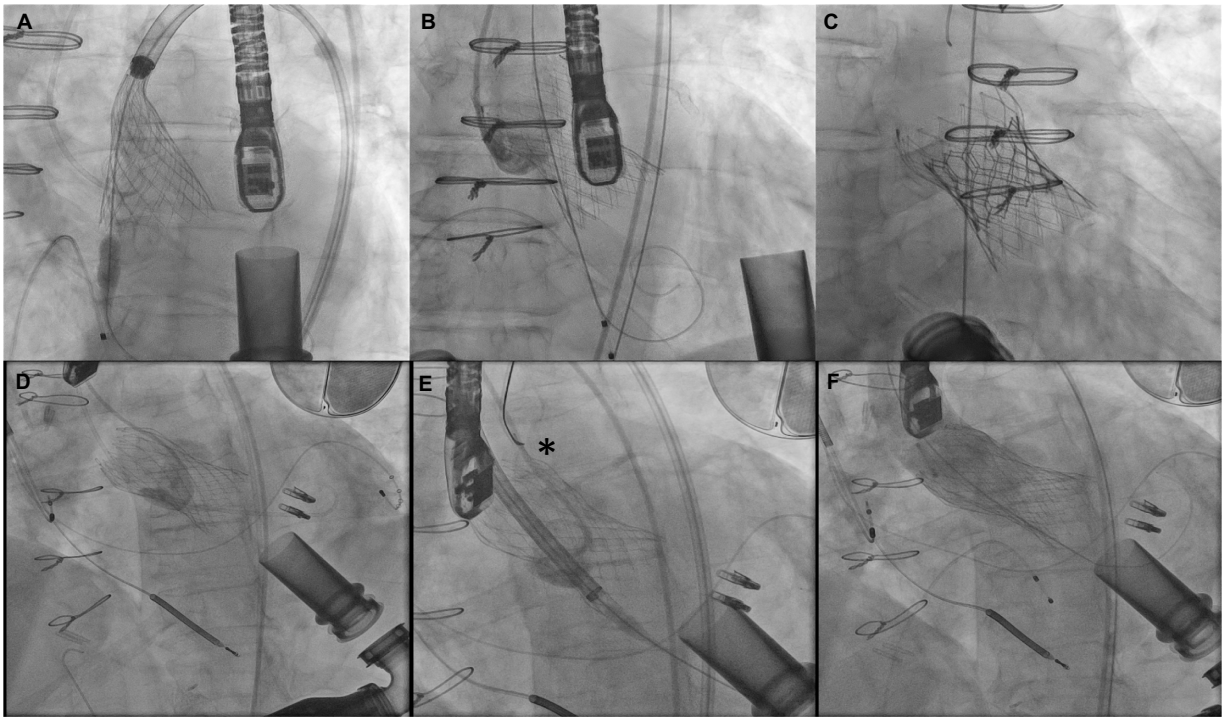


FIGURE 9
(A–C) Attempted Evolut R implant with ventricular migration immediately after release stabilized with 29 mm Sapien 3 implant inside the malpositioned Evolut. **(D–F)** Ventricular migration of Evolut R valve in another patient with repositioning using a gooseneck snare (asterisk) and implantation of a second Evolut R inside with post dilation reducing aortic insufficiency to trace.

patients also did not survive to 3 months. In a retrospective multi-center study evaluating TAVR for native AI, newer generation valve systems like the Evolut had significantly less chance of having a malposition and greater than moderate leak compared to first generation Core valve (67).

Kar et al. reported three cases using the balloon expandable Sapien 3 platform—two cases with 26 mm and one with a 29 mm valve (68). There were no immediate complications and there was significant resolution of AI in all patients. One patient was transplanted >2 years post procedure, another was reported alive 1,120 days post TAVR with mild AI while the third patient died at home 616 days post TAVR with unknown cause of death. The introduction of other balloon expandable valve options has widened the scope of use in aortic insufficiency cases. Recently, a patient with LVAD associated AI was treated successfully with a 32 mm MyVal valve (69).

Beyond self-expanding and balloon expandable platforms, a leaflet anchoring new valve platform is now CE mark approved in Europe (70). The JenaValve system has three locators which anchor to the three AV cusps. There are case reports of this valve system being used for LVAD associated AI cases without any major instability or complications (71). The JenaValve transfemoral system is being studied with the ALIGN-AR trial currently. The *J*-Valve is a valve based on a similar concept with three "rings" to clasp the native leaflets. There are a wide variety of sizes available (22–34 mm) (72). Although not fully mature, with more experience, leaflet anchoring valve platforms will likely be the mainstay of treating native AV insufficiency, making decision making for LVAD associated AI simpler.

Outcomes

Despite the pathophysiologic derangements, several early single-center studies did not show a consistent association of *CF*-LVAD-AI with worsened clinical outcomes or higher mortality. Cowger and colleagues evaluated a single-center cohort of 166 HeartMate two patients, of whom 131 were bridged to transplant. Moderate or higher AI was present in 33% of patients at 2 years but was not associated with a higher hazard of developing worsening mitral regurgitation or RV dysfunction. No survival difference was observed between those with moderate or higher degrees of AI vs. lesser degrees of AI. Only three of 35 deaths were attributed directly to AI (73). Another single-center study of 79 patients (87% DT indication) found development of mild or greater AI in 52% at a median of 187 days f/u. There were no significant differences in heart failure hospitalizations or BP in those with vs. without AI. Mortality was increased in patients with AI, and AI was a significant predictor of death (OR 3.14, $p = 0.005$) but no statistically significant difference in survival curves by log-rank test was observed (74). In a single-center study from the United Kingdom evaluating 93 patients with both HeartMate II and Heartware, longer duration of support and persistently closed AV were associated with development of AI, but no association of mild or greater AI with mortality was noted (75). Another single-center study of 210 Heartmate II patients with 79% of the cohort being bridge to transplant and median support duration 582 days, moderate or severe AI developed in 15.2%. No deaths were directly attributed to AI and there was no difference in survival in those with or without significant AI (76). Important limitations of several of these studies were small numbers of patients, single center practice pattern nuances, predominantly bridge to transplant populations with short-term follow-up with very low numbers of at-risk patients at later time-points, and lack of time-varying analyses.

In the largest published experience to date from INTERMACS, compared to patients with no/mild AI, those with moderate/severe AI hade lower systolic blood pressures, higher left ventricle end diastolic diameter, higher pro-Brain Natriuretic Peptide, and higher degree of at least moderate regurgitation. Patients who developed significant AI in the first year of device support had lower freedom of hospitalization at 2 years, without significant differences in stroke, arrhythmia, and bleeding. Most importantly, survival was also affected: those who developed moderate–severe AI had lower survival (49.1 vs. 36.5% at 5 years, $p < 0.001$) compared to those who had no-mild AI. Differences in survival persisted after adjustment for age, INTERMACS profile, and chronic kidney disease, and on a conditional analysis of 1-year survivors (6).

Special populations

Aortic stenosis

Significant aortic stenosis in patients with severe LV systolic dysfunction should be addressed promptly as surgical or transcatheter AV replacement may improve LV function enough to obviate the need for LVAD. Aortic balloon valvuloplasty is generally not advised other than as palliative therapy and may complicate matters if significant AI results. Aortic stenosis *per se* does not affect LVAD function. However, severe aortic stenosis may impair LV recovery and reduced aortic excursion may lead to further leaflet fusion and risk late AI. Therefore, surgical or transcatheter AV replacement should be considered on a case-by-case basis.

Pre-existing prosthetic AV

Patients with a functioning bioprosthetic AV at the time of LVAD implant do not need additional AV intervention. Those with a degenerated bioprosthetic AV are likely best treated with another bioprosthetic AV, but evidence is scant. In general, mechanical AV should be replaced with a bioprosthetic AV at the time of LVAD implant. Closure of mechanical AV is technically feasible but is associated with poorer outcomes, renders the patient completely LVAD dependent, and does not permit LV recovery, and is therefore not recommended as a first line therapy. Another technique recently reported involves breaking the inner leaflets of the mechanical AV and sewing a bioprosthetic valve on top of the mechanical valve ring (77).

Conclusion

Aortic insufficiency is a common LVAD-associated problem. Incidence increases with duration of support and can lead to morbidity and mortality. Pathophysiology is complex and involves

patient-related, medical management-related and device-related factors. Management can be challenging and incorporates medical, device engineering, percutaneous, and surgical approaches. There is an unmet need for larger scale randomized studies to provide more robust evidence on optimal approaches to prevent and treat AI.

Author contributions

DA: conception. DA, AC, DR, TA, and TK: draft. DA, TK, DR, TA, EB, EJ, RL-R, KL, RS, and AC: editing and critical revisions and final approval. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Transcatheter valvular therapies in patients with left ventricular assist devices

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Aortic, mitral and tricuspid valve regurgitation are commonly encountered in patients with continuous-flow left ventricular assist devices (CF-LVADs). These valvular heart conditions either develop prior to CF-LVAD implantation or are induced by the pump itself. They can all have significant detrimental effects on patients' survival and quality of life. With the improved durability of CF-LVADs and the overall rise in their volume of implants, an increasing number of patients will likely require a valvular heart intervention at some point during CF-LVAD therapy. However, these patients are often considered poor reoperative candidates. In this context, percutaneous approaches have emerged as an attractive "off-label" option for this patient population. Recent data show promising results, with high device success rates and rapid symptomatic improvements. However, the occurrence of distinct complications such as device migration, valve thrombosis or hemolysis remain of concern. In this review, we will present the pathophysiology of valvular heart disease in the setting of CF-LVAD support to help us understand the underlying rationale of these potential complications. We will then outline the current recommendations for the management of valvular heart disease in patients with CF-LVAD and discuss their limitations. Lastly, we will summarize the evidence related to transcatheter heart valve interventions in this patient population.

KEYWORDS

transcatheter heart valve interventions, LVAD (left ventricular assist device), TAVR—transcatheter aortic valve replacement, percutaneous valve intervention, valvular heart disease (VHD), aortic regurgitation (AR), tricuspid regurgitation (TR), mitral regurgitation (MR)

1. Introduction

The transition from pulsatile to continuous-flow left ventricular assist devices (CF-LVAD) has allowed significant prolongation of LVAD support because of improved reliability, durability and survival (1). As a result, the therapeutic use of CF-LVADs has expanded from bridge-to-transplant or bridge-to-candidacy strategies to destination therapy for end-stage congestive heart failure. The lack of donor organ availability and the change in organ allocation system are also creating a strong demand for durable

LVAD implantation, with prolonged expected waiting time on the transplant list, up to five years even as bridge-to-transplant (2). However, the growing use of LVAD support has been accompanied by a greater recognition of their side effects and complications over time. One of the most noticeable aspects of their adverse events profile is the progression or *de novo* development of valvular heart disease (VHD), particularly aortic insufficiency (3). VHD can negatively impact the quality of life and survival of this patient population (4, 5). The increasing appreciation of the detrimental effects VHD can have on patients with CF-LVAD has led societal guidelines to advocate for a more aggressive management (6).

Many surgical techniques can be used to address these pathologies but they introduce major risks for a patient subgroup who is already particularly vulnerable (7).

Transcatheter heart valves (THV) interventions have revolutionized the management of VHD. The field has evolved rapidly since the first introduction of transcatheter aortic valve replacement (TAVR) for the treatment of aortic stenosis in 2002 (8). Within two decades, indications for THV interventions have extended not only to lower-risk patients, but also to off-label use for patients with no other therapeutic options (9–12). This has stimulated interest in less invasive treatment alternatives for VHD in LVAD patients who are poor surgical candidates. Since the first reported case of TAVR for LVAD-induced aortic insufficiency in 2012, an increasing number of case reports have shown encouraging results (13). Nonetheless, THV interventions in patients with CF-LVAD come with unique decision-making and technical challenges.

After a brief overview of the pathophysiology of VHD in the setting of CF-LVAD support, we will present the current recommendations for their management. This will be followed by a discussion on the available evidence describing THV in patients with CF-LAVD.

2. Pathophysiology of valvular heart disease induced by LVAD support

Aortic valve insufficiency, mitral valve insufficiency and tricuspid valve insufficiency are the types of VHD that are most commonly encountered in patients under CF-LVAD support (3). They are either induced by the CF-LVAD itself or precede its implantation.

2.1. Aortic valve insufficiency

Unlike mitral regurgitation, aortic regurgitation is rarely present before LVAD implantation (14); when present, it is usually managed at the time of LVAD implant. However, it becomes an increasing concern over time after initiation of LVAD support. More than 25% of patients develop at least moderate aortic regurgitation within the first year of CF-LVAD therapy (15–18). This risk seems to be time-dependent: Cowger et al. showed that between 6 months and 18 months post LVAD, the proportion of patients who had moderate to severe aortic regurgitation went from 11% to 51% (17). The underlying pathophysiology is likely multifactorial, but the most commonly proposed phenomenon is sometimes referred to as the "disuse theory" (18).

The CF-LVAD draws blood from the left ventricle and directs it in parallel into the ascending aorta *via* an outflow cannula, thus bypassing the aortic valve. This effectively increases forward flow and decompresses the left ventricle, but it occurs at the expense of a reduced or absent aortic valve opening. The increased flow in the ascending aorta, coupled with unloading of the left ventricle create a continuous positive transvalvular pressure gradient across the aortic valve, further promoting aortic valve closure. The constant apposition of the coronary cusps stimulates collagen production and proteolytic enzymes activity (19). This eventually leads to leaflet adherence and fusion of the commissures (19). In addition, the high-velocity and turbulent flow in the ascending aorta generates high-shear stress which can cause aortic valve damage and aortic sinus dilation through smooth muscle cell apoptosis (20). The increase in aortic wall stress is directly influenced by the anastomotic angle of the outflow cannula (21). All these factors lead to retraction of the leaflet tips and creation of a fixed central orifice. The pan-cyclic positive transvalvular pressure gradient and high retrograde pressures from the inflow cannula produce a continuous regurgitant jet into the left ventricle. Aortic valve degeneration is further accelerated by thrombus formation on the left ventricular surface owing to the limited antegrade flow and resultant stasis of blood (19). Initiation of CF-LVAD support may also exacerbate pre-existing aortic regurgitation *via* these same mechanisms (22).

The "disuse theory" has been supported by observational studies. It was found that aortic regurgitation occurs 6 times more frequently in patients in whom the aortic valve remains closed compared to patients with frequent aortic valve opening (16).

The physiologic and clinical consequences of aortic regurgitation are significant. The regurgitant blood is diverted from the left ventricle into the pump. The pump then propels this blood forward to the ascending aorta, but it returns back into the left ventricle down the continuous pressure gradient owing to the aortic insufficiency. This creates a closed loop circulation, rendering the CF-LVAD output ineffective (23). Recirculating blood in the left ventricle also increases left ventricular volumes and pressures, which leads to recurrence of heart failure symptoms (24). Early identification and evaluation of the severity of aortic insufficiency under CF-LVAD support may be challenging since traditional echocardiographic criteria, which are based on diastolic volume overload, markedly underestimate the severity of this regurgitation (21). Although small amounts of aortic regurgitation can be tolerated, more severe regurgitation requires intervention as it can lead to end-organ malperfusion (17).

2.2. Mitral valve insufficiency

Most cases of mitral insufficiency in LVAD patients are functional in nature and can be attributed to ventricular

remodeling and left ventricular dilatation present prior to LVAD implantation (3). Close to 60% of CF-LVAD recipients have at least moderate mitral regurgitation at the time of CF-LVAD implantation (25). However, unlike aortic regurgitation, the severity of mitral regurgitation can be decreased with the use of CF-LVAD alone: left ventricular decompression reduces left ventricular dimensions and increases mitral leaflet coaptation (26). In a retrospective study of 100 consecutive CF-VADs, Morgan et al. showed that CF-LVAD significantly decreased the proportion of patients having moderate or severe mitral regurgitation from 76% at 1 month to 8% at 6 months (26). Unfortunately, this beneficial effect of CF-LVAD support does not occur in all patients. In a single-center retrospective analysis, persistent moderate or severe mitral regurgitation was still observed in 26% of patients after 6 months of CF-LVAD therapy (27). The absence of improvement in mitral regurgitation could be explained by suboptimal left ventricular decompression. Several factors can prevent effective ventricular unloading: significant aortic regurgitation, intractable fluid retention, inadequate pump speed, inadequate pump position, pump thrombosis or frequent suction events. These factors cannot always be corrected without an invasive intervention. For example, malalignment of the apical inflow cannula could result in an obstruction of its orifice owing to an inward bowing of the interventricular septum or ventricular free wall. This situation usually warrants surgical intervention (28). Several studies have documented the effects of residual mitral regurgitation after CF-LVAD implantation. It was found to be associated with persistent pulmonary hypertension, worse right ventricular hypertension, higher risk of renal failure, repeat hospitalizations and increased mortality (29–31).

2.3. Tricuspid valve insufficiency

Tricuspid insufficiency in patients under LVAD support is typically functional (32). One-third to two-thirds of patients with advanced heart failure will have associated tricuspid insufficiency (32). Functional tricuspid regurgitation (TR) often appears in conjunction with left-sided valve disease and left ventricular dysfunction despite the presence of a structurally normal tricuspid valve. It is caused by dilatation of the right ventricle with secondary annular enlargement, apical leaflet displacement and resultant tethering and incomplete coaptation. This condition triggers a vicious cycle where tricuspid regurgitation further contributes to right ventricular failure through right-sided volume overload and decreased ejection. The evolution of tricuspid regurgitation under CF-LVAD support can take many forms. On one hand, by allowing mechanical unloading of the left ventricle, CF-LVAD support decreases left ventricle end-diastolic pressure and pulmonary venous pressure which, in turn, decreases right ventricular afterload (3). Since the right ventricle is highly afterload-sensitive, a decrease in pulmonary pressures improves right ventricular contractility and decreases right ventricular end-diastolic dimensions, as well as tricuspid annular diameter. On the other hand, by reducing left ventricular volumes, the CF-LVAD can also acutely exacerbate tricuspid regurgitation (3). First, it may cause a leftward shift of the interventricular septum, resulting in a restriction of the tricuspid leaflets (33). Second, as systemic flows improve with CF-LVAD support, venous return and right ventricular preload also increase, which can worsen an already marginal right ventricular function and tricuspid regurgitation (34). Given the opposing effects of CF-LVAD on tricuspid regurgitation, progression of this VHD is difficult to predict in patients with CF-LVAD. Furthermore, patients with chronic heart failure often develop pulmonary hypertension from pulmonary arterial vasoconstriction and remodelling resulting from the chronically increased left-heart filling pressure (35). Although pulmonary hypertension usually improves with CF-LVAD support, it may not be normalized in all patients (36). Residual pulmonary hypertension in patients under CF-LVAD support contributes to right-sided heart failure, and thus secondary tricuspid regurgitation (34).

In a retrospective study of 127 patients with over 1 year of LVAD support, the incidence of moderate to severe residual tricuspid regurgitation was found to be 24% (37). The regurgitant fraction impairs transpulmonary flow, thereby reducing CF-LVAD filling and systemic output (38). In addition, the increased diastolic pressure in the right ventricle can cause septal shift and compression of the left ventricle, which may also reduce LVAD filling (38). Systolic reversal of flow in the vena cava may be responsible for end-organ venous congestion. This could negatively affect liver and renal functions, to the point where cardiac transplantation alone becomes contraindicated. Uncorrected moderate or severe tricuspid regurgitation is associated with increased duration of inotropic support and hospitalization, increased rates of right ventricular assist devices, as well as decreased survival in patients with CF-LVAD (32, 39).

3. Indications for intervention

The most recent recommendations for the management of VHD in the context of anticipated long-term LVAD support were published in 2013 by the International Society for Heart and Lung Transplantation (6). They are only based on expert opinion or small retrospective studies and concern mainly management of VHD at the time of LVAD implantation.

3.1. Aortic valve

Given that aortic regurgitation almost invariably progresses under CF-LVAD support and given its significant hemodynamic and clinical consequences, addressing moderate to severe aortic regurgitation at the time of LVAD implantation is a class I indication (level of evidence (LOE) C) (6). In the presence of any concomitant aortic stenosis, bioprosthetic aortic valve replacement should be favored over other surgical interventions (Class I, LOE C) (6). Pre-existing aortic stenosis is less of a concern since pump output does not depend on aortic valve

opening. Accordingly, aortic valve replacement for severe aortic stenosis is a class IIb recommendation (LOE C) (6).

3.2. Mitral valve

Since there is an expected improvement in mitral valve regurgitation under CF-LVAD support, recommendations for the surgical management of mitral regurgitation remain conservative. As per these international guidelines, routine surgical intervention for severe mitral insufficiency is not recommended, unless there is expectation of cardiac recovery (class III, LOE C) (6). Significant mitral stenosis impairs left ventricular filling, thus CF-LVAD filling. Guidelines therefore recommend a mitral valve replacement at the time of CF-LVAD implant for at least moderate mitral stenosis (6). Other authors have suggested considering concomitant mitral valve intervention in the following select scenarios: (i) patients with severe mitral regurgitation and pulmonary hypertension who are bridge-to-transplant or bridge-to-candidacy, (ii) severe mitral regurgitation with posterior displacement of the coaptation point, and (iii) destination therapy patients with borderline right ventricular function (34).

3.3. Tricuspid valve

Guidelines advocate a liberal approach to concomitant tricuspid valve repair in the presence of moderate to severe tricuspid regurgitation with long-term LVAD support (class IIa, LOE C) (6). However, this approach is still controversial and largely debated. Recent studies, including one randomized clinical trial—the TVVAD trial (NCT03775759) –, found that concurrent tricuspid valve repair at the time of LVAD implantation does not appear to lower the incidence of right heart failure (40–42).

Only one study compared concomitant tricuspid valve repair and replacement during LVAD implant (40). After a mean time of 12.3 ± 9.7 months, they found that late mortality and the magnitude of reduction in regurgitation severity was similar between groups.

4. THV interventions

While current guidelines address the presence of VHD at the time of LVAD implantation, there is no consensus yet on the management of VHD once LVAD support has been initiated. While for the majority of cases, tricuspid or mitral regurgitation may be dealt with at the time of LVAD implantation, aortic regurgitation develops as a consequence of LVAD support. In addition, previously implanted prosthetic valves might eventually fail over time. This is especially true for bioprosthetic valves in the aortic position since they are prone to the disuse phenomenon (43). With the overall increase in CF-LVAD support duration, more and more patients may reach a point where valve intervention is deemed necessary. Conventional surgical procedures are certainly feasible, but they hold a high risk of complications (34). Patients with CF-LVAD often have a high burden of comorbidities, a history of prior sternotomy and poor right ventricular function. Therefore, there is an understandable reticence to prolong CF-LVAD surgery or to expose these patients to another invasive cardiac surgery after CF-LVAD implant. In this context, transcatheter heart valve interventions appear as an attractive alternative. However, literature detailing these approaches is largely confined to case reports and small case series (**Table 1**).

4.1. Aortic valve

Transcatheter options include TAVR and aortic valve closure with a percutaneous septal occluder.

4.1.1. TAVR

TAVR has been widely adopted for aortic stenosis. It has also been established as a therapeutic option for aortic insufficiency from degenerative bioprosthesis (94). However, several important technical challenges have limited the suitability of TAVR for native aortic insufficiency. With or without CF-LVAD, native aortic insufficiency typically exists in non-calcified valves. Most TAVR systems rely on the radial tension applied by the prosthesis on the aortic complex, as well as on the interaction of the stent frame with aortic calcifications for proper anchoring. In the setting of aortic insufficiency induced by LVAD, the lack of calcifications may compromise prosthesis stability (95). Furthermore, the presence of aortic root dilation is not uncommon in patients under CF-LVAD (96). These changes can occur as early as within the first 6 months after initiation of CF-LVAD support and are thought to be caused by an increase in aortic wall sheer stress (64). The absence of an anchoring support leads to an increased risk of device misplacement or migration and paravalvular regurgitation from an incomplete seal (95). These can be corrected by using a valve-in-valve strategy in which a second valve is delivered to hold the first valve in place and prevent its migration (44, 64). If not properly anchored, the prosthesis could migrate into the left ventricular outflow tract or the left ventricle, where it could obstruct the inflow cannula of the CF-LVAD. These catastrophic scenarios occur suddenly and require emergent sternotomy and salvage surgery (44, 45). The risk of migration during TAVR deployment is further increased by the hydrodynamic forces exerted by the LVAD: on one hand, the inflow cannula creates a continuous suction effect towards the apex of the left ventricle, and on the other hand, the flow from the outflow cannula causes an opposing force against the valve during its deployment. To minimize this risk, LVAD flows should be temporarily decreased or turned off during valve deployment (44).

In patients with pure aortic regurgitation who are not under CF-LVAD support, systematic reviews from observational studies showed promising results with TAVR, especially with newer generation systems, despite the need to perform a valve-in-valve procedure in 7 to 30% of cases (95, 97, 98). In a meta-analysis of 12 studies, representing a population of 638 patients, Haddad

TABLE 1 Percutaneous devices used so far and potential complications of transcatheter heart valve interventions under left ventricular assist device support.

Valve	Percutaneous devices used so far	Number of reported cases	References	Reported complications	Ways to prevent or to manage
Aortic	CoreValve, Evolut R, Evolut Pro	41	(44–63)	Valve migration	Valve oversizing, valve-in-valve, valve-in-ring, self-fixating prosthesis
	Sapien, Sapien XT, Sapien 3	17	(13, 46, 47, 55, 64–72)	Paravalvular leak	Valve oversizing, balloon overinflation (for balloon-expandable models), valve-in-valve
	ACURATE Neo	1	(73)		
	JenaValve	1	(74)	Valve deterioration by disuse	Ramp study to allow at least partial aortic valve opening
	Melody	1	(43)	Valve thrombosis	Ensure optimal anticoagulation, prompt recognition and diagnosis
	Unknown (TAVR)	87	(75)		
	Amplatzer Occluder	34	(46, 76–89)	Hemolysis (with septal occluders)	Avoid peridevice regurgitant flow
Mitral	MitraClip	33	(90–92)	Increased transvalvular pressure gradients/iatrogenic mitral stenosis	Appropriate patient selection to identify best suited valve morphology, Avoid excessive adduction of the anterior and posterior leaflets
	Valve-in-Valve (Sapien XT)	1	(52)	Inter-atrial shunt	Avoid placing >2 MitraClips, Percutaneous ASD closure
Tricuspid	MitraClip XTR		(93)	Residual regurgitant jet	Additional clips deployment
				Leaflet tear	Caution with MitraClip G4 systems
				Conduction abnormalities	Avoid excessive radial strain with valve deployment
		1		Single-leaflet device attachment	Additional clips deployment
				Valve thrombosis	Ensure optimal anticoagulation, prompt recognition and diagnosis
				Stent migration (TriCinch or CAVI)	Avoid if bridge-to-transplant or if vena cava are too dilated

ASD: atrial septal defect, CAVI: caval vale implantation, TAVR: transcatheter aortic valve replacement.

et al. compared the short-term outcomes of non-LVAD patients with pure native aortic regurgitation who underwent TAVR between 2007 and 2016 (98). Mean logistic EuroScore II was 11.7 ± 12.9% in first generation valves and 9.3 ± 6.4% in second generation valves (98). The mean STS score in first generation valves was 13.1 ± 2.0% compared to 9.1 ± 3.6% in second generation valves (98). The rate of device success was 92% (95% CI from 83% to 99%) in second generation valves compared to 68% (59%–77%) for first generation valves (98). The occurrence of residual moderate or severe aortic regurgitation went from 16% (6%–29%) with first generation valves to 1% (0%–5%) with second generation valves (98). Conversion to surgical aortic valve replacement was also lower in second generation valves, 1% (95% CI from 0% to 4%), compared to first generation valves, 2% (95% CI from 0% to 6%) (98).

Newer generation transcatheter aortic valves offer many benefits, including repositionability, self-positioning geometry, and specific fixation mechanisms, that have the potential to improve the performance of TAVR in patients with native aortic regurgitation (95). The JenaValve (JenaValve Technology, Inc., Munich, Germany) and the ACURATE TA (Symetis, Ecublens, Switzerland) are currently the only devices with *Conformité Européenne* mark for the treatment of aortic regurgitation. They also received approval from the United States Food and Drug Administration for the conduct of clinical trials. The JenaValve is a self-expanding porcine valve on a nitinol frame made of three integrated feelers (also called locators). The locators allow to align the device with native aortic valve anatomy and clip onto the native leaflets which forms a natural seal and fixation independent of valve calcification (99). The first case series of TAVR in aortic regurgitation using the JenaValve showed a procedural success of 97%–100% (100–102). Ranard et al. recently reported the first use of the JenaValve to address severe aortic regurgitation in a CF-LVAD patient (74). The procedure was uncomplicated and there was no transvalvular or paravalvular leak after deployment of one prosthesis. The ACURATE TA system (Symetis, Ecublens, Switzerland) features a self-fixing mechanism made of two crowns, suitable for larger annuli, but requires transapical access (99). Other promising systems include Direct Flow Valve System (Direct Flow Medical, Santa Rosa, California), J-Valve (Jie Cheng Medical Technologies, Suzhou, China), Engager valve (Medtronic Inc., Minneapolis, MN, United States) and the Lotus valve (Boston Scientific, Natick, Massachusetts) (99).

While awaiting the approval of these devices, the CoreValve (Medtronic Inc., Minneapolis, MN, United States) and Sapien (Edwards Lifesciences Inc., Irvine, California) systems have shown good results (46). However, given the paucity of data on TAVR in patients supported with LVADs, there is a lack of consensus on which of the two systems is better suited for this off-label use. The CoreValve has the advantage of aortic fixation, while the SAPIEN, with its balloon-expandable deployment, applies enhanced radial force on the ring and is associated with lower paravalvular leakage. Some authors deliberately oversize the valve to further increase radial pressure and improve anchoring. In the first reported case of TAVR in a patient with LVAD, D'Ancona et al. used a 29 mm SAPIEN valve within a 21 mm annulus that would normally require a 23 mm valve (13). Pal et al. successfully deployed a 31 mm CoreValve -oversized by 17%- followed by a 29 mm valve-in-valve SAPIEN-3 in two

patients with CF-LVAD (47). The CoreValve fixation within the aorta served as a scaffold to anchor the SAPIEN-3 in the absence of annular calcifications, while the SAPIEN-3 eliminated paravalvular leakage once overinflated. However, due to the costs associated with the use of two prostheses, this technique cannot be universally used. In our local practice, we favor the CoreValve over the Sapien valve. The ability to recapture and reposition the CoreValve at up to 80% deployment is very advantageous in this clinical context. After positioning the valve, it is deployed right before the point of no recapture and the pump speed is increased slowly. The operator then ensures that the valve remains stable before completing deployment, reducing the risk of valve embolization.

In patients under LVAD support with a history of aortic valve replacement, the prosthesis itself can be used for anchoring. Yap et al. used a 26 mm SAPIEN-3 in a structurally deteriorated 29 mm Toronto Freestyle (65). The fibrotic response at the sewing ring provided sufficient resistance to allow proper anchoring and the TAVR was placed in a subannular position. Chung et al. proposed a novel solution by placing an internal aortic annuloplasty ring in a patient with mild aortic regurgitation at the time of LVAD implantation, which could serve as an anchor for subsequent TAVR, in the event of progressive aortic regurgitation (48) but this strategy needs to be further studied.

Regarding access planning for TAVR in patients with aortic regurgitation, the transapical approach is most commonly used (42%–55% of cases), closely followed by transfemoral approach (39%–41% of cases) (95, 97). Any TAVR procedure relies on the measurements of aortic annulus, aortic root, and iliofemoral anatomy for access planning and valve selection. Patients under LVAD with end-stage ischemic heart disease may have significant peripheral vascular disease, precluding transfemoral access. Transapical access has been reported, but care should be taken not to compromise the LVAD inflow cannula (13). A preoperative chest computed tomography helps identify a safe route for access through the apex (13). TAVR deployment directly *via* the LVAD inflow cannula has also been done (66). This approach was performed in the context of concomitant LVAD pump exchange, which already required initiation of cardiopulmonary bypass and LVAD pump removal (66). Because of the short length of the LVAD inflow graft, a Dacron graft was anastomosed end-to-end to the LVAD inflow graft in order to provide additional working length for the placement of the large bore sheath of the TAVR (66).

Transcatheter valves are also vulnerable to LVAD-induced structural deterioration. Derryberry et al. described complete fusion of an Evolut R leaflets within 5 months of LVAD support (49). The patient was a bridge-to-transplant and was therefore not affected by this premature deterioration. Parry et al. reported complete fusion of a CoreValve 33 days after implantation in a 64-year-old patient with a "bridge-to-recovery" scenario (50). This complication was discovered in the operating room while attempting LVAD explant. Less than a week later, the patient died from an extensive stroke. Autopsy revealed the presence of organizing thrombus covering the ventricular surface of the CoreValve with overlying recent thrombus, despite appropriate anticoagulation therapy (50). This unfortunate case demonstrates that the unique physiology of an LVAD might lead to worrying complication and early TAVR deterioration. Efforts to maintain regular valve opening by running the LVAD at lower speed than usual might prevent bioprosthetic aortic valve thrombosis, although cusps may be difficult to visualize due to the metal frame of the TAVR. If that is the case, a high pulsatility index may indicate probable opening of the aortic valve. Transesophageal echocardiography or multiphase computed tomography can be performed in case of high suspicion for thrombosis and inconclusive transthoracic echocardiogram, such as in the event of increasing valvular gradients or visual thickening of the valve (51). Noteworthy, the recent recommendations for the management of antithrombotic therapy in patients undergoing TAVR do not mention LVAD patients (103). After diagnosing TAVR thrombosis in a LVAD patient, Rao et al. started unfractionated heparin and increased LVAD speed to minimize risk of aortic valve opening, and therefore attempt to mitigate the risk of embolization (51). However, intravenous anticoagulation was complicated by gastrointestinal bleeding requiring multiple transfusion and the high LVAD speed could not be maintained due to persistent suction events (51). Luckily, the patient remained stable while awaiting transplantation (51). This case illustrates the therapeutic dilemma in patients with LVAD who develop TAVR thrombosis.

4.1.2. Percutaneous transcatheter aortic valve closure

Percutaneous transcatheter aortic valve closure with a septal occluder such as the Amplatzer Multi-Fenestrated Septal Occluder device (St Jude Medical, Saint Paul, MN), is essentially the same as a surgical left ventricular outflow closure in which the aortic valve is oversewn. However, similarly to TAVR, this procedure has only been reported in a few small case series, with a lack of long-term data (76–86). Potential complications include device migration, thrombus formation, hemolysis from peri-device regurgitant flow, erosion in aorto-mitral curtain and coronary ostia obstruction. In order to reduce the risks of residual shunting, hemolysis, and device embolization, some authors have been using an oversizing strategy (87). Acceptable results have also been reported with smaller device/annulus ratios (88).

Despite the lack of sufficient data to perform a comparative analysis between TAVR and transcatheter aortic valve closure, the latter technique was found to have a higher mortality rate compared to TAVR (46, 88). In addition, closing the aortic valve results in complete LVAD dependency, which could be fatal in case of sudden power loss, pump thrombosis or other mechanical failure. For all these reasons, the use of percutaneous transcatheter aortic valve closure in LVAD patients has been almost exclusively abandoned in favor of TAVR.

4.2. Mitral valve

In 2020, the American College of Cardiology/American Heart Association (ACC/AHA) Valvular Heart Disease Guidelines

incorporated transcatheter edge-to-edge repair using the MitraClip (Abbott Vascular, Santa Clara, California) as a Class IIa recommendation for intervention for secondary mitral regurgitation in patients with persistent severe symptoms despite treatment with guideline-directed medical therapy (104). Therefore, it is expected that an increasing number of CF-LVAD candidates will have a MitraClip in place at the time of CF-LVAD implantation. A number of case reports and small case series have documented the feasibility and safety of LVAD implantation in patients with prior MitraClip (105–108). Transcatheter mitral valve repair did not impact hemodynamic nor mortality in patients with LVAD (105–108). On the other hand, in patients with end-stage heart failure and secondary mitral regurgitation, it remains unclear whether MitraClip has any value as a bridge to transplant or bridge to LVAD and whether it would be more beneficial to perform a mitral valvuloplasty at the time of LVAD implantation (109–111).

A few cases of MitraClip procedures performed following CF-LVAD implantation have been reported (90–92). The largest series was comprised of 30 patients (92). In this registry study, Tanveer et al. compared the short-term outcomes of patients with LVAD who underwent MitraClip ($n = 30$) vs. surgical mitral repair ($n = 199$) between 2016 and 2018 in the United States (92). Patients who underwent MitraClip implantation were older on average (61.2 vs. 56.4 years, $p = 0.223$) and had a higher prevalence of renal failure, peripheral vascular disease, atrial fibrillation, smoking history and previous permanent pacemaker/implantable cardioverter defibrillator. In-hospital mortality was higher in the MitraClip group (Cell count < 11 out of 30 patients for MitraClip vs. 6.9% for surgical repair). Nonfatal complications including acute kidney injury, bleeding requiring transfusion and vascular complications were lower in the MitraClip group. Patients who underwent MitraClip intervention also had, on average, a shorter hospital stay and lower hospital costs. Given the small sample size and retrospective nature of the study, these findings remain hypothesis-generating, but they certainly show a promising

potential for MitraClip in patient with LVAD.

Some authors questioned whether the presence of >2 MitraClips -an uncommon event- could negatively affect LVAD therapy by: (i) affecting right ventricular function due to the presence of an inter-atrial shunt through the residual atrial septal defect and (ii) decreasing left ventricular filling and LVAD flow as a result of a reduced valve area combined with the increased flow rates after LVAD initiation (112, 113). Raghunathan et al. reported a case of bidirectional -predominantly right-to-left- shunting immediately after the delivery of two MitraClip XTR in an LVAD patient with right ventricular dysfunction (91). Percutaneous closure of the transseptal puncture with an Amplatzer occluder device led to symptomatic improvement of the patient's heart failure symptoms (91). Of note, less than 30% of patients have a residual iatrogenic atrial septal defect 1 year from MitraClip treatment (114). This proportion is however unknown in the presence of an LVAD and abnormal right-sided pressures. Meduri et al. reported a successful mitral valve replacement in a patient with LVAD and severely stenotic bioprosthetic mitral valve. A 29 mm Sapien XT was deployed in a stenotic 27 mm Carpienter-Edwards Perimount mitral prosthesis (Edward Lifesciences, Irving, CA) *via* transseptal access (52). The patient also developed symptoms from a significant right-to-left shunt secondary to iatrogenic atrial septal defect and required percutaneous closure (52). While these adverse events may seem anecdotal, they should be investigated further.

From a procedural standpoint, care should be taken not to damage the LVAD inflow cannula when crossing the mitral valve with the mitral valve devices. In addition, the LVAD can create a prominent "waterfall" color Doppler artifact, interfering with the evaluation of transmitral flows pre- and post-procedure (115).

4.3. Tricuspid valve

Currently used tricuspid valve catheter devices can be divided into four categories, according to their mode of action: annuloplasty devices, edge-to-edge repair devices, valve replacement devices and caval valve implantation (116). The type of device should be tailored to the underlying mechanism of tricuspid valve disease and should take into account the presence of pacemaker leads. The indication for LVAD implantation should also be taken into account when choosing the optimal transcatheter tricuspid valve procedure. For example, an edge-to-edge repair might be favored over a replacement approach as an acceptable shorter-term solution in bridge-to-transplant or bridge-to-recovery therapies while avoiding the extra costs of transcatheter bioprosthesis. In a bridge-to-transplant strategy, the TriCinch system (4Tech Cardio, Galway, Ireland) or caval valve implantation would not represent an optimal solution due to the risk of stent migration in the inferior vena cava during the heart transplantation. Transcatheter tricuspid technologies are still under preclinical or initial clinical evaluation but early safety and feasibility trials conducted to date have shown promising results (117). In addition, tricuspid valve regurgitation is typically addressed at the time of LVAD implantation. These factors explain the lack of data on percutaneous tricuspid valve interventions in patients with CF-LVAD. Furthermore, multivariate analysis of the Transcatheter Tricuspid Valve Therapies (TriValve) registry data revealed the existence of multiple factors associated with lower procedural success, independent of the device used: increased coaptation depth, larger annular diameter and increased pulmonary artery pressure (118). Although patients from this registry were not under LVAD support, these results suggest that transcatheter tricuspid interventions should be performed earlier, preceding the development of severe right ventricular remodeling, in order to increase the chance of procedural success. Therefore, in patients with CF-LVAD who frequently have some degree of right ventricular dysfunction, the optimal timing to address the tricuspid regurgitation might very well be at the time of LVAD implantation.

To our knowledge, only one case report to this date has described a transcatheter tricuspid valve intervention on a patient under LVAD support (93). The patient was a 59-year-old female who previously underwent a HeartMate III implantation and

tricuspid annuloplasty with a 32 mm rigid ring as a bridge to transplantation. After two months, she developed recurrent severe tricuspid regurgitation with right ventricular decompensation needing continuous inotropic support. The cause of the tricuspid regurgitation was identified as being a partial detachment of the prosthetic ring. She was successfully treated with a transcatheter edge-to-edge repair using the MitraClip XTR system. A first device was used to clip the antero-septal commissure, and, because of a residual regurgitant jet, a second clip was placed between the septal and the posterior leaflet. This is reminiscent of the "triple orifice technique" or the "clover technique" originally described in conventional tricuspid repair surgery (119, 120). Using these two MitraClips, the tricuspid regurgitation was reduced by 50%, leading to a postoperative effective regurgitant orifice area of 0.7 cm^2 (93). The patient's demands for inotropic support stabilized and she was successfully transplanted 30 days after the clipping procedure (93).

The off-label use of the MitraClip has been the first-choice approach for high-risk patients with secondary tricuspid regurgitation, likely because of wide availability and operator familiarity with the device (11). However, steering the MitraClip through the right atrium remains challenging given the anatomic obstacles inherent to right-sided interventions and its use in tricuspid procedures will certainly become obsolete with the commercial availability of the dedicated TriClip system (Abbott Vascular, Santa Clara, California) (121). The TriClip has a similar configuration as the MitraClip, including a clip delivery system and a steerable guide. It's safety and efficacy were recently shown in the TRILUMINATE trial (121). Moreover, the next-generation TriClip G4 system (NT, XT, NTW, and XTW) has wider clip arms and allows independent leaflet capture, which should facilitate leaflet grasping even in the presence of broader coaptation gap. The TriClip and TriClip G4 are currently being tested in the TRILUMINATE Pivotal Trial (NCT03904147). The rate of single-leaflet device attachment will certainly deserve attention as large coaptation gaps are commonly found in patients with functional TR and advanced ventricular remodeling, often requiring multiple grasping attempts and clips.

Regarding transcatheter tricuspid valve replacement, many devices are actively being studied in early feasibility trials (116). Factors that could hinder prosthetic valve positioning in patients with CF-LVAD include the lack of annular calcifications, a large annular size and the presence of pre-existing cardiac implantable electronic devices (11). Improper anchoring may lead to device malfunction, paravalvular leak, valve embolism, or valve thrombosis. On the other hand, too much radial strain could compromise the atrioventricular node or bundle of His and lead to conduction abnormalities. Indeed, conduction abnormalities seem to occur more frequently with transcatheter tricuspid valve replacement compared to surgical or transcatheter repair (122). In addition, since right-sided valves are exposed to low pressures and low velocity flows, the risk of valvular thrombus formation is believed to be higher than that of left-sided valves (123).

The unique procedural challenges related to the characteristics of the tricuspid valve (leaflet fragility, large non calcific annulus, angulation in relation to the vena cava, presence of chief surrounding structures) make multimodality imaging key not only for preprocedural planning, but also for intraprocedural monitoring. In patients with LVAD, imaging guidance might be limited by the presence of shadowing or artefacts. Transesophageal echocardiography imaging might also be limited by the anterior location of the tricuspid valve, making the use of intracardiac echocardiography an appealing alternative (37).

5. How do THV interventions compare to surgery in CF-LVAD patients?

Patients under LVAD support have a high-risk profile and may be deemed unfit to sustain conventional redo open-heart surgery, which involves general anesthesia, endotracheal intubation, cardiopulmonary bypass and aortic cross clamping. In this context, percutaneous approaches are, understandably, an attractive "off-label" option. However, the techniques are still in their infancy and there is still a lot of uncertainty regarding long-term outcomes.

Few observational studies compared the short-term and midterm outcomes of secondary surgical aortic valve replacement (SAVR) vs. TAVR in patients with CF-LVAD. Zaidi et al. conducted a retrospective analysis of all relevant patient information extracted from the Nationwide Readmission Database in the United States between 2016 and 2018 (75). A total of 148 patients were included, 87 in the TAVR group and 61 in the SAVR group. The inpatient mortality in the SAVR group was numerically higher compared to the TAVR group, but did not reach statistical significance (<16% vs. <8%, adjusted odds ratio (aOR) 2.45, confidence interval (CI) 0.41–14.7, $p = 0.32$). Mean length of hospital stay was significantly higher in the SAVR group (40 vs. 13.8 days, aOR 19.9, CI 9.65–30.1, $p < 0.001$). Thirty-day all-cause readmission rate, cardiogenic shock, bleeding and vascular complications were also higher in the SAVR group compared to the TAVR group. Rali et al. reviewed patients from the National Inpatient Sample database from 2015 to 2018 (124). During the study period, a total of 105 TAVR implantations and 50 SAVR procedures were performed in LVAD patients. Patients undergoing TAVR were older but had a lower comorbidity index compared to the SAVR group. They were also more likely to undergo the procedure electively. The difference in baseline characteristics is counter-intuitive since one would expect TAVR to be favored in sicker patients. This might reveal a certain hesitation from surgeons and interventionalists to use an emerging off-label technique in higher risk situations. The composite outcome of in-hospital mortality, stroke, transient ischaemic attack, myocardial infarction, pacemaker implantation, need for open aortic valve surgery, vascular complications and cardiac tamponade was higher among patients undergoing SAVR (30%) compared with those undergoing TAVR (14%), including after multivariable adjusted analyses (aOR 0.24; 95% CI [0.06–0.97]; $p = 0.045$). The prevalence of postprocedural moderate-to-severe paravalvular regurgitation (TAVR: 14%; SAVR: 0%), acute kidney injury (TAVR: 33%; SAVR: 60%) and bleeding requiring transfusions (TAVR: 0%; SAVR: 20%) did not significantly differ

between the two groups after adjustments in the multivariable model.

The long-term outcomes of TAVR in LVAD patients are very limited. A small single-center study reported a one-year survival post TAVR of 73% (125). All survivors experienced an improvement in their left ventricle end-diastolic diameter (mean reduction of 6.8 ± 4.4 mm), NYHA functional class and the Kansas City Cardiomyopathy Questionnaire score at 1 year. For almost two-thirds of these patients, the improvement in their Kansas City Cardiomyopathy Questionnaire score was >20 points. The long-term outcomes of secondary SAVR in LVAD patients have also been poorly investigated. In a single-center study that included 6 LVAD patients undergoing secondary SAVR between 2009 and 2020, survival was 67% after a median follow-up of 29 (6–64) months (126). Causes of death were pneumogenic sepsis 1 month after surgery and immune reaction following heart transplant. It is worth nothing that survival rates and long-term outcomes are difficult to compare in LVAD patients since they are strongly influenced by the heart failure status and management, the etiology, the support strategy (bridge to transplant, destination strategy, etc.) and occurrence of heart transplant. Gathering long-term outcome data on patients with LVAD for destination therapy is important not only because they constitute a rising proportion of LVAD recipients, but also because it would inform as to whether TAVR and/or secondary SAVR improve the prognosis of the underlying cardiomyopathy. Until then, the evidence so far, albeit scarce, suggests that both SAVR and TAVR are viable treatment options for aortic regurgitation in patients with CF-LVAD. With TAVR, the risk of device migration and significant postimplant paravalvular leak should be kept in mind, owing to the intrinsic anatomical and technical challenges presented previously. With SAVR, postoperative morbidity such as stroke, significant bleeding or right heart failure remain a concern. There are currently no guidelines that recommend one approach over the other. Some authors have suggested choosing TAVR over secondary SAVR in destination therapy patients or bridge-to-transplant patients who are faced with long waiting times (125, 126). TAVR might also be used in certain emergent/rescue interventions: Wilson et al. reported a successful emergent TAVR in a patient with a fused aortic valve who suffered a cardiac arrest as a result of sudden LVAD pump failure (53). On the contrary, SAVR might be a better option in patients for whom heart transplantation is closely available, especially in the presence of aortic root dilation and absence of valve calcification,

Finally, no study to date has compared mitral or tricuspid valve replacement with THV interventions and long-term outcomes are largely unknown. However, these devices are not exposed to the same hemodynamic environment as the aortic valve, and the risks of sudden, catastrophic intraprocedural complications are less of a concern compared to TAVR.

6. What's next?

Initial experience in the field of THV interventions is largely limited to the aortic valve and has shown that most procedures are well tolerated, have high procedural success and low in-hospital and early mortality. However, anatomical, mechanical and functional features of VHD in patient under CF-LVAD support introduce unique challenges which are still managed on a case-by-case basis due to the lack of evidence-based guidelines. These challenges are both clinical (early recognition, decision to intervene, optimal timing, balancing the risks and benefits, etc.) and technical in nature. In particular, the continuous flow, annular dilation, and absent annular calcifications encountered in CF-LVAD patients can precipitate device migration in TAVR. However, delays in management may lead to refractory heart failure. Data from case reports have suggested that individual patient-tailored considerations for device selection and choice of access are of paramount importance for the success of the procedure. This certainly requires a multidisciplinary heart team approach, involving specialists from every field of the cardiac sciences (imaging, heart failure and interventional cardiologists, intensivist, cardiac anesthesiologist, cardiac surgeon, LVAD coordinator, etc.). As more data will become available, guidelines will certainly evolve to address the management of VHD not only at the time of LVAD implantation but also after LVAD initiation. They will probably also incorporate guidance about transcatheter therapies as part of that management.

Optimal THV device selection and sizing algorithms are not well described at the present time and will be an important topic for further study. Procedural techniques, including the use of rapid pacing and CF-LVAD pump speed modulation to optimize THV stability during deployment will also require further refinement. Therefore, there is a crucial need to gather more data from multicenter registries or prospective trials.

Advances in THV technology will continue to address life threatening complications such as device migration which is a unique challenge in CF-LVAD patients due to the combined effects of hydrodynamic forces exerted by the LVAD, the absence of annular calcifications and the presence of ventricular or aortic root dilation. On the other hand, the accumulation of patient-specific data will be an opportunity to develop patient-specific simulation-based planning to help predict outcomes after THV interventions in this high-risk patient population. Promising computational models have already been applied to various branches of percutaneous cardiac procedures (127–129).

7. Conclusion

Patients under CF-LVAD who require intervention for VHD are considered poor reoperative candidates. The rise of multiple transcatheter technologies therefore represents an appealing therapeutic avenue for these patients. A growing body of evidence has shown that THV procedures are feasible and safe in patients with CF-LVAD when adequate perioperative imaging and a tailored interventional strategy are adopted. However, the lack of data on mid- to long-term outcomes and the occurrence of distinct complications such as device migration, valve thrombosis or hemolysis remain of concern with these approaches (**Table 1**). Future studies assessing larger patient

cohorts are required to sufficiently evaluate the efficacy of these techniques.

Author contributions

WBA, OD, AD, PN, AA and TM designed the project and its main conceptual ideas. OD performed the research strategy, data collection, data analysis and interpretation, drafted the manuscript, and designed the table, with input from all authors. MSC performed additional research strategy and data collection to complement the findings. All authors provided critical revisions to the article and approved the final version for publication. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Considerations of valvular heart disease in children with ventricular assist devices

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Ventricular assist devices have become a valuable tool in the treatment of heart failure in children. The use of ventricular assist devices has decreased mortality in children with end-stage heart failure awaiting transplant. It is not uncommon for children with end-stage heart failure associated with cardiomyopathy or congenital heart disease to have significant systemic semilunar and atrioventricular valve regurgitation, which can impact the efficiency and efficacy of hemodynamic support provided by a ventricular assist device. Therefore, implanting clinicians should carefully assess for valve abnormalities that may need repair and impact device selection and cannulation strategy to effectively support this diverse population. The purpose of this review is to provide an overview of this important and relevant topic and to discuss strategies for managing these patients.

KEYWORDS

pediatric, heart failure, ventricular assist device, valvular heart disease, valve surgery (or cardiac surgery)

1. Introduction

The treatment of heart failure in children and adults has been revolutionized by the advent of ventricular assist devices (VADs) which can reliably restore normal levels of cardiac output. VADs that are used for long-term support in children, which in the United States currently include the EXCOR Pediatric device (Berlin Heart GmbH, Berlin, Germany) and the HeartMate 3 device (Abbott Cardiovascular, Plymouth, MN, USA), can serve as a bridge to heart transplant or, in rare cases, as a bridge to recovery in children with end-stage heart failure. The majority of children undergoing heart transplantation either have cardiomyopathy or end-stage congenital heart disease (CHD) that results in severe systolic and/or diastolic ventricular dysfunction and over the past two decades, the presence of VAD support in children eventually undergoing heart transplantation has doubled (1). Although the prevalence of valvular heart disease in children undergoing VAD implantation and support has not been specifically defined, it is not uncommon for patients with cardiomyopathy or CHD to also have concomitant valvular heart disease (2, 3). In some patients, valvular heart disease may be the result of a poorly functioning ventricle and in other instances, a chronically malfunctioning heart valve may be the cause of ventricular dysfunction (4, 5). Regardless of the etiology, the presence of valvular heart disease can impact the efficacy of VAD support and thus may require surgical intervention at the time of or after VAD implantation. In this review, we will discuss the extent, impact, diagnosis, and treatment of valvular heart disease in

children with end-stage heart failure who are being considered for VAD therapy. Much of the discussion presented here is based on evidence from studies in adult VAD patients, however, the pathophysiological considerations of valvular heart disease are similar and thus relevant to pediatric patients.

2. Pathophysiology

The affected heart valve, type of valve lesion (i.e., stenosis or regurgitation), type of VAD, and VAD cannulation sites influence the impact of valvular heart disease on the efficiency of VAD support. In the following discussion of each abovementioned factors, we will use the scenario of a VAD supporting the systemic circulation in a biventricular heart. This discussion can be extended to the scenario of a VAD-supported pulmonary circulation as well as a VAD-supported single ventricle heart.

In general, all VADs have an inflow and outflow and there should be at least one competent valve somewhere between the VAD inflow position and the aorta (VAD outflow position). In the most common situation of the VAD inflow cannula placed in the left ventricle and the VAD outflow connected to the aorta, aortic valve insufficiency (AI) would lead to the recirculation of VAD flow and thus loss of systemic cardiac output (6, 7) (**Figure 1**). The extra regurgitant volume may also lead to increased mitral regurgitation (MR), less emptying and decompression of the left atrium and pulmonary venous bed, increased pulmonary artery pressure and right ventricle workload, right ventricular failure, and congestive heart failure symptoms. Aortic insufficiency in left ventricle assist device (LVAD) patients can lead to an increase in left ventricle end-diastolic pressures, which has been associated with poorer clinical outcomes (8). Aortic valve insufficiency in adult VAD patients develops over time and has been associated with poor clinical outcomes including increased mortality (9, 10). Also, mild AI that is present at the time of VAD implantation in adult patients can worsen with time (10–13). The tendency of the aortic valve to leak or become more regurgitant after VAD implantation (especially continuous flow VADs) is likely secondary to ultrastructural and degenerative changes in the leaflets (14, 15). The expression of genes encoding the inflammatory cytokines interferon gamma, interleukin 1 beta, and tumor necrosis alpha have been found to be increased in the aortic valve leaflet tissue of VAD patients (16). Furthermore, the angle at which the VAD outflow graft is anastomosed to the aorta has been found to influence the development of AI in adult VAD patients (17) and the same investigators have confirmed this finding in a large animal model (18). The increased transvalvular gradient present in both systole and diastole in the VAD-supported systemic circulation has also been postulated to contribute to aortic valve leaflet degeneration and insufficiency (19). A computational fluid dynamics study revealed that adult VAD patients who developed *de novo* AI after VAD implantation have higher localized wall shear stress on the aortic valve leaflet tips as compared to VAD patients who did not develop AI (20).

Since the AI is often continuous with continuous-flow VADs, even "mild to moderate" continuous AI can be deleterious (21). Because AI has been determined to be a time-dependent phenomenon in adult patients, we surmise that in pediatric patients the development of new AI may be less important since the duration of VAD support tends to be shorter in children (22). However, with longer-term therapy and the increasing number of destination devices in recent years (23), we can expect to see more AI in these chronically-supported children.

In the scenario of the VAD inflow cannula placed in the left atrium, mitral valve insufficiency (MR) may be well tolerated *as long as* the aortic valve is competent. The same cannulation strategy can also be successful in the setting of heart failure with preserved systolic function, a competent mitral valve, and a

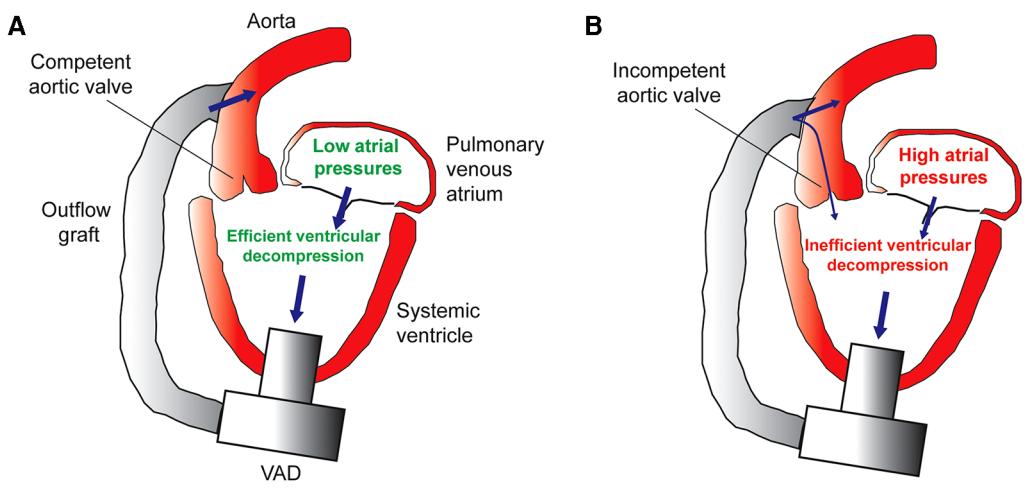

FIGURE 1
(A) Efficient decompression of the systemic ventricle and pulmonary venous atrium in the setting of a competent aortic valve. (B) Inefficient VAD support caused by aortic insufficiency leads to incomplete ventricle decompression, high atrial pressures, pulmonary venous congestion, and heart failure symptoms.

mildly insufficient aortic valve. In this scenario, VAD recirculation would be prevented by the competent mitral valve and the LV with normal systolic function should be able to eject the regurgitant volume from the mildly insufficient aortic valve. Certainly, this arrangement would not be tolerated if the left ventricular systolic function was decreased as left ventricular dilation would result in subsequent MR and impact right ventricle function.

Mitral valve stenosis can limit the efficiency of VAD output if the inflow cannula is positioned in the left ventricle and significant gradients (mean > 10 mmHg) have been recommended as a reason to intervene on the mitral valve in adult patients (7). If the VAD inflow is positioned in the left atrium, then mitral stenosis should have no effect on VAD support. Aortic stenosis without AI is usually well tolerated and should not affect VAD support efficacy.

The type of VAD can also influence the clinical impact of mitral valve regurgitation. The EXCOR Pediatric VAD is a paracorporeal, pulsatile device and is used in infants and small children (24, 25). The HeartMate 3 VAD is an implantable, continuous flow device that can be utilized in larger children and adolescents with heart failure (26). Mitral insufficiency may be tolerated with a continuous flow VAD with the inflow positioned in the left ventricle as long as the ventricle is effectively offloaded by the VAD throughout all stages of the cardiac cycle, and thus the ventricular dilatation and regurgitant volume into the left atrium may be decreased. In a small pediatric patient with mitral regurgitation and the same cannulation strategy, a pulsatile flow VAD may not be as effective in decompressing the ventricle during diastole and thus mitral regurgitation may be more important. The inefficient unloading of the left ventricle during systole may even be more significant if a large size Berlin pump is utilized with a slower pump rate. Therefore, in small children with significant MR who are being considered for an Excor Pediatric VAD with the inflow positioned in the left ventricle, intervention for the mitral valve should be considered.

3. Epidemiology

There is a paucity of data on valve dysfunction and concomitant valve procedures performed at the time of VAD implant in pediatrics. One series of 45 patients with Fontan circulation supported with VAD reported severe atrioventricular valve regurgitation in 43%, mild aortic insufficiency in 28%, and moderate aortic insufficiency in 8% of patients (27). The precise prevalence of valvular heart disease in children undergoing VAD implantation is not known.

4. Diagnosis of valvular heart disease in children undergoing VAD implantation

Diagnosis of valvular heart disease in pediatric patients considered for VAD support or after the initiation of VAD support is usually diagnosed by transthoracic echocardiography (28). Transesophageal echocardiography in the operating room can further define the presence, extent, and mechanism of valvular disease prior to VAD implantation (28). Importantly, a transesophageal echocardiogram is utilized to monitor the presence of existing or the development of new AI immediately after VAD implantation. Intraoperatively, an epicardial echocardiogram (29, 30) may provide alternative views of the semilunar or atrioventricular valves if the transthoracic or transesophageal approaches do not provide a complete assessment of the valves. Cardiac magnetic resonance, usually obtained to assess ventricular function, fibrosis, and cardiac anatomy, can be particularly useful for quantifying the degree of valvular regurgitation or stenosis prior to VAD implantation (31, 32).

In patients who develop *de novo* or progressive AI after VAD implantation because of the increased transvalvular gradient caused by enhanced pressurization of the aorta (33), the combination of echocardiography and cardiac catheterization during a ramp trial may be informative as to the degree of ventricular congestion and low systemic cardiac output caused by the AI (8, 34). Furthermore, it has been proposed that aortic valve regurgitant volume can be calculated by multiplying the proximal isovelocity surface area by the aortic regurgitant time (both echocardiography-determined parameters), although this approach needs further validation (35).

5. Management of valvular heart disease at the time of VAD implantation

In general, surgical intervention for regurgitant heart valves are either repair or replacement. A multitude of techniques have been developed for mitral valve repair and several options exist for mitral valve replacement in older children (36–38). Techniques for aortic valve repair in children are not as developed, especially in smaller patients. Concomitant surgical valve repair or replacement in the setting of VAD implantation setting should be expedient and lead to durable resolution of the valve lesion. With these goals in mind, in the following section, we provide discussion of relevant surgical interventions for valvular heart disease in children undergoing VAD implantation.

5.1. Mitral valve disease

There is a dearth of literature describing mitral valve procedures in pediatric patients undergoing VAD implantation. The adult-focused literature, on the other hand, has demonstrated that significant, functional MR is common in patients undergoing VAD implantation (7, 39, 40), and that MR usually improves with continuous flow VAD support (41). Interestingly, though, there are recent, adult-focused data that suggest that there are a subset of patients undergoing continuous flow VAD implantation, with severe MR, who benefit from concomitant mitral valve repair (42–44).

On the other hand, in children being considered for pulsatile flow VAD implantation, those with moderate or greater

regurgitation should undergo mitral valve repair. In children with hypertrophic or restrictive cardiomyopathy and with a continuous flow device, mitral valve replacement may not be appropriate for the smaller hearts, for whom an atrial location for the inflow cannula or complete excision of the obstructing systemic atrioventricular valve is indicated. While complex and elegant repair techniques have been developed for regurgitant mitral valves (38), these often are not indicated during VAD implantation because of the additional cardiopulmonary bypass and cross-clamp times needed to execute them. The most common mitral valve procedures at the time of VAD implantation include mitral valve repair: edge-to-edge approximation (45) or partial or complete annuloplasties (46). Finally, in the patient in need of concomitant mitral surgery—in whom repair is not felt to be feasible—mitral replacement with a bioprosthesis should be considered.

The edge-to-edge technique of mitral valve repair was introduced in the late 1990s by Alfieri and colleagues (47). The original technique was first established for complex repair of degenerative MR in adults, however, its use has expanded over the past twenty years to other modalities of MR (Barlow's, functional, etc.). In patients undergoing VAD implantation, edge-to-edge repair is performed transapically, while on cardiopulmonary bypass, but without arresting the heart (44, 45). After the left ventricle apex has been cored and excised, blood in the left ventricle and left atrium are suctioned with a cardiotomy suction to aid in visualization of the mitral valve. The anterior and posterior leaflets of the mitral valve are fixed to one another at the A2/P2 position with a mattress-fashioned, Polypropylene suture, which is tied down over a felt pledget. Importantly, this suture is placed and tied down on the *ventricular* side of the mitral valve apparatus. The remainder of the VAD procedure is undertaken. The edge-to-edge technique adds little cardiopulmonary bypass time and does not require a separate access incision to visualize the mitral valve. It is, however, a view of the mitral valve that surgeons are not particularly familiar with, which leads many surgeons to be uncomfortable about employing this technique.

Annuloplasty repair techniques for mitral valve repair are popular as adjuncts to complex mitral valve repair in the setting of degenerative MR in adults. In the setting of VAD implantation, annuloplasty is typically performed *via* a trans-septal incision, while on cardiopulmonary bypass, and without arresting the heart (46). Unlike in repair of degenerative MR, functional MR in the adult undergoing VAD implantation is typically repaired with a complete ring. Pediatric patients may undergo limited or partial annuloplasty, as ring sizes are often too large for this patient population. In concomitant mitral valve repair with an annuloplasty, the left ventricle apex is cored to fully decompress the ventricle and prevent air embolism, the atrial septum is incised in a longitudinal fashion, and a self-retaining retractor is placed to expose the mitral valve. Horizontal mattress sutures are placed, circumferentially, in the mitral valve annulus. An annuloplasty ring is sized and selected, the sutures are placed through the ring, the ring is seated, and the sutures are tied down. In a pediatric patient that is not undergoing ring placement, a limited or partial annuloplasty is performed. The atrial septum is closed and the remainder of the VAD procedure is undertaken. Notably, the annuloplasty technique of repair does add a significant amount of time to the VAD procedure, however it provides access to the mitral valve in the surgeon's conventional view.

5.2. Aortic valve disease

Multiple single center studies have demonstrated that AI post LVAD implantation in adult patients can lead to poor clinical outcomes and ongoing heart failure (10, 48, 49). However, a recent analysis of the ISHLT Mechanically Assisted Circulatory Support (IMACS) Registry spanning the years of 2013–2017 demonstrated several notable findings (50). First, survival was not significantly different in VAD patients with moderate to severe AI who underwent aortic valve intervention (replacement or repair) as compared to patients who did not receive any intervention (50). Second, when considering all patients who underwent aortic valve procedures (i.e., those with all grades of AI), survival was observed to be inferior to patients who did not receive aortic intervention (50), suggesting that those with no or only mild AI had especially worse survival who underwent aortic valve surgery than those who did not undergo aortic valve surgery. These results are difficult to interpret, given that the recurrence of AI after aortic valve surgery was not noted and is an important limitation of this registry study. Furthermore, the degree of variability in the assessment of the severity of AI and heterogeneous criteria for the indications used by caregivers to proceed with aortic valve surgery are other important confounding factors not accounted for in this study. Nonetheless, we believe that ongoing and significant heart failure symptoms in the setting of systemic VAD support and at least moderate AI are indications for aortic valve intervention. The appearance and persistence of new, moderate AI just after systemic VAD implantation in children despite decreasing pump speed to the lowest, tolerable speed also warrants careful consideration of immediate aortic valve intervention in the operating room, as described in the following paragraphs.

The insufficient aortic valve in the pediatric patient undergoing VAD implantation can be repaired with a central coaptation stitch (51). In this method, which was originally described in adults, left ventricular ejection will still allow for opening of the aortic valve, though the effective orifice is reduced. During VAD implantation, the heart is arrested, and the ascending aorta is incised on its rightward surface—in the location of the eventual outflow graft anastomosis site. Via the aortotomy, the aortic valve is inspected to determine the mechanism of AI. If no other repair is deemed appropriate, a pledget-supported polypropylene suture is used to approximate the three nodules of Arantius (51). The outflow graft is then sewn to the aortotomy site in an end-to-side fashion, and the remainder of the VAD procedure is completed. The central coaptation stitch is feasible and has been utilized in pediatric patients. Aortic valve repair by placement of a subannular annuloplasty ring along with leaflet free-edge

plication has been described in an adult patient undergoing a temporary VAD placement (52). Such a technique can be employed in larger children with sufficient aortic valve annulus size, and can likely be implanted in the same amount of time as a prosthetic valve. Transcatheter or open rapid-deployed aortic valve prosthesis are also other options that that have been described in adults and can be conceivably used in older, adult-sized children (53).

Another strategy to eliminate aortic valve insufficiency in pediatric VAD patients is complete valve closure. In this technique, if the leaflets are durable enough to hold sutures, then suturing them together can be more expedient than replacement. In infants with especially thin aortic leaflets, valve closure can be accomplished by excising the leaflets and suturing a patch to the annulus to accomplish a partition between the left ventricle aorta (54). An important consideration in aortic valve closure is that all of the cardiac output is delivered by the VAD and thus any significant device malfunction or inflow/outflow obstruction would have immediately dire consequences. Nonetheless, the closure technique is especially useful in the infant and small child where no traditional prosthetic valve options exist. Percutaneous aortic valve closure has also been reported in adults using an Amplatzer device (Abbott Cardiovascular, Plymouth, MN, USA) as a rescue strategy for a very large regurgitant valve after VAD implantation (55). In patients with a Damus-Kaye-Stansel connection with neoaortic regurgitation, external ligation of the neoaorta has also been described (56).

5.3. Tricuspid and pulmonary valve disease

Tricuspid regurgitation can be the result of primary annular dilation as well as leaflet and subvalvar apparatus abnormalities. In the setting of a biventricular circulation with a VAD supporting a failing, systemic left ventricle, a leftward septal shift can induce tricuspid regurgitation, which can be prevented by titrating VAD speed gradually under echocardiographic monitoring of septal position and tricuspid valve function (57). Tricuspid regurgitation can also be the result of a dysfunctional, dilated, or pressure-overloaded right ventricle. In the latter setting, tricuspid regurgitation generally improves with the placement of a systemic VAD (58), possibly because of the reduced the reduced right ventricle afterload.

However, significant tricuspid regurgitation that persists or develops after LVAD implantation in adult patients is associated with increased mortality (58, 59). One can speculate that the hemodynamically significant persistent or *de novo* tricuspid regurgitation that is associated with increased mortality after LVAD implantation is a surrogate marker of right ventricle dysfunction and poor right heart cardiac output. Tricuspid valve repair may be beneficial in instances where there is primary morphological abnormalities of the valve and adequate or recoverable right ventricle function. However, it is not as evident if tricuspid valve repair in the setting of functional tricuspid regurgitation and a dysfunctional right ventricle would provide any benefit. Further, it has been reported that tricuspid valve repair for at least moderate tricuspid regurgitation does not confer any survival benefit after LVAD implantation in adults, possibly due to a significant recurrence of tricuspid regurgitation (59). Data regarding the impact of *de novo* or preexisting tricuspid regurgitation on outcomes in pediatric VAD patients are lacking. Nonetheless, most pediatric heart surgeons are familiar with tricuspid valve repair techniques, and thus we feel that it is reasonable to repair an insufficient tricuspid valve in pediatric patients with depressed right ventricle function. In smaller children, a suture annuloplasty at the commissures is usually sufficient, while in larger children, an annuloplasty ring can be implanted.

Pulmonary valve insufficiency can occur in pediatric patients with congenital heart disease who had prior transannular patch or right ventricle to pulmonary artery conduit placement. These patients would need replacement with a valved conduit or bioprosthetic valve in the setting of a right-sided VAD placement should there be significant native or conduit valve insufficiency.

6. Case example

The patient was a 9-day-old, 2.7 kg female born at full term who presented with tachypnea, retractions, and cyanosis. An echocardiogram in clinic was notable for poor left ventricle function and she was immediately admitted to the intensive care unit. She was intubated for respiratory distress and started on empiric antibiotics. She was then transferred to our center for further care. Echocardiogram upon transfer demonstrated severely reduced left ventricle systolic function, mildly depressed right ventricle systolic function, and no semilunar or atrioventricular valve insufficiency. She was then evaluated and listed for heart transplantation. Five days after admission, the patient developed hemodynamic instability despite increased inotrope infusions and thus underwent urgent cannulation for venoarterial extracorporeal membrane oxygenation followed by balloon atrial septostomy for additional decompression of the left heart. She was then transitioned to a Berlin Heart EXCOR VAD two weeks later. Echocardiogram prior to VAD implantation demonstrated the presence of a nonrestrictive atrial septal defect with left to right shunting, severely depressed left ventricle systolic function, left ventricle dilation, mild mitral insufficiency, moderate and continuous AI (**Figure 2A**), mildly reduced right ventricle function, trivial tricuspid insufficiency, and mild to moderate mitral insufficiency. Given the degree of aortic insufficiency, an aortic valve repair was also undertaken in addition to the atrial septal defect closure and VAD placement. Via median sternotomy, cardiopulmonary bypass was accomplished with ascending aorta and bicaval cannulation. A 5 mm inflow cannula was inserted through the left ventricle apex. Cardioplegic arrest was then accomplished by administering Del Nido solution into the aortic root. A longitudinal aortotomy was then performed on the anterior ascending aorta and extended into the noncoronary sinus to expose the aortic valve. The leaflets were very thin and were noted not to coapt centrally. Because the leaflets were too fragile

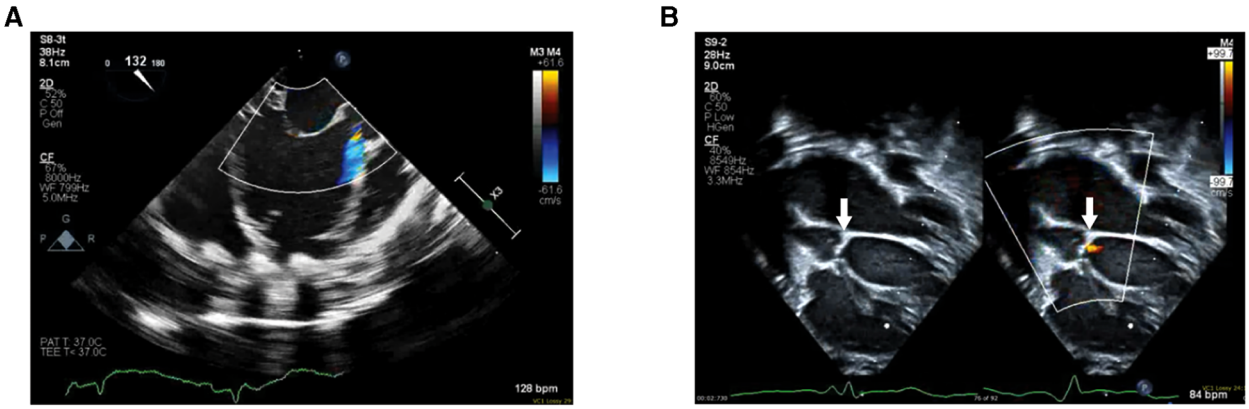

FIGURE 2
(A) Pre-VAD implantation echocardiogram with color doppler mapping demonstrating significant AI. (B) Post-VAD implantation 2D echocardiogram (left) with color-doppler comparison (right) demonstrating the patch placed at the ventriculoaortic junction (white arrows) and trivial patch margin leak.

to hold a central coaptation stitch, we elected to close the ventriculoaortic junction with a patch of bovine pericardium. The leaflets were excised and the bovine pericardial patch was sewn to the annulus with a continuous 7-0 polypropylene suture. The aortotomy in the noncoronary sinus region was then closed, and a slightly beveled 8 mm vascular graft was anastomosed to the anterior aortotomy. The vascular graft was then connected to a 5 mm Berlin outflow cannula that had been previously tunneled through the body wall. The atrial septal defect was closed with a Gore-Tex patch. The VAD cannulae were connected to a 10 ml Berlin Heart Excor blood pump. The heart and VAD were deaired and the aortic cross-clamp was removed. The patient was weaned off cardiopulmonary bypass with the level of VAD support titrated while using echocardiogram to determine ventricular septal position and the degree of tricuspid regurgitation. Total cardiopulmonary bypass time was 169 min, with an aortic cross-clamp of 75 min. Transesophageal and epicardial echocardiogram demonstrated a trivial ventriculoaortic patch margin leak (**Figure 2B**), no residual atrial level shunting, good right ventricle function, and laminar flow into the inflow cannula. The patient recovered uneventfully and then underwent orthotopic heart transplantation two months after VAD implantation. The patient required the placement of a gastric tube for feeding difficulties and was discharged 6 weeks after heart transplantation.

7. Summary

Durable VADs have improved the outcomes of children with end-stage heart failure. The efficacy of VAD therapy in children is affected by valvular heart disease. Clinicians treating pediatric VAD patients need to understand how valvular heart disease can impact the efficacy of VAD support in the varying scenarios of cannulation arrangement, type and location of the valvular heart disease, and type of device. Knowledge of the different surgical techniques to address an insufficient semilunar or atrioventricular valve in the pediatric VAD patient is also important in maximizing the efficacy of VAD therapy while minimizing the risk of surgery and preserving ventricular function. Much of the evidence guiding the current management of pediatric VAD patients with valvular heart disease is taken from the published experience in adult VAD patients and therefore future investigation should specifically study this area to provide pediatric-relevant practice guidelines.

Author contributions

VS, RB, DP, and MS participated in the planning, writing, and editing of this manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Blood flow kinetic energy is a novel marker for right ventricular global systolic function in patients with left ventricular assist device therapy

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Objectives: Right ventricular (RV) failure remains a major concern in heart failure (HF) patients undergoing left ventricular assist device (LVAD) implantation. We aimed to measure the kinetic energy of blood in the RV outflow tract (KE-RVOT) – a new marker of RV global systolic function. We also aimed to assess the relationship of KE-RVOT to other echocardiographic parameters in all subjects and assess the relationship of KE-RVOT to hemodynamic parameters of RV performance in HF patients.
Methods: Fifty-one subjects were prospectively enrolled into 4 groups (healthy controls, NYHA Class II, NYHA Class IV, LVAD patients) as follows: 11 healthy controls, 32 HF patients (8 NYHA Class II and 24 Class IV), and 8 patients with preexisting LVADs. The 24 Class IV HF patients included 21 pre-LVAD and 3 pre-transplant patients. Echocardiographic parameters of RV function (TAPSE, St', Et', IVA, MPI) and RV outflow color-Doppler images were recorded in all patients. Invasive hemodynamic parameters of RV function were collected in all Class IV HF patients. KE-RVOT was derived from color-Doppler imaging using a vector flow mapping proprietary software. Kruskal-Wallis test was performed for comparison of KE-RVOT in each group. Correlation between KE-RVOT and echocardiographic/hemodynamic parameters was assessed by linear regression analysis. Receiver operating characteristic curves for the ability of KE-RVOT to predict early phase RV failure were generated.
Results: KE-RVOT (median ± IQR) was higher in healthy controls (55.10 [39.70 to 76.43] mW/m) than in the Class II HF group (22.23 [15.41 to 35.58] mW/m, $p < 0.005$). KE-RVOT was further reduced in the Class IV HF group (9.02 [5.33 to 11.94] mW/m, $p < 0.05$). KE-RVOT was lower in the LVAD group (25.03 [9.88 to 38.98] mW/m) than the healthy controls group ($p < 0.005$). KE-RVOT had significant correlation with all echocardiographic parameters and no correlation with invasive hemodynamic parameters. RV failure occurred in 12 patients who underwent LVAD implantation in the Class IV HF group (1 patient was not eligible due to death immediately after the LVAD implantation). KE-RVOT cut-off value for prediction of RV failure was 9.15 mW/m (sensitivity: 0.67, specificity: 0.75, AUC: 0.66).

Conclusions: KE-RVOT, a novel noninvasive measure of RV function, strongly correlates with well-established echocardiographic markers of RV performance. KE-RVOT is the energy generated by RV wall contraction. Therefore, KE-RVOT may reflect global RV function. The utility of KE-RVOT in prediction of RV failure post LVAD implantation requires further study.

KEYWORDS

right ventricular failure, left ventricular assist device, vector flow mapping, kinetic energy, echocardiography

Introduction

The increasing number of patients with advanced heart failure has resulted in longer waiting times and increased mortality for patients listed for heart transplantation (1, 2). Due to the limited number of available organs, left ventricular assist device (LVAD) implantation has been used as an effective alternative to heart transplantation (3, 4). LVAD therapy improves outcomes in patients with advanced heart failure, especially after the introduction of continuous-flow LVAD technology in 2008 (5, 6). Although LVAD support improves exercise tolerance and reduces end-organ dysfunction, right ventricular failure (RVF) post-LVAD implantation continues to be a major cause of poor post-operative outcomes. The incidence of RVF is reported to be between 10% and 40% and is associated with increased mortality, morbidity, and hospital length of stay (7–9). Additional RVAD support is required in a proportion of patients with post-LVAD RVF. However, emergent conversion of LVAD support to biventricular mechanical circulatory support results in worse outcomes compared to elective establishment of biventricular mechanical circulatory support (10, 11). As a result, various models that utilize hemodynamic and echocardiographic parameters to predict post-LVAD RVF preoperatively, have been proposed (7, 12–24). No single prediction tool has gained universal support.

The kinetic energy of blood in the RV outflow tract (KE-RVOT)—a new marker of RV global systolic function—is a dynamic pressure that reflects the energy generated by the entire RV. We aimed to assess the relationship between KE-RVOT and well-established echocardiographic and hemodynamic parameters of RV performance. We also aimed to investigate whether KE-RVOT predicts RV failure post-LVAD implantation.

Methods

Patient population

This prospective study was approved by the institutional review board of our institution, and written informed consent was obtained from all participants. Healthy volunteers, outpatients with heart failure (NYHA Class II) or with an LVAD already implanted, and inpatients with heart failure (NYHA Class IV) were enrolled between November 2017 and March 2019.

Echocardiographic and hemodynamic parameters

Echocardiographic parameters of RV function - tricuspid annular plane systolic excursion (TAPSE), St', Et', isovolumic acceleration (IVA), myocardial performance index (MPI)) - were assessed in accordance with published guidelines (25). Parasternal RV outflow views with color Doppler were recorded using transthoracic echocardiography (TTE) on all subjects (25). MPI was assessed using the tissue Doppler method, not the pulsed wave Doppler method. KE-RVOT was derived from the color Doppler parasternal RV outflow image using iTECHO® (Cardio Flow Design, Tokyo, Japan), a vector flow mapping (VFM) software. Invasive hemodynamic parameters of RV function - central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), systolic pulmonary artery pressure (sysPAP), diastolic pulmonary artery pressure (diaPAP), mean pulmonary artery pressure (mPAP), RV stroke volume - were collected during right heart catheterization in the patients with NYHA Class IV heart failure. RV stroke work index (RVSWi) and pulmonary artery pulsatility index (PAPi) were calculated from invasive hemodynamic parameters (16, 26). RVSWi was calculated as: [(mPAP – CVP) × RV stroke volume index × 0.0136] mmHg • liter/m^2. PAPi was calculated as: [(sysPAP–diaPAP)/CVP]. RV failure risk score (RVFRS) was also assessed in the patients with NYHA Class IV heart failure (12). Among the subjects with NYHA Class IV HF, those who underwent LVAD implantation were followed and assessed for RVF. Post-LVAD RVF was defined as the need for intravenous inotropic support for >14 days, inhaled nitric oxide for ≧48 h, right-sided circulatory support (extracorporeal membrane oxygenation or right ventricular assist device), or hospital discharge with an intravenous inotropic medication. The decision to utilize these interventions was made by the treating physician and was based on clinical signs of RV dysfunction.

Image acquisition and determination of KE-RVOT

Echocardiographic parameters were assessed, and color Doppler images were stored using a standard diagnostic ultrasound system, Vivid E95 (GE Healthcare, Chicago, USA). To calculate KE-RVOT, color Doppler images were processed using the VFM software. Digitized two-dimensional color Doppler cine-loop images were obtained in the parasternal RV outflow view. Images

were stored with the VFM configuration, the region of interest was maximized, and the Nyquist limit was set to mitigate aliasing. The ultrasound frequency was 3 MHz, with a frame rate of 30–40 using an M5Sc-D probe. The stored cine-loop images were transferred to EchoPAC® (GE Healthcare, Chicago, USA) and converted into HDF-5 files. The HDF-5 files were imported into the VFM software and analyzed. One cardiac cycle was selected for analysis by using two consecutive QRS complexes from the electrocardiogram as the beginning and end points. The right ventricular cavity-endocardial border and pulmonary artery wall were manually traced on the initial frame, and two-dimensional wall tracking was applied to detect wall motion (**Figure 1**). If the aliasing phenomenon was observed in the cine-loop images, the aliased pixels were manually corrected. Kinetic energy values were calculated from the vectors passing through RVOT over one cardiac cycle and averaged over three cardiac cycles.

Principles of vector flow mapping

Velocity vectors of intraventricular blood flow are visualized by a two-dimensional continuity equation applied to color Doppler echocardiography of blood flow and wall-tracking method of the myocardium boundary, optical flow method (27–31). The velocity vectors of each pixel that are calculated from both the left-side and right-side boundaries are integrated by summation of the vectors according to a weight function (28). The KE-RVOT can be calculated according to the following equation:

$$\boldsymbol{KE} = \int \frac{1}{2}\rho v^2 \times v dL,$$

where ρ is the density of the blood (1,060 kg/m^3), v is the velocity vector of the blood flow, and dL is an minute increment of the cross-sectional line (29).

Statistical analysis

Statistical analysis was performed using JMP software (version 12.0.1 for Macintosh, from SAS). Continuous variables are represented as the median ± IQR. Kruskal-Wallis test was performed for comparison of each group. Tukey Kramer test was performed for further analysis if significant difference was confirmed. Correlation between KE-RVOT and echocardiographic/hemodynamic parameters was assessed by linear regression analysis. Receiver operating characteristic curves for the ability of the KE-RVOT, CVP/PCWP, RVSWi, PAPi, and RVFRS to predict early post-LVAD RVF were generated. p values <0.05 were considered to indicate significant differences.

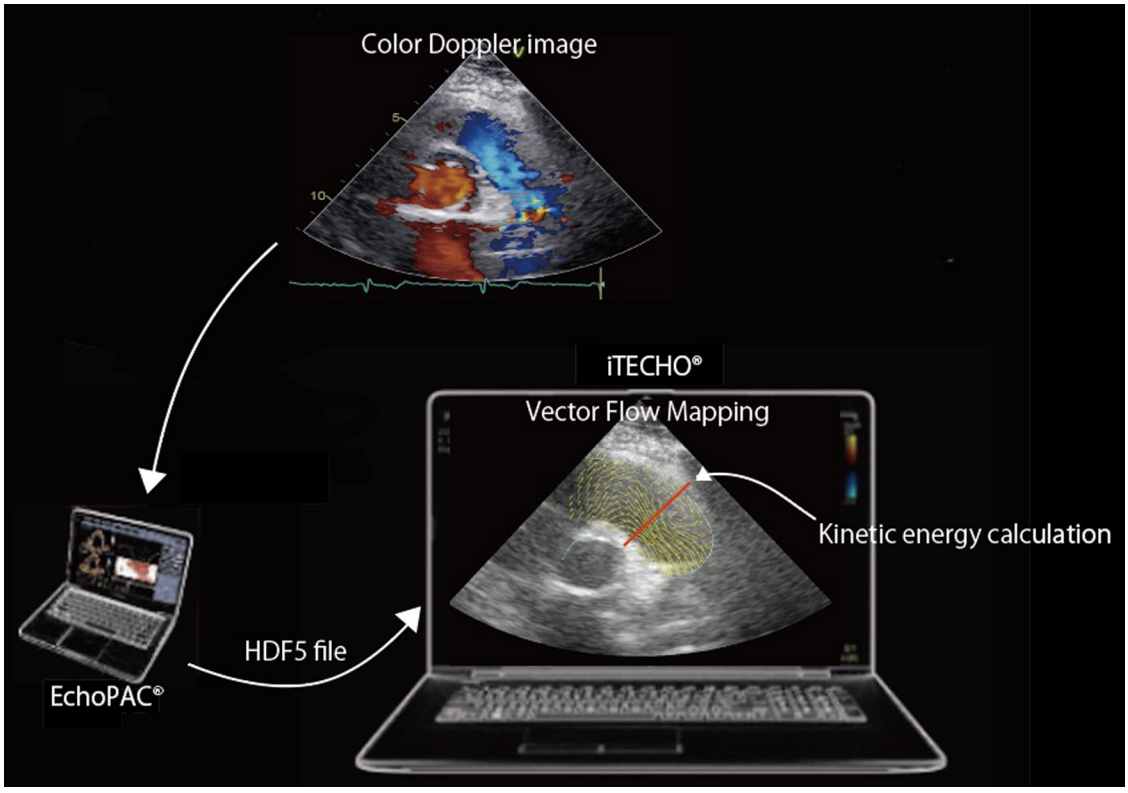

FIGURE 1
Color Doppler cine-loop image of the parasternal RV outflow view and its corresponding Vector Flow Mapping image. The stored cine-loop image is transferred to EchoPAC® (GE Healthcare, Chicago, USA) and converted into HDF-5 files. The HDF-5 file is imported into the VFM software (iTECHO®) and analyzed. Kinetic energy can be calculated from the vectors passing through RVOT (red line) over one cardiac cycle.

Results

Patient characteristics

51 subjects were prospectively enrolled and separated into 4 groups: 11 in the healthy control group (C), 8 in the NYHA Class II group (II), 24 in the NYHA Class IV group (IV), and 8 with preexisting LVADs (LVAD). Among the 24 subjects in group IV, 21 subjects subsequently underwent LVAD implantation, and 3 subjects subsequently underwent orthotopic heart transplantation. Patients' clinical characteristics are shown in Table 1. There were no significant differences in the baseline characteristics between the different groups, except for LVEDD, LVESD, LVEF. There were 10 INTERMACS 2 subjects and 14 INTERMACS 3 subjects in group IV (Table 2). In group IV, all patients who subsequently underwent LVAD implantation received a HM3 device. In the group with preexisting LVADs, 6 subjects had a HM II device and 2 subjects had a HM3 device (Table 2).

Kinetic energy of the RVOT

KE-RVOT was significantly higher in group C (55.10 [39.70 to 76.43] mW/m) than in group II (22.23 [15.41 to 35.58] mW/m, $p < 0.005$), group IV (9.02 [5.33 to 11.94] mW/m, $p < 0.0001$), and the preexisting LVAD group (25.03 [9.88 to 38.98] mW/m, $p < 0.005$) (Figure 2A). KE-RVOT in group IV was also significantly lower than in group II ($p < 0.05$) (Figure 2A).

TABLE 1 Patients' clinical characteristics.

	Healthy ($n = 11$)	NYHA II ($n = 8$)	NYHA IV ($n = 24$)	with LVAD ($n = 8$)	p-value
Age	52.8 ± 9.2	58.1 ± 11.4	59.5 ± 12.9	60.1 ± 18.0	0.31
Gender (male)	9 (81.8%)	4 (50%)	4 (83.3%)	6 (75%)	0.27
Height (cm)	169.6 ± 5.1	168.9 ± 5.2	174.8 ± 6.6	170.1 ± 10.4	0.05
Weight (kg)	70.6 ± 8.7	93 ± 39.1	88.7 ± 19.1	92.6 ± 40.7	0.16
BMI (kg/m^2)	24.5 ± 2.1	32.3 ± 11.6	29.0 ± 5.1	31.1 ± 10.5	0.08
BSA (m^2)	1.81 ± 0.13	2.00 ± 0.39	2.04 ± 0.23	2.02 ± 0.45	0.14
LVEDD (mm)	41.7 ± 5.4[a]	59.0 ± 9.1	63.6 ± 9.9	57.1 ± 9.4	<0.0001
LVESD (mm)	26.6 ± 3.7[a]	49.8 ± 8.9	56.0 ± 9.4	50.9 ± 11.9	<0.0001
LVEF (mm)	64.2 ± 3.5[a]	29.5 ± 8.1	19.3 ± 6.2	20.5 ± 5.3	<0.0001
Systolic BP (mmHg)	123 ± 11	117 ± 23	111 ± 15	111 ± 20	0.15
Diastolic BP (mmHg)	78 ± 8	71 ± 12	72 ± 12	82 ± 8	0.05
Etiology					0.96
Ischemic		2	7	2	
Nonischemic		6	17	6	

[a]LVEDD, LVESD, and LVEF were significantly different in the healthy controls group compared to other groups.

TABLE 2 INTERMACS profile and LVAD device in the NYHA Class IV group and preexisting LVAD group.

	NYHA IV ($n = 24$)	With LVAD ($n = 8$)
INTERMACS 1	0	N/A
INTERMACS 2	10	N/A
INTERMACS 3	14	N/A
HM II/HM3	0 / 21	6 / 2

Echocardiographic parameters

The TAPSE values of were 22 [21 to 25], 14.8 [13 to 17.53], 12 [8.1 to 14.75], and 6.5 [5 to 9.5] in groups C, II, IV, and LVAD respectively. There were significant differences between groups C and II ($p < 0.0005$), groups C and IV ($p < 0.0001$), groups C and LVAD ($p < 0.0001$), groups II and LVAD ($p < 0.005$), and groups IV and LVAD ($p < 0.05$) (Figure 2B). The values of St' were 11 [10 to 12], 9 [6.25 to 10], 6.5 [4 to 9], and 4 [2.25 to 5] in groups C, II, IV, and LVAD respectively. There were significant differences between groups C and IV ($p < 0.0005$), groups C and LVAD ($p < 0.0001$), groups II and LVAD ($p < 0.005$), and groups IV and LVAD ($p < 0.05$) (Figure 2C). The values of Et' were 10 [9 to 11], 6.5 [5.25 to 7.75], 6 [5 to 8.75], and 4.5 [4 to 8.75], in groups C, II, IV, and LVAD respectively. There were significant differences between in groups C and II ($p < 0.05$), groups C and IV ($p < 0.01$), and groups C and LVAD ($p < 0.01$) (Figure 2D). The values of IVA were 1.93 [1.73 to 2.42], 1.42 [0.9 to 1.53], 1.42 [1.02 to 1.77], and 0.81 [0.62 to 1.53] in groups C, II, IV, and LVAD respectively. There were significant differences between groups C and II ($p < 0.005$), groups C and IV ($p < 0.005$), and groups C and LVAD ($p < 0.0005$) (Figure 2E). The values of MPI were 0.28 [0.24 to 0.39], 0.6 [0.48 to 0.78], 0.67 [0.52 to 0.86], and 0.56 [0.49 to 0.67] in groups C, II, IV, and LVAD respectively. There was a significant difference between groups C and IV ($p < 0.005$) (Figure 2F).

Hemodynamic parameters

In the patients with NYHA Class IV HF, CVP/PCWP, RVSWi, and PAPi were 0.39 [0.33 to 0.52], 6.68 [5.23 to 7.79], and 3.32 [2.22 to 5.89] respectively. As for RVFRS, 17 patients had score 0, 1 patient had score 2, 2 patients had score 2.5, and 1 patient had score 4.5.

Correlation of KE-RVOT with other parameters

KE-RVOT had significant correlation with all echocardiographic parameters and no correlation with invasive hemodynamic parameters (Table 3).

RV failure prediction

RV failure occurred in 12 patients among those who underwent LVAD implantation (1 patient was not eligible due to mortality

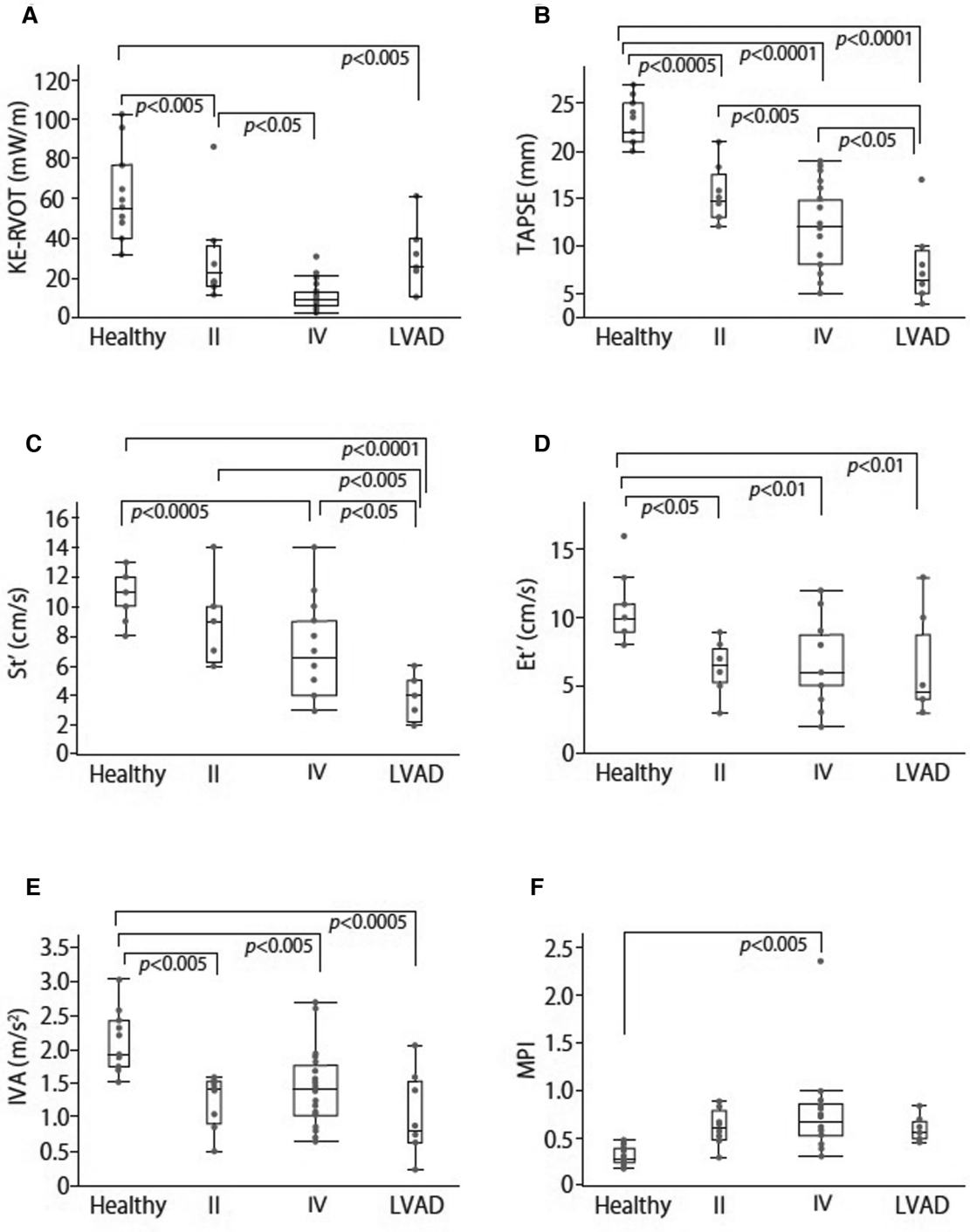

FIGURE 2
Box-and whisker plot compares KE-RVOT (A), TAPSE (B), St' (C), Et' (D), IVA (E), and MPI (F) values between each group.

immediately after the LVAD implantation). The overall performance for the prediction of RVF was greatest for KE-RVOT (AUC KE-ROVT 0.66; CVP/PCWP 0.56; RVSWi 0.47; PAPi 0.61; RVFRS 0.55) (**Figure 3**). Sensitivity and specificity were optimal with a KE-RVOT cut-off 9.15 mW/m (sensitivity: 0.69, specificity: 0.75).

Discussion

Orthotopic heart transplantation is the most effective treatment for end-stage heart failure (32). Due to the limited number of donors, many potential recipients die before transplantation. LVAD support has been utilized as an alternative destination

TABLE 3 Correlation of KE-RVOT with echocardiographic parameters and invasive hemodynamic parameters.

Parameters	Correlation coefficient	*p* value
TAPSE	0.59	<0.0001
St'	0.36	<0.01
Et'	0.37	<0.01
IVA	0.42	<0.005
MPI	−0.43	<0.005
CVP/PCWP	0.78	0.12
RVSWi	0.77	0.07
PAPi	0.38	0.18
RVFRS	−0.85	0.07

therapy for end-stage heart failure patients. However, RVF is a significant and frequent complication in the postoperative period after LVAD implantation, and its prediction is still difficult. We evaluated a novel parameter, KE-RVOT, using vector flow mapping, as a potential marker for RVF in heart failure patients.

This study demonstrates that KE-RVOT can be used as an indicator of RV function and may be useful as a predictor of post-LVAD RVF. KE-RVOT was significantly lower in the heart failure groups and the preexisting LVAD group compared with healthy controls. The significant reduction in KE-RVOT in the preexisting LVAD group compared to healthy controls may be due to a reduction in RV pulsatility in the preexisting LVAD group. Reduced pulsatility decreases the peak velocity of flow and reduces kinetic energy. There was a non-significant increase in KE-RVOT in the preexisting LVAD group compared to groups II and IV, which is likely due a higher cardiac output in patients with preexisting LVADs. KE-RVOT in group IV was significantly lower than in group II. The overall findings indicate that KE-RVOT may reflect RV function.

Although there was significant correlation between KE-RVOT and traditional echocardiographic parameters such as TAPSE, St', IVA, and MPI, KE-RVOT is distinct from traditional echocardiographic parameters. Traditional echocardiographic parameters typically assess regional function. The RV is an anatomically complex three-dimensional structure. It is triangular in shape in sagittal section and crescent-shaped in cross section. Furthermore, RV shape and function are influenced by the interventricular septum, which in turn is affected by ventricular loading conditions. Therefore, it is difficult to assess global RV function with traditional echocardiographic parameters.

In contrast, KE-RVOT assesses the flow energy that the entire RV ejects into the RVOT, which reflects both global RV function and pulmonary vascular resistance. KE-RVOT is the hydrodynamic pressure generated by the whole RV pushing blood against pulmonary vascular resistance. Han et al. evaluated KE-RVOT in patients with pulmonary arterial hypertension (WHO functional class I or II) and healthy subjects using 4D flow MRI (33). They demonstrated that patients with pulmonary

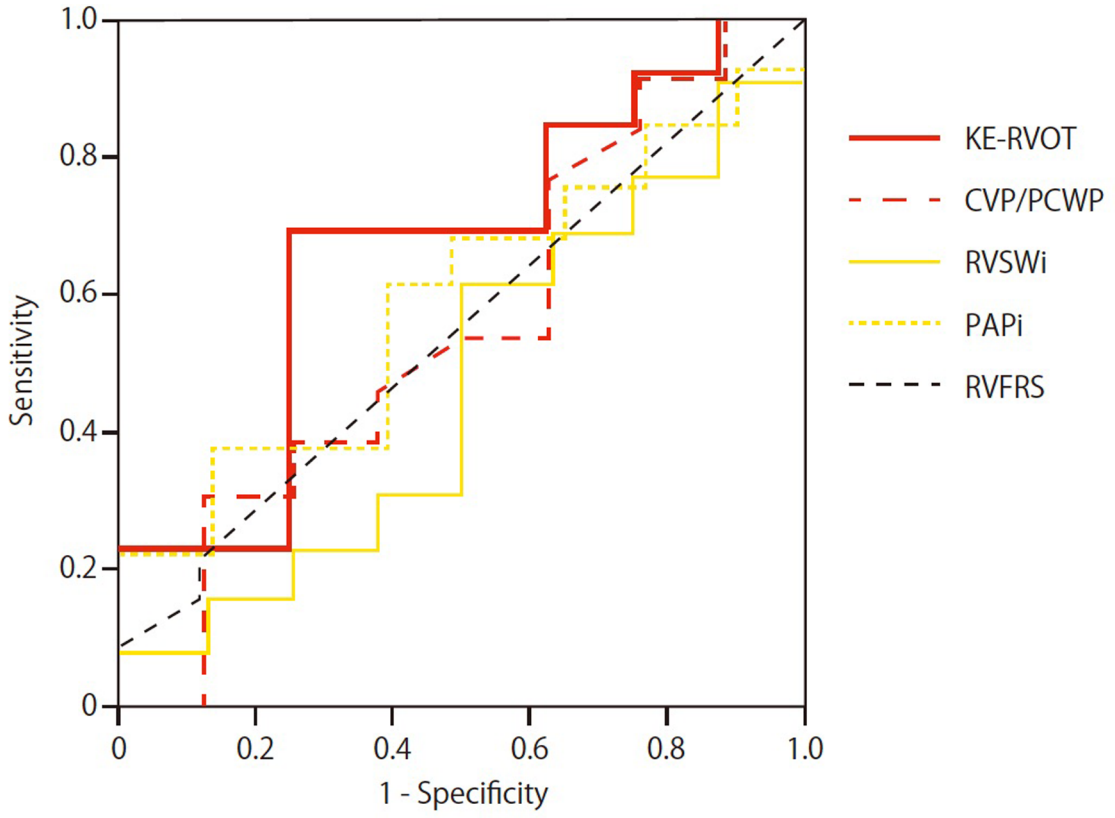

FIGURE 3
Receiver operating characteristic (ROC) curves and area under the curve (AUC) are shown for KE-RVOT, CVP/PCWP, RVSWi, PAPi, and RVFRS for prediction of RVF in the group IV patients undergoing LVAD implantation.

arterial hypertension had lower KE- RVOT than healthy subjects. RV ejection fraction was lower in the patients with pulmonary arterial hypertension than in the healthy subjects. The lower KE-RVOT of the patients with pulmonary arterial hypertension was thought to be due to both hypokinetic RV wall motion and high pulmonary vascular resistance. Their study also indicated that KE-RVOT reflects RV-PA coupling. Fredriksson et al. investigated the difference in KE-RV between patients with mild ischemic heart disease and healthy controls using 4D flow MRI (34). Although there was no significant RV functional difference between the patients with high left ventricular end diastolic volume index and healthy subjects based on conventional MRI and echocardiographic indices, KE-RV was lower in the patients with high left ventricular end diastolic volume index compared to the patients with low left ventricular end diastolic volume index and heathy subjects. They concluded that subtle impairment of RV function can be detected by KE-RV. Finally, Rao et al. underlined the importance of KE-RVOT because KE forms a greater proportion of the total energy in the pulmonary circuit when compared to the systemic circuit (the pressure in the pulmonary artery is one-sixth of the pressure in the aorta, but the KE is similar in magnitude in both vessels) (35).

KE-RVOT may also be a good predictor of RVF post-LVAD implantation similar to other well-known predictors such as CVP/PCWP, RVSWi, PAPi, RVFRS. Right to left ventricular end-diastolic diameter ratio is another predictor of RVF before isolated LVAD implantation, however we did not acquire the specific images needed to accurately calculate this ratio in our study (36). Elevated CVP and laboratory abnormalities related with congestion, and reduced PAP are the preoperative parameters that are associated with increased risk of RV failure (7, 37–42). However, several studies have shown that preoperative elevation of CVP does not reliably predict risk for RVF (37–42). Although PAPi is well-known index for RV function, we found that PAPi did not correlate with KE-RVOT. This may be due to the fact that PAP and CVP (pressure parameter) may be more susceptible to change depending on patient's condition than KE-RVOT (fluid dynamic parameter). Additionally, KE-RVOT may be a better marker for RV-PA coupling. In other hemodynamic parameters (CVP/PCWP, RVSWi) as well, since they are calculated from pressure information and volume information, they may be susceptible to change depending on the situation. Therefore, these hemodynamic parameters did not correlate with KE-RVOT. Regarding RVFRS, because it is an index based on both laboratory data and vasopressor requirement, it is likely that there was no correlation with KE-RVOT. Notably, CVP/PCWP, RVSWi, and PAPi are combined indices which require invasive pulmonary artery catheter placement. In contrast, KE-RVOT analysis can be done with only echocardiographic imaging.

Study limitations

The analysis of KE-RVOT requires adequate color Doppler imaging of the parasternal RV outflow view with accurate delineation of the RVOT. The sample size in this study was limited. However, we were able to obtain adequate imaging in all subjects in this study. Larger prospective studies are needed to assess the usefulness of KE-RVOT as a marker for RV function and predictor of post-LVAD RVF.

Conclusion

KE-RVOT is a novel noninvasive measure of RV function that differentiate patients at various degree of heart failure patients, and may carry prognostic implication for patients undergoing LVAD implantation. KE-RVOT may reflect global RV function. However, additional studies are required to further evaluate the KE-RVOT and its clinical role.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Columbia University IRB. The patients/participants provided their written informed consent to participate in this study.

Authors contributions

KA, PC, MY, HT: study design. KA, ES, RJ, IW: data collection. KA, PC, ES, RJ, IW, KI, SM, TN, NN, YN, BM, KT, MY, HT: data analysis. KA, IW: writing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Tricuspid regurgitation in the setting of LVAD support

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Tricuspid valve regurgitation (TR) is a common complication of end-stage heart failure. Increased pulmonary venous pressures caused by left ventricular (LV) dysfunction can result in a progressive dilation of the right ventricle and tricuspid valve annulus, resulting in functional TR. Here, we review what is known about TR in the setting of severe LV dysfunction necessitating long-term mechanical support with left ventricular assist devices (LVADs), including the occurrence of significant TR, its pathophysiology, and natural history. We examine the impact of uncorrected TR on LVAD outcomes and the impact of tricuspid valve interventions at the time of LVAD placement, revealing that TR frequently improves after LVAD placement with or without concomitant tricuspid valve intervention such that the benefit of concomitant intervention remains controversial. We summarize the current evidence on which to base medical decisions and provide recommendations for future directions of study to address outstanding questions in the field.

KEYWORDS

left ventricular assist device (LVAD), tricuspid regurgitation, heart failure, right ventricular (RV) failure, prognosis, management, tricuspid valve procedures

1. Introduction

Heart failure with reduced ejection fraction (HFrEF) is a complex syndrome where cardiac output is unable to meet metabolic demands and accommodate venous return; the only curative treatment is cardiac transplantation (1). The relative paucity of organs for transplantation has led to the adoption of left ventricular assist devices (LVADs) to durably support circulation in select individuals. LVADs have proven superior to optimal medical therapy in trials and registry data (2–4). Current best data suggest a 1-year survival rate of more than 80% with LVAD therapy (5).

Functional tricuspid regurgitation (TR) is present to some degree in 88% of patients with HFrEF (6). In patients with significant left ventricular (LV) dysfunction warranting isolated LVAD support, the prevalence rate of severe TR is 11.7% (5). TR is associated with worse outcomes in patients undergoing LVAD implantation—the duration of postoperative inotropic support, hospital stay, and temporary right ventricular assist device (RVAD) requirement are all increased in patients with significant preimplant TR (7). Furthermore, there is a concern over decreased survival rates (7).

An understanding of the pathophysiology, clinical significance, and best management of TR in the setting of LVAD support is necessary, given the prevalence and impact of TR in this population, and this is the focus of this review.

2. Pathophysiology of functional tricuspid regurgitation

There is a close relationship between TR and left and right ventricular (RV) dysfunction. In patients under consideration for LVAD therapy, the underlying cardiomyopathy results in severe LV dysfunction. Chronic volume and pressure overload of the left heart leads to cardiac remodeling with ventricular dilation and hypertrophy.

The increased left-sided pressure results in WHO group 2 pulmonary hypertension (PH) and transmission of the hydrostatic pressure to the RV via the pulmonary vasculature. Functional TR is thus strongly linked to the severity of PH (8). The increased afterload causes RV geometric changes (9). In addition, the underlying cardiomyopathy may affect the RV muscle directly, causing RV dysfunction and RV pressure/volume overload.

Geometric changes include enlargement of the RV apically, lengthening of the ventricle, annular dilation of the tricuspid valve (TV), and papillary muscle displacement, leading directly to tricuspid regurgitation (10, 11). Annular dilation and annular area have been linked to the severity of TR (8, 12). Frequently, these patients also suffer from chronic atrial fibrillation, which contributes to dilation of the right atrium (RA) and tricuspid annulus (13). The geometric changes in the RV pull the papillary muscles outward, restricting or tethering/tenting the leaflets of the TV (11, 13, 14). Although TV leaflet tethering is most strongly associated with RV size and geometry, LV function is an independent and weaker contributor (15). This contribution of LV dysfunction may be explained by a displacement of the septal RV papillary muscle and apical displacement of the anterior papillary muscle seen with LV dilation (8, 12, 16). Tethering of the TV leaflets is sufficient to induce regurgitation in patients even in the absence of significant annular dilation (15). Both annular dilation alone and isolated papillary muscle displacement have been confirmed to cause TR in a porcine *in vitro* model (17).

A positive feedback loop compounds the issue with an increase in volume, worsening geometric changes, and progression of the TR unless the loop is successfully interrupted (**Figure 1**) (18). Chronic TR results in irreversible cardiac remodeling (19).

3. Natural history and impact of uncorrected TR in LVAD placement

RV function is known to be critical to successful LVAD placement (20). As the pathophysiology of TR affects RV function, there are concerns around the clinical impact of significant TR in patients requiring LVAD placement. A review of 2,527 patients in the INTERMACS registry associated the presence of moderate and severe TR pre-LVAD implantation with worse long-term survival (21). Indeed, long-term survival is worse in patients with both preimplant RV dysfunction and preimplant significant TR, suggesting a synergistic detrimental effect (22).

It has been hypothesized that an acute increase in venous return and RV stroke volume from the LVAD can lead to worsening RVF and TR. Conversely, LVAD placement has the potential to interrupt the cycle of volume and pressure overload and improve TR through direct LV unloading.

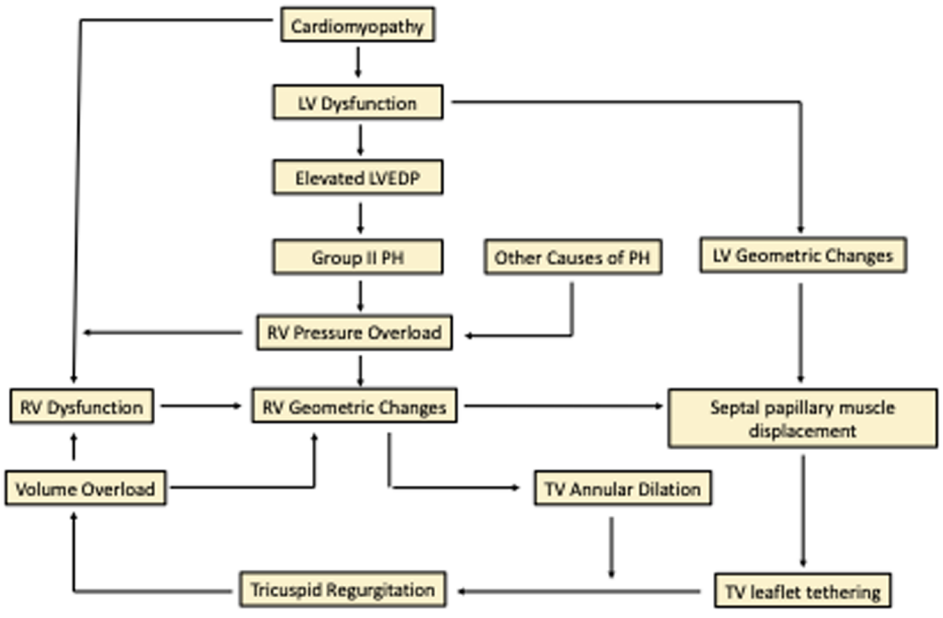

FIGURE 1
Pathophysiology of tricuspid regurgitation. LV, left ventricle; RV, right ventricle; PH, pulmonary hypertension; TV, tricuspid valve; LVEDP, left ventricular end diastolic pressure.

In examining the effect of LVAD placement in offloading the LV, significant reverse cardiac remodeling was noted within 40 days of implant in hearts explanted at the time of transplant (23). Multiple studies have demonstrated improvements after LVAD placement in pulmonary artery pressures, pulmonary vascular resistance (PVR), pulmonary capillary wedge pressures, and in RV and TV function (22, 24–30). TR improvement after LVAD placement was seen more in patients with a higher PVR, which is likely, as such patients gain from LVAD placement through a substantial decline in PVR (29). Significant echocardiographic improvement in moderate to severe TR occurs in 55%–81% of patients (22, 25, 28, 29). These findings are noted early in the postoperative period, and TR continues to improve over a longer-term follow-up (22, 30). However, not all patients with significant TR show improvement in TV function, and a proportion of patients experience a worsening of TR after LVAD implantation (27, 31).

3.1. Effect of preoperative TR on early and late RV function

A study of first-generation LVADs showed that 75% of patients with Grade III or IV TR developed early RVF post-LVAD placement compared with only 12% of patients with grade I or II TR (32). With the continuous flow HeartMate II LVAD, severe preoperative TR was identified as one of several independent predictors for early biventricular support (30). In a randomized trial of LVAD placement with a similar incidence of moderate to severe preoperative TR in both arms (approximately one-quarter), RVF requiring RVAD placement was low and did not vary between the axial flow HeartMate II and the centrifugal flow HeartMate 3 devices (33). In comparison, when looking exclusively at patients with moderate to severe TR undergoing mostly HeartMate 3 placement without TV surgery, the incidence of severe RVF was higher—inotropic support for more than 14 days was needed in 37.5% of patients, and 14.3% of patients required RVAD support (34). Preimplant TR, in combination with elevated RA pressure and end-organ dysfunction, was associated with an increase in early mortality after continuous flow LVAD placement in a large study of the EUROMACS registry (22). These data underline the early hazards related to significant TR.

Late RVF, occurring in 12% of LVAD recipients, is noted to be a frequent cause of death beyond the first year of implant and linked to worse long-term survival (35–37). Preimplantation significant TR was identified as the strongest independent predictor for late RVF; up to 81.2% of patients with late RVF had preimplant moderate or severe TR (38).

3.2. Persistent/residual TR after LVAD placement

Critically, patients with residual TR have been identified to have increased long-term mortality, and the persistence of significant TR after LVAD placement is associated with a decline in RV function (22, 29, 31). **Table 1** summarizes studies examining the late effects of TR after LVAD placement.

Several authors have attempted to identify factors that might predict persistent TR after LVAD placement. In one study, residual TR was associated with preoperative TV annulus diameter but not with leaflet tethering (31). Patients with atrial fibrillation are less likely to see an improvement in TR post-LVAD placement, probably because the etiology of their TR includes RA dilation from atrial fibrillation and is less positively impacted by LVAD implantation (29). Atrial fibrillation has also been weakly associated with a progression of TR after LVAD placement (39).

4. Impact of concomitant TV surgery at LVAD implant

While significant TR is frequently identified in patients undergoing LVAD placement, the decision to opt for concomitant tricuspid valve intervention (TVI) is controversial. Intervention at the time of LVAD placement could consist of tricuspid valve repair (TVr) or replacement. In practice, repair with an annuloplasty ring has been the dominant mode of TVI (40). Performance of a TVI increases cardiopulmonary bypass (CPB) time and may require cardiac arrest; both of which have the potential to increase operative risk and RVF (26, 41).

Initial experience in a cohort with older-generation LVADs showed a reduction in inotrope use, renal dysfunction, and length of hospital stay in patients of the TVI group as well as a non-significant reduction in the use of RVADs (42). A more recent study of continuous flow LVADs comparing concomitant TVI with isolated LVAD placement in patients with severe TR found a decrease in 30-day readmissions with TVI (43). However, there was no difference in RVF, survival, or TR recurrence.

Two small series identified no substantial difference in outcomes for patients undergoing TVI with LVAD placement and those receiving LVAD implants without TVI, but the groups without TVI did not have significant TR, rendering the comparison difficult (44, 45). Others, including a meta-analysis, found no outcome benefit to TVI, including in clinical measures of RVF or survival (21, 41, 46). A recent propensity-matched cohort of the EUROMACS registry identified patients undergoing TVI to have an intensive care unit (ICU) stay lengthened by 4 days with no benefit in clinical outcomes (26). In this cohort, moderate to severe TR was less prevalent in patients with TVI immediately after surgery but became comparable with time.

A large single-center series with a mix of continuous flow LVADs revealed an improvement in TR with TVI at the expense of increased bleeding and transfusion and no improvement in clinical outcomes (47).

Of concern, TVI was associated with increases in operative time, length of inotropic support, ventilatory support, and ICU stay as well as morbidities such as bleeding, transfusion, RVF, and renal failure in three small single-center series (48–50). In a

TABLE 1 Summary of studies examining long-term results with significant preoperative TR that is not corrected at LVAD placement.

Author, date, journal	Study groups	Outcomes	Key results	Limitations
Nakanishi et al. (2018). *American Journal of Cardiology* (33)	A total of 274 patients who underwent continuous-flow LVAD placement between 2007 and 2016.	TV annulus and RVF	Greater TV annulus diameter was associated with late RVF with a hazard ratio of 1.221 and diameter measurements of 43.9 vs. 38.2 mm. $p < 0.001$	Retrospective single-center study.
Nakanishi et al. (2018). *Journal of American Heart Association* (31)	A total of 127 patients who underwent isolated LVAD placement between 2007 and 2016.	TV annulus and residual TR after LVAD placement	Greater preoperative TV annulus was associated with increased residual TR. $p = 0.017$	Retrospective single-center study.
		Clinical impact of persistent TR	Residual TR was significantly associated with mortality with a hazard ratio of 5.01. $p < 0.001$	
Gonzalez-Fernandez et al. (2019). *American Journal of Cardiology* (36)	A total of 156 patients who underwent LVAD placement between 2009 and 2018.	Late RVF	A small percentage (10.3) of patients developed late RVF.	Retrospective single-center study.
		Preoperative TR and late RVF	Moderate to severe TR was an independent predictor of late RVF. Hazard ratio 5.50 $p = 0.02$	
Veen et al. (2021). *European Journal of Cardio-Thoracic Surgery* (22)	A total of 2,496 patients who underwent LVAD placement between 2005 and 2018 (EUROMACS registry).	Preoperative TR and 30-day mortality	No significant difference in 30-day morality was seen between mild vs. moderate/severe TR. 10.8% vs. 10.9%. $p = 0.99$	Registry data. Mix of LVADs implanted, limited the ability to determine the impact of a specific device.
		Preoperative TR, RV dysfunction, and long-term survival	The long-term survival rate was lower in patients with moderate/severe TR and RV dysfunction compared with those with good RV function and mild/no TR. 54% vs. 68%	
		Effect of LVAD placement on TR	Moderate/severe TR decreased to mild/none post-LVAD placement in ~65% patients.	
		Clinical impact of persistent TR	Persistent TR post-LVAD placement was associated with increased mortality with a hazard ratio of 1.16. $p = 0.001$	
Zadok et al. (2022). *Adult Circulatory Support* (29)	A total of 121 patients who underwent LVAD placement between 2009 and 2018.	Effect of LVAD placement on TR	A total of 55% of patients with moderate to severe TR had insignificant TR by 1-year follow-up.	Retrospective single-center study. Some echocardiographic data were missing during the follow-up.
		Clinical impact of persistent TR	Those with persistent TR post-LVAD showed a worsening of RV function, decline in RV work index, and higher loop diuretic use but no significant difference in long-term survival.	

LVAD, left ventricular assist device; RVF, right ventricular failure; TR, tricuspid regurgitation; RV, right ventricle; TV, tricuspid valve.

larger study of patients with moderate to severe TR from the STS database, LVAD placement with concomitant TVI, in comparison with LVAD alone, did not affect RVAD use or death but did increase the risk for renal failure, transfusion, reoperation, ventilator, ICU, and hospital length of stay. Similarly, an analysis of the INTERMACS database associated TVI with increased bleeding, arrhythmia, stroke, and mortality (51).

Methodological concerns in these studies include their retrospective nature, unequal comparator groups particularly with respect to TR severity, and the possibility of selection bias. The TVVAD study randomized patients at a single center with moderate or severe TR to LVAD alone or with concomitant TVI and utilized a primary endpoint of RVF. This study predominantly utilized the current generation of continuous flow LVAD (HeartMate 3, Abbott). Early published results demonstrate an improvement in TR with no substantive clinical benefit, including in the primary endpoint, survival, or adverse events (34). The parameter of quality of life measured by using the Kansas City Cardiomyopathy Questionnaire was also similar between the two groups.

Long-term failure of TVr is an additional concern. In 156 patients with continuous flow LVADs, 37.8% were identified as having a failed TVr defined as moderate or severe TR on any postoperative echocardiographic follow-up (52). Postintervention significant TR (recurrent TR) has been associated with RVF and worse heart failure-free outcomes (46, 52).

Taken together, the data do not currently support TVI at the time of LVAD placement for patients with significant TR. Clinical benefit has not been conclusively demonstrated, and risks such as bleeding, organ dysfunction, and prolongation of various indices of hospital care have been identified and are likely a sequela of prolonging CPB.

Why is TV surgery not helpful for this patient population despite the association of preoperative TR with worse post-LVAD clinical outcomes? There are several hypotheses, and the following are some of them: (1) TR improves in the majority of patients with LVAD therapy such that TVI for all would

"overtreat"; (2) TR persists in some patients despite TVI raising the possibility that a different surgical strategy might be more effective in the long-term treatment of TR; (3) TR develops *de novo* in some patients who do not have significant TR at LVAD implant, thus making it hard to draw meaningful comparisons with a control "no pre-operative TR" group; (4) TR is a marker of ventricular dysfunction, does not directly affect clinical outcomes, and thus, interventions aimed at TR do not improve outcomes; and (5) TV surgery involves operative time and risk that negate the benefit.

5. *De novo* significant tricuspid regurgitation after LVAD placement

During the follow-up of LVAD recipients, incidence rates range from 6% to 20% of the development of significant TR in patients with none or mild preoperative TR (22, 28, 29, 31). The function of the RV in this subpopulation has not been defined in the available literature and no preoperative clinical/echocardiographic or operative parameters that predict the development of TR after LVAD placement have been identified (28, 29). It is unclear whether this subset of patients with *de novo* TR carries a risk of RVF or worse long-term prognosis compared with patients with insignificant TR or resolved TR after LVAD placement; this is an area for future investigations.

6. Future directions

Several outstanding questions related to the natural history and best management of TR in the setting of LVAD therapy remain, which should guide future directions of study (**Table 2**).

It remains unclear whether TR is a marker for RV dysfunction and a predictor of worse clinical outcomes in LVAD recipients or whether it is a causative agent. Longer-term follow-up of the randomized TVVAD trial will be important to clarify the predictors of worse clinical outcomes, the role of TVI, the durability of TVr, and the clinical impact of persistent or recurrent TR.

It is possible that the particular unloading pattern (axial vs. centrifugal flow) of the LVAD implanted affects TR in a way that has not been well defined. In addition, the setting of the LVAD might be impactful with a higher speed unloading the LV more but also, perhaps, increasing venous return. Most published studies include a heterogenous group of LVADs. Future studies of advancing LVAD technology, or studies that include historical devices, separate based upon the type of LVAD based on the LVAD implanted and also to examine the effect of LVAD setting on TR.

Subgroups of patients with significant TR that might benefit from concomitant TVI should be studied. These could include those with TR pathophysiology least likely to respond to isolated LVAD placement. Potential candidates would be patients (1) with severe TR, as most studies to date combine moderate and severe TR, (2) with a dilated TV annulus, (3) with tethered leaflets, and (4) with preoperative atrial fibrillation, as it contributes to the pathophysiology of TR and is associated with persistent TR after LVAD placement. Similarly, if subgroups with the highest early RVF risk are identified, they might be preferred for heart transplantation over LVAD placement.

The current preferred strategy for TVr with an annuloplasty needs re-evaluation. In a non-LVAD setting of TV repair with annuloplasty, TV tethering was the strongest predictor of residual TR (53). Based on TV pathology, certain patients, such as those with significant TV tethering, may warrant a consideration of complex repairs or valve replacement (53, 54). What is the role of percutaneous TVI with edge-to-edge repair in this population? Benefits might lie in avoiding prolongation of the index operation and shifting the focus on patients with TR after LVAD placement.

Patients with TR after LVAD placement could be classified as persistent, recurrent after TVI, or *de novo*. They warrant more attention through heightened surveillance and an understanding of the etiology of their TR, natural history, and best management.

TABLE 2 Future directions for understanding and managing tricuspid regurgitation in the setting of LVAD support.

Future directions
Identify patients with preoperative TR at the greatest risk for early RV dysfunction after LVAD placement and direct such patients toward preoperative optimization and biventricular strategies including cardiac transplantation.
Identify subsets of patients with significant preoperative TR who might benefit from concomitant TV intervention at LVAD placement.
Tailor the TV surgical technique and intervention to the individual TV and RV geometry for achieving best long-term results.
Examine the effect of LVAD settings on TR. Examine independently the impact of future LVAD designs on TR.
Focus on surveillance and management of patients with TR *after* LVAD placement.
Investigate the role of percutaneous TV interventions particularly for patients with TR after LVAD placement.
Identify patient populations at risk of developing *de novo* TR after LVAD placement; understand its natural history and impact.

TR, tricuspid regurgitation; LVAD, left ventricular assist device; TV, tricuspid valve; RV, right ventricle.

7. Conclusion

Significant TR is commonly found in patients with severe LV dysfunction under consideration for LVAD placement. Although its pathophysiology is delineated, and it has been linked to worse clinical outcomes, the best management of significant TR at the time of LVAD placement and afterward remains unclear. TR after LVAD placement is of particular concern as it is linked to progressive RV dysfunction and associated morbidity. These patients warrant further study to understand their best management.

Author contributions

AM and AS outlined the manuscript together. AM wrote the preliminary draft. AS edited and provided additions to the manuscript significantly. Both AM and AS worked on the

manuscript revisions, figures, and tables. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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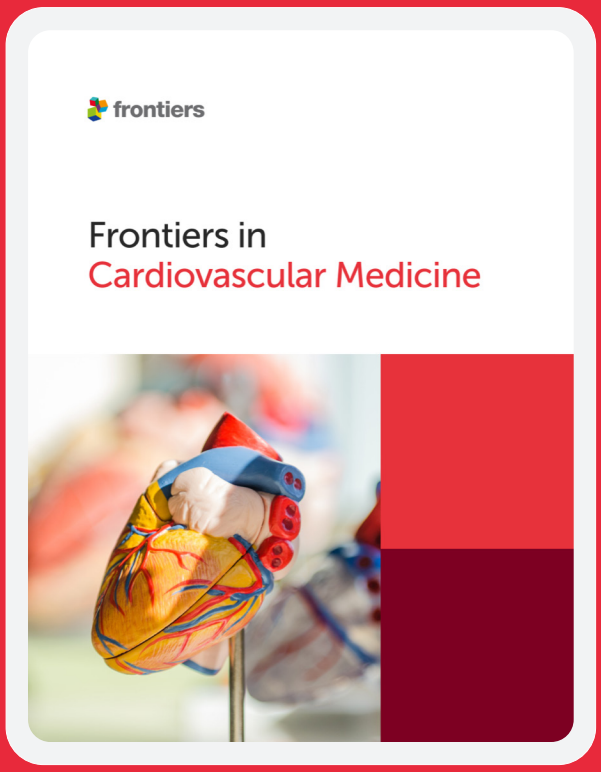

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