Journal of Cardiac Failure Vol. 25 No. 10 2019

Aortic Insufficiency and Hemocompatibility-related Adverse Events in Patients with Left Ventricular Assist Devices

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ABSTRACT

Aim: Hemocompatibility-related adverse events (HRAE) are a major cause of readmissions in patients with left ventricular assist devices (LVAD). The impact of aortic insufficiency (AI) on HRAE remains uncertain. We aimed to investigate the impact of AI on HRAE.

Methods and Results: Patients who underwent LVAD implantation between August 2014 and July 2017 and had echocardiograms 3 months post-LVAD implantation were enrolled. AI severity was assessed by measuring the systolic/diastolic ratio of flow and the rate of diastolic flow acceleration using Doppler echocardiography of the outflow cannula. Regurgitation fraction was derived from these parameters. Significant AI was defined as regurgitation fraction > 30%. Among 105 patients (median age, 56 years; 76% male), 36 patients (34%) had significant AI. Baseline characteristics were statistically not significantly different between those with and without significant AI except for higher rates of ischemic etiology and atrial fibrillation in the significant AI group ($P < 0.05$ for both). One-year survival free from HRAE was 44% in patients with AI compared to 67% in patients without significant AI ($P = 0.018$). The average hemocompatibility score, which defines the net burden of HRAE, was higher in the AI group (1.72 vs 0.64; $P = 0.009$), due mostly to higher tier I (mild HRAE; $P = 0.034$) and tier IIIB scores (severe HRAE; $P = 0.011$).

Conclusion: Significant AI, as assessed by Doppler echocardiographic parameters, was associated with HRAE during LVAD support. (*J Cardiac Fail 2019;25:787−794*)

Key Words: Heart failure, hemodynamic, bleeding.

INTRODUCTION

Aortic insufficiency (AI) is a significant complication that develops following the implantation of continuous-flow left ventricular assist devices (LVADs). Approximately 30% of patients have at least mild AI at 1 year after LVAD implantation,[1] and the prevalence and severity increase progressively with longer durations of LVAD support.[2] AI is associated with elevated cardiac filling pressures and right ventricular dysfunction.[3] However, the impact of AI on morbidity and mortality remains controversial.[4−8] Particularly, the impact of AI on hemocompatibility-related adverse events (HRAEs), which include both bleeding and thromboembolic events,[9] is unknown.

One reason for conflicting results regarding the clinical impacts of AI may result from the difficulty in quantifying AI severity in the context of continuous-flow physiology. Traditional transthoracic echocardiography (TTE) measurements for grading AI severity, including vena contracta, jet width/left ventricular outflow tract diameter and proximal isovelocity surface area, may not quantify AI accurately.[10,11]

Recently, we introduced 2 novel TTE measurements to quantify the magnitude of AI using Doppler echocardiography of the outflow graft: peak systolic-to-diastolic (S/D) velocity ratio and the rate of diastolic flow acceleration (DA).[12] In addition, we demonstrated that the traditional parameters used to grade AI tend to underestimate its severity.[13]

In this study, we investigated the prognostic impacts of AI, quantified by these novel TTE parameters, on HRAE, which were assessed using a recently developed hemocompatibility score (HCS).[9]

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Manuscript received January 29, 2019; revised manuscript received June 18, 2019; revised manuscript accepted August 6, 2019.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.08.003

METHODS

Patient Selection

In this retrospective study, patients implanted with the HeartMate II LVAD (Abbott, Abbott Park, Illinois, USA) or the HeartWare Ventricular Assist Device LVAD (Medtronic, Minneapolis, Minnesota, USA) at our center between August 2014 and July 2017 were enrolled. Patients underwent TTE at 3 months following LVAD implantation (time 0) and were followed for 1 year from the time of the TTE. Invasive hemodynamic testing was also performed 6 months post-LVAD. Both tests were performed as routine standard clinical practice. Clinical events data, including the occurrence of any HRAE, were collected during the study period. The study was approved by the institutional review board at the University of Chicago.

Echocardiographic Imaging

All patients underwent comprehensive 2-dimensional and Doppler echocardiographic evaluation by expert sonographers using the iE3 3 imaging system and S5 transducer (Philips Healthcare, Andover, Massachusetts, USA). Conventional measurements, including opening of the aortic valve and visual estimation of AI grading, were performed on the day of the echocardiogram. Measurements of novel parameters were retrospectively performed by 2 independent reviewers (TI and DN).

From the parasternal window, the frequency of aortic valve opening was assessed by using the M-mode view for 10 cardiac cycles. Opening of the aortic valve in 10 of 10 cycles was defined as regular. Opening in 3–9 of 10 cycles was defined as intermittent. Opening in fewer than 3 of 10 cycles was defined as none. Conventional assessment of the degree of aortic regurgitation was performed by qualitative visual estimation as per guidelines.[11]

Right ventricular (RV) end-diastolic area and RV end-systolic area were traced from the apical 4-chamber RV-focused view, and RV fractional area change was calculated. The right atrial area was also traced from the same view at end-systole. An M-mode cursor was oriented at the junction of the tricuspid valve plane and the RV free wall to measure tricuspid annular plane systolic excursion. Lateral tricuspid annular systolic motion velocity was measured by tissue Doppler imaging.

From the modified right parasternal window, the S/D ratio and the DA were measured at the LVAD outflow cannula by using the pulse-wave Doppler method (Figure 1, A).[12] The S/D ratio was calculated by dividing the peak systolic velocity by the peak end-diastolic velocity. The DA was obtained by measuring the diastolic slope from the onset of diastole to end-diastole.

As described previously,[13] the regurgitant fraction (RF) was extrapolated from the corresponding correlation lines for both the S/D ratio [$RF_{S/D} = -(S/D - 10.8)/19.3$] and the DA [$RF_{DA} = (DA + 0.5)/165.4$]. RF_{AVG} was obtained by

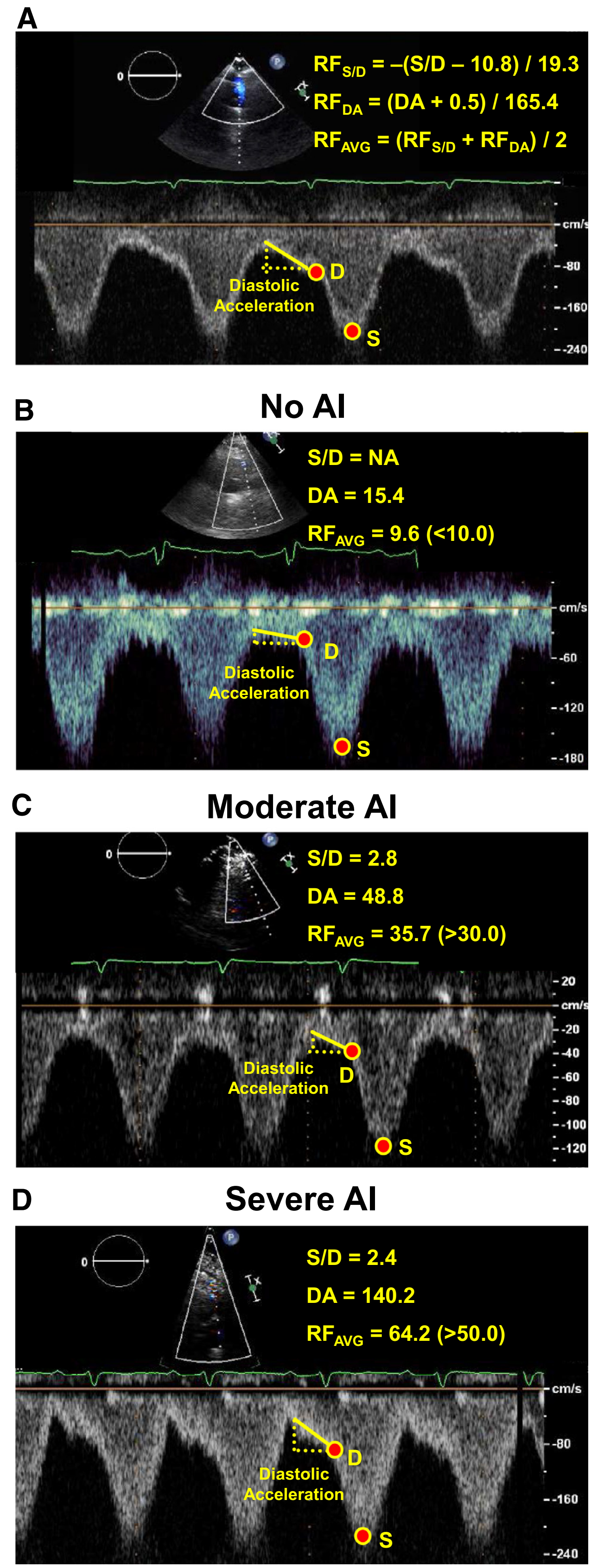

Fig. 1. How to calculate RF_{AVG} by using the Doppler echocardiography at LVAD outflow graft (A) and examples of Doppler echocardiography at LVAD outflow graft in patients with no AI

averaging $RF_{S/D}$ and RF_{DA} for each patient. Three RF_{AVG} were calculated in each case and averaged to minimize beat-to-beat errors. Patients were categorized into no AI ($RF_{AVG} < 10\%$), trace−mild AI ($10\% \leq RF_{AVG} < 30\%$), moderate AI ($30\% \leq RF_{AVG} < 50\%$), and severe AI ($RF_{AVG} \geq 50\%$). Moderate and severe AI were defined as significant. Examples of Doppler measurements of each grade of AI are shown in Figure 1, B−D.

Hemodynamic Assessment

At 6 months post-LVAD, standard invasive hemodynamic testing was performed. Central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and mean blood pressure were measured, and pulmonary artery pulsatility index (PAPi) was calculated.

Follow-up Protocol

All patients received guideline-directed medical therapy, including aspirin and warfarin, with an international normalized ratio (INR) goal of 2.0−3.0 (HVAD) or 2.0−2.5 (HeartMate II) unless significant HRAE occurred during the 1-year study period. The results of standard echocardiograms, including visual estimation of AI, were used for standard management of patients, whereas the novel Doppler echocardiographic procedures were retrospectively measured, and the results were completely blinded to the clinicians.

Hemocompatibility-related Adverse Events

These clinical adverse events attributable to LVAD-related bleeding or thrombosis were classified as HRAE: 1) nonsurgical bleeding: gastrointestinal or other nonsurgical bleedings; 2) neurologic events: stroke or other neurologic events such as seizures; 3) thromboembolic events: pump thrombosis that was medically or surgically treated or arterial thrombosis with or without organ involvement.[9] Death and hospital readmissions due to HRAE were collected and validated by 2 independent researchers (TI and DR). Events were classified according to the Interagency Registry for Mechanically Assisted Circulatory Support definitions.

Hemocompatibility Score

An HCS was calculated for each patient by classifying each event based on its clinical relevance so as to determine the aggregate net HRAE burden (Appendix Table A1).[14] Multiple events could contribute to the score, if applicable.

(B), moderate AI (C) and severe AI (D). $RF_{S/D}$ is calculated from the formula using S/D ratio, which is the ratio of velocity between systole and end-diastole. RF_{DA} is calculated from the formula using DA, which is a slope of diastole velocity. RF_{AVG} is an average of both $RF_{S/D}$ and RF_{DA} and indicates the quantified severity of AI. DA, diastolic acceleration; RF, regurgitant fraction.

Statistical Analyses

Statistical analyses were performed with SPSS Statistics 22 (IBM, Armonk, New York, USA). Two-sided P values < 0.05 were considered statistically significant. Continuous variables were expressed as mean and standard deviation or median (25% quartile, 75% quartile) based on their distribution. Some variables were expressed as mean for clarity, despite a non-normal distribution.

RF_{AVG} was obtained from 2 independent reviewers, and the values were averaged. The inter-rater reliability between the reviewers was assessed by the intraclass correlation coefficient. Freedom from events were assessed by Kaplan-Meier analysis and compared between the groups using the log-rank test. Cox proportional hazard ratio regression analyses were performed to investigate the impact of significant AI on death or HRAE after adjusting for potential confounders. Variables with $P < 0.10$ in the univariate analyses were evaluated in the multivariable model after the confirmation that all variables met the proportional hazards assumption.

RESULTS

Baseline Characteristics

Of 111 patients who received LVAD implantation and were alive at least 3 months afterward, 105 were enrolled and received echocardiographic assessment at a median of 3.0 (1.3, 6.0) months following LVAD implantation (Table 1). Six patients (5%) did not receive the assessment because of poor image quality, and they were excluded from this study. Median age was 56 (48−65) years of age, and 80 (76%) were male. Most patients were implanted as destination therapy. There were no patients who had significant AI before LVAD implantation. Preoperative PAPi was not statistically different between those with and without significant AI ($P = 0.89$).

Classification of AI by the Novel Parameters

By visual estimation, 52 patients (50%) had no AI, 50 (48%) had trace−mild AI, 2 (2%) had moderate AI, and no patients (0%) had severe AI.

By using the novel parameters for quantifying AI, 36 patients (34%) had at least moderate AI (ie, significant AI), with distributions shown in Figure 2, A. Specifically, 53 patients (50%) had no AI, 16 (15%) had trace−mild AI, 31 (30%) had moderate AI, and 5 (5%) had severe AI (Figure 2, B). Intraclass correlation coefficient (2, 2) for the inter-rater reliability of RF_{AVG} by 2 reviewers was 0.989 ($P < 0.001$).

Comparison of Patient Characteristics

Patients with significant AI had higher rates of ischemic heart failure and atrial fibrillation ($P < 0.05$ for both) (Table 1). Otherwise, there were no significant differences between those with and without significant AI. The magnitude of antiplatelet and anticoagulation therapies was

Table 1. Comparison of Baseline Characteristics and Aortic Valve Variables

	Total (N = 105)	Significant AI (n = 36)	No Significant AI (n = 69)	*P* Value
Demographics				
Age, years	56 (48, 65)	58 (49, 67)	55 (48, 65)	0.47
Gender, male	80 (76%)	29 (81%)	51 (74%)	0.31
Body mass index	29.8 ± 7.4	30.3 ± 7.5	31.3 ± 6.8	0.51
Ischemic etiology	34 (32%)	17 (47%)	17 (25%)	0.013
Destination therapy	82 (78%)	25 (69%)	57 (83%)	0.074
HeartMate II LVAD	79 (75%)	23 (64%)	56 (81%)	0.060
Hypertension	59 (56%)	21 (58%)	38 (55%)	0.39
Diabetes mellitus	30 (29%)	12 (33%)	18 (26%)	0.26
History of stroke	16 (15%)	4 (11%)	12 (17%)	0.31
Atrial fibrillation	34 (32%)	16 (44%)	18 (26%)	0.036
Chronic kidney disease	37 (35%)	14 (39%)	23 (33%)	0.32
Mild AI before LVAD implantation	12 (11%)	6 (17%)	6 (9%)	0.22
Hemodynamics before LVAD implantation				
CVP, mmHg	11 (7, 17)	12 (5, 17)	11 (7, 16)	0.80
PAWP, mmHg	24.7 ± 9.5	24.2 ± 9.5	25.1 ± 9.6	0.67
CI, L/min/m^2	1.90 (1.50, 2.31)	1.90 (1.33, 2.40)	1.90 (1.60, 2.30)	0.60
Pulmonary artery pulsatility index	2.4 (1.5, 4.0)	2.5 (1.4, 4.7)	2.4 (1.6, 3.7)	0.89
MAP, mmHg	89.9 ± 13.6	82.5 ± 14.2	80.0 ± 13.3	0.44
Aortic valve parameters at time 0				
Visually estimated AI				
No AI	52 (50%)	1 (3%)	51 (74%)	< 0.001
Trace/mild AI	50 (48%)	33 (92%)	17 (25%)	< 0.001
Moderate AI	2 (2%)	2 (6%)	0 (0%)	0.050
Severe AI	0 (0%)	0 (0%)	0 (0%)	-
Aortic valve opening				
None	48 (46%)	24 (67%)	24 (35%)	0.002
Intermittent	9 (8%)	5 (14%)	4 (6%)	0.16
Regular	48 (46%)	7 (19%)	41 (59%)	< 0.001
LVAD outflow Doppler echo variables				
S/D ratio	2.9 (2.4, 4.0)	2.4 (2.1, 2.7)	3.2 (2.8, 4.5)	< 0.001
Diastolic acceleration slope, cm/sec^2	23.0 (0, 52.5)	63.3 (49.4, 83.7)	5.7 (0, 22.9)	< 0.001
AI RF_{AVG}, %	18.3 (0.3, 38.0)	41.0 (37.3, 47.1)	3.2 (0.3, 18.1)	< 0.001
Echocardiographic RV parameters at time 0				
RA area, cm^2	16.0 (12.4, 21.3)	17.0 (13.4, 25.8)	14.7 (11.3, 18.0)	0.035
RVEDA, cm^2	23.9 (20.2, 31.7)	27.1 (21.7, 32.0)	22.4 (18.5, 28.5)	0.044
TAPSE, cm	0.90 (0.67, 1.12)	0.79 (0.63, 1.00)	1.03 (0.84, 1.16)	0.002
TV S', cm/sec	5.9 (5.4, 7.7)	5.7 (5.0, 7.6)	6.6 (5.6, 8.1)	0.059
RVFAC, %	28.0 (19.4, 39.2)	22.0 (12.1, 36.5)	29.4 (22.9, 43.1)	0.008
TR grade, degree	1 (0.5, 2)	1 (0.5, 3)	1 (0.5, 2)	0.73
Device parameters at time 0				
LVAD speed, rpm				
HeartMate II LVAD	9000 (9000, 9200)	9000 (8600, 9400)	9000 (9000, 9200)	0.33
HVAD LVAD	2660 (2600, 2800)	2620 (2600, 2690)	2760 (2520, 2860)	0.32
LVAD flow, L/min	4.8 (4.4, 5.7)	5.0 (4.4, 6.0)	4.7 (4.4, 5.4)	0.46
Mean arterial pressure at time 0	86 (80. 96)	89 (76, 97)	85 (80, 95)	0.77
LVAD duration before echo tests (time 0), months	3.0 (1.3, 6.0)	3.0 (2.0, 6.0)	2.0 (1.0, 5.8)	0.077

AI, aortic insufficiency; CI, cardiac index; CVP, central venous pressure; LVAD, left ventricular assist device; MAP, mean arterial pressure; PAWP, pulmonary artery wedge pressure; RA, right atrium; RVEDA, right ventricular end-diastolic area; RVFAC, right ventricular fraction area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV S', lateral tricuspid annular systolic motion velocity.

The severity of tricuspid regurgitation was graded as 0, none; 1, trace; 2, mild; 3, moderate; 4, severe. Variables were compared by using the unpaired *t* test, Mann-Whitney U test or Fischer exact test, as appropriate.

statistically comparable in both groups at time of enrollment and at 1 month and 3 months after TTE ($P > 0.05$ for all) (Appendix Table 2A).

Among 102 patients who were visually estimated to have less than moderate AI (ie, nonsignificant AI), 34 (33%) were reclassified into the moderate or greater AI group (ie, significant AI) by using novel parameters (Table 1). The mean AI RF was 41.0% in the significant AI group vs 3.2% for the group without significant AI ($P < 0.001$). The aortic valve was closed in 67% of the patients in the significant AI group, whereas it was closed in only 35% of the group without significant AI.

Comparison of Right Heart Function

Patients with significant AI had significantly larger right ventricles and worse RV function, with lower tricuspid annular plane systolic excursion and RV fraction area change compared to those without significant AI ($P < 0.05$ for all) (Table 1).

Comparison of Hemodynamics

Hemodynamics were measured at a median of 2.0 (0−5.4) months following the TTE measurements (time 0) in 62 of 105 patients (Appendix Table 3A). CVP and

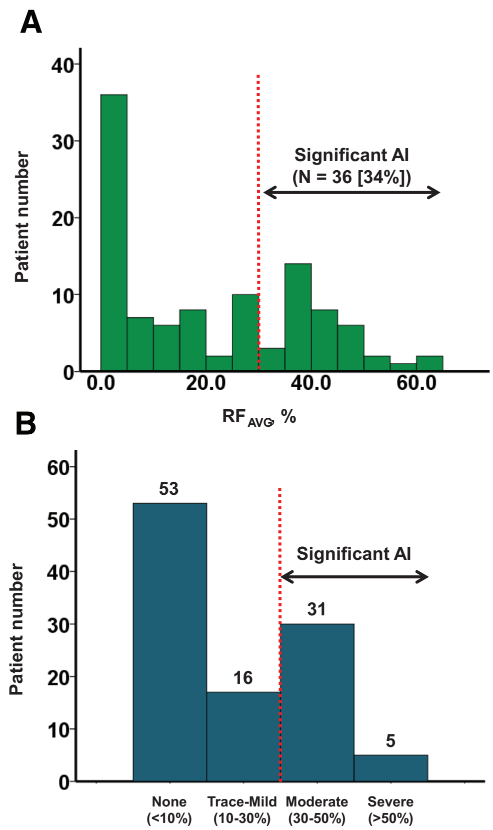

Fig. 2. Distribution of RF_{AVG} (A) and grading of AI by using RF_{AVG} (B). RF_{AVG} <10%, no AI; 10% ≤ RF_{AVG} <30%, trace−mild AI; 30% ≤ RF_{AVG} <50%, moderate AI; 50% ≤ RF_{AVG}, severe AI. Significant AI is defined as RF_{AVG} ≥ 30%.

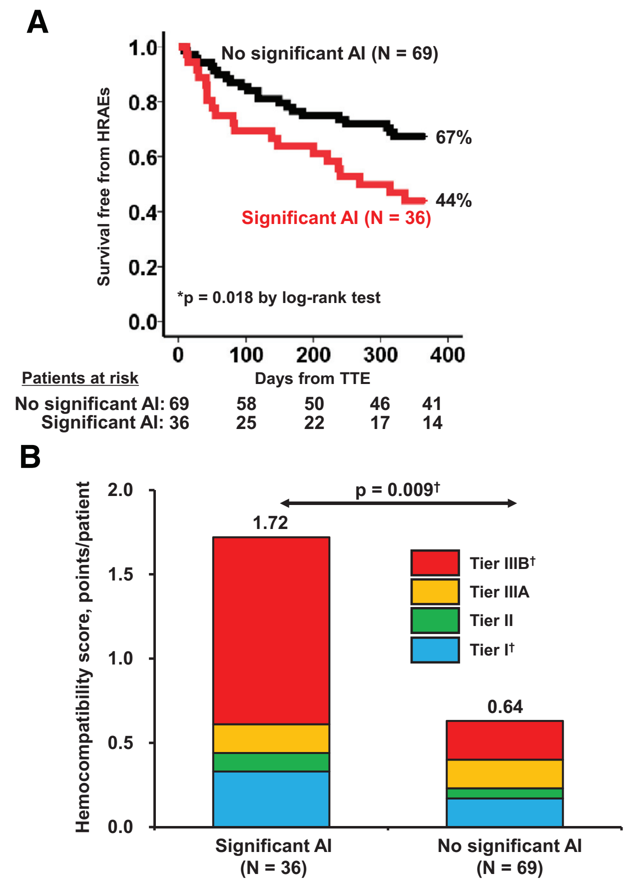

Fig. 3. One-year survival free from HRAEs stratified by the existence of significant AI (A) and Comparison in HCS (B). Significant AI is defined as a moderate or greater AI (RF_{AVG} ≥ 30%). HCS, hemocompatibility score. $^{*}P < 0.05$ by log-rank test. $^{\dagger}P < 0.05$ by Mann-Whitney U test.

PCWP were higher, and PAPi was lower, in the significant AI group ($P < 0.05$ for all).

Freedom from HRAEs

In the significant AI group (n = 36), 11 patients died (1 gastrointestinal bleed, 2 strokes, 2 pump thrombosis, 1 sepsis, and 5 others); 17 experienced HRAE; and 20 had death or HRAEs during the 1-year observational period, whereas in the group without significant AI (n = 69), 8 died (1 stroke, 1 pump thrombosis, 4 sepsis, and 2 others); 16 experienced HRAEs; and 22 died or had HRAEs.

One-year survival free from HRAE was significantly lower in the significant AI group than in the group without significant AI (44% vs 67%, $P = 0.018$) (Figure 3, A). The 1-year survival free from HRAE decreased as AI grade increased: 92% in the no AI group, 64% in the trace/mild AI group, 52% in the moderate AI group, and 0% in the severe AI group ($P = 0.007$).

The presence of atrial fibrillation and an ischemic heart failure etiology did not have statistically significant impact on survival free from HRAEs ($P = 0.30$ and $P = 0.15$, respectively). In the same manner, age > 65 years, device type and LVAD support duration before the enrollment > 3 months did not have statistically significant impacts on survival free from HRAEs ($P = 0.47$, $P = 0.14$ and $P = 0.94$, respectively).

Significant AI had significant impact on 1-year freedom from bleeding (67% vs 86%, $P = 0.037$) and from stroke (84% vs 97%, $P = 0.019$), whereas 1-year freedom from pump thrombosis was statistically comparable, irrespective of significant AI (82% vs 89%, $P = 0.49$).

Comparison of HCS

Net HCS was higher in the significant AI group (1.72 vs 0.64 points per patient, $P = 0.009$) (Figure 3, B). The difference between the 2 groups was most prominent in Tier I and Tier IIIB events, both of which were significantly higher in the significant AI group ($P < 0.05$ for both). Specifically, there were higher rates of bleeding ($P = 0.08$), disabling stroke ($P = 0.09$) and hemocompatibility-related death ($P = 0.012$) in the significant AI group (Table 2). There were a total of 26 bleeding events with mean INR of 2.26 ± 0.48 in the overall cohort.

Table 2. Average Points per Patient Associated With Events Contributing to Net HCS

	Significant AI (n = 36)	No Significant AI (n = 69)	*P* Value
Tier I			
Nonsurgical bleeding (≤ 2 events)	0.25	0.12	0.078
Medically managed PT	0.08	0.06	0.62
Tier II			
Nonsurgical bleeding (> 2 events)	0.06	0.03	0.64
Nondisabling stroke	0.06	0.03	0.64
Tier IIIA			
Surgically managed PT	0.12	0.12	0.96
Tier IIIB			
Disabling stroke	0.44	0.12	0.087
HC-related or inconclusive death	0.68	0.12	0.012

AI, aortic insufficiency; HCS, hemocompatibility score; PT, pump thrombosis; TE, thromboembolic.

Note: Variables are expressed as average score per patient and compared between groups by using Poisson analyses.

Predictors of Death or HRAE

After adjusting for 3 variables with $P < 0.10$ in the univariate analyses, including age > 65 years, ischemic etiology and INR > 3.0 at time of enrollment, $RF_{AVG} > 30\%$ (ie, significant AI) still had a statistically significant impact on death or HRAE in the multivariable Cox analysis (hazard ration 2.5 [95% confidence interval 1.2−4.8], $P = 0.015$) (Table 3).

DISCUSSION

In this study, we quantified the magnitude of AI by using novel Doppler echocardiographic measurements obtained at the LVAD outflow cannula 3 months following LVAD implantation. We then investigated the impact of significant AI (defined as moderate or greater AI with $RF_{AVG} > 30\%$) on HRAE during 1 year of LVAD support.

Our main findings are as follows. First, only 2 patients (2%) had significant AI (moderate or greater AI, ie, AI $RF_{AVG} \geq 30\%$) when visually estimated, whereas 36 (34%) had significant AI when using the novel TTE measurements. Second, patients with significant AI had more enlarged right ventricles and reduced RV function. Also, patients with significant AI had higher CVP and PCWP and lower PAPi despite a nonsignificant difference in preoperative PAPi. Third, 1-year survival free from HRAE was significantly lower in the group with significant AI. Fourth, net HCS was higher in the group with significant AI. And finally, significant AI was an independent predictor of death or HRAE in the multivariable model.

Novel TTE Measurements to Quantify the Magnitude of AI

Previous studies used a visual estimation or vena contracta method to quantify the severity of AI. However, these procedures have limitations in the setting of continuous flow and eccentric regurgitant jets, both of which are features of AI in patients with LVADs.[10] Recently, our team proposed a novel Doppler echocardiographic procedure obtained at the LVAD outflow cannula to quantify the magnitude of AI, and we demonstrated a better correlation with actually measured cardiac load.[12] In this study, 33 of 50 (66%) patients had AI that was underestimated using conventional visual estimation and were reclassified from trace−mild to moderate severity by using novel TTE procedures.

The results of this study support the findings of our earlier work, which indicate that when measured accurately, AI does have a clinical impact in the population with LVADs. Identifying AI earlier in its course may offer the opportunity to alter management in a way that prevents its progression and reduces the incidence of adverse events. Interventions could range from tighter blood pressure management to LVAD speed adjustment or early valve replacement (either percutaneously or surgically).[15]

AI and HRAE

HRAEs are common following LVAD implantation and are considered the Achilles heel of the technology.[9] As such, identifying a correctable problem that causes HRAE is important.

In the current study, we demonstrated an association between AI and HRAE.[9] The next step is to assess whether prevention or treatment of AI will be associated with a reduction in the incidence of HRAE.

We previously demonstrated that failure to achieve hemodynamic optimization is associated with HRAE.[16] Furthermore, we showed in this study that patients with AI have higher CVP and PCWP and lower PAPi on hemodynamic testing, and they have larger right ventricles and more reduced RV function by echocardiogram, although preoperative PAPi was statistically not different between the groups. These factors may explain a mechanistic link for the current findings; that is, AI leads to worse hemodynamics, and the hemodynamic perturbance is the cause of the increased rate of HRAE.

Bleeding events may be explained by RV failure, which is associated with hepatic congestion, worsened coagulopathy and lower arterial pulsatility, leading to higher inflammatory responses, increased abnormal angiogenesis and the formation of arteriovenous malformations and refractory gastrointestinal bleeding.[17] Our finding of INR within therapeutic range at the time of bleeding events may also support the above hypothesis. The current findings and our previous study showing that significant AI was associated with heart failure readmissions[13] serve as the basis of a trial of early intervention in patients with significant AI. Elevated inflammatory response due to systemic congestion might serve as a trigger of thromboembolic events, although further biologic assessments to clarify the relationship among AI, RV failure and stroke are warranted.

Table 3. Cox Hazard Ratio Regression Analyses for Death or any HRAEs

	Univariate Analyses Hazard Ratio (95% CI)	*P* value	Multivariable Analyses Hazard Ratio (95% CI)	*P* Value
Demographics				
Age, years	1.02 (0.99−1.05)	0.10		
Age > 65 years	1.74 (0.91−3.35)	0.097	1.66 (0.82−3.34)	0.16
Gender, female	0.57 (0.25−1.29)	0.18		
Body mass index	0.98 (0.94−1.03)	0.45		
Ischemic etiology	2.46 (1.33−4.54)	0.004	2.20 (1.13−4.28)	0.021
Destination therapy	1.17 (0.54−2.53)	0.69		
HeartMate II LVAD	0.64 (0.33−1.23)	0.18		
Hypertension	0.90 (0.50−1.80)	0.88		
Diabetes mellitus	1.21 (0.62−2.35)	0.58		
History of stroke	1.24 (0.55−2.81)	0.61		
Atrial fibrillation	1.40 (0.74−2.68)	0.31		
Chronic kidney disease	1.27 (0.67−2.40)	0.47		
Hemodynamics before LVAD implantation				
CVP, mmHg	1.00 (0.96−1.05)	0.98		
PAWP, mmHg	0.99 (0.96−1.03)	0.59		
CI, L/min/m^2	1.58 (0.97−2.58)	0.12		
Pulmonary artery pulsatility index	0.99 (0.92−1.07)	0.88		
MAP, mmHg	0.98 (0.95−1.01)	0.12		
Medications at time of enrollment				
Aspirin	0.55 (0.27−1.13)	0.14		
INR	1.43 (0.82−2.52)	0.21		
INR < 2.0	0.99 (0.48−2.04)	0.98		
INR > 3.0	2.97 (1.05−8.36)	0.040	3.68 (1.28−10.6)	0.016
AI RF_{AVG} > 30% (significant AI)	2.05 (1.12−3.76)	0.020	2.54 (1.18−4.84)	0.015

AI, aortic insufficiency; CI, cardiac index; CVP, central venous pressure; HRAE, hemocompatibility-related adverse event; INR, international ratio; LVAD, left ventricular assist device; MAP, mean arterial pressure; PAWP, pulmonary artery wedge pressure; RF, regurgitant fraction.

Note: Variables with $P < 0.10$ in the univariate analyses were rolled into the multivariate analyses.

Limitations and Future Directions

This is a single-center study with a relatively small cohort size, but it includes comprehensive echocardiographic and detailed follow-up data. All patients completed 1-year follow-up, limiting the assessment of the impact of AI on long-term clinical outcomes. We tried to exclude the effects of confounders, but we may not have completely excluded their impact on clinical outcomes. Although we performed multivariable analyses to investigate the impact of significant AI adjusted by several confounders, optimal multivariable models, including more variables, might be constructed when using a larger scale cohort. Our cohort consisted of populations with HeartMate II and HVAD. The prevalence of AI and its impact on HRAE in the HeartMate 3 population remains a future area for investigation.

We did not analyze alternative traditional parameters, including jet width/LV outflow tract diameter and proximal isovelocity surface area. The validity of any noninvasive parameters, including our novel TTE measurement, is limited by the lack of a universally agreed-upon direct measurement of AI magnitude to serve as a gold standard.[12] We defined significant AI as $RF_{AVG} \geq 30\%$ in this study to maintain consistency with previous studies. Considering our subanalysis stratifying patients into 3 groups (no, intermediate or severe AI), detailed categorization and/or statistically calculated cutoffs for RF need to be assessed in future larger scale cohort studies. Also, we excluded 5% of patients whose results had poor image quality. We should state that this methodology may not be used for all LVAD patients. On the contrary, the measurements were performed with high reliability between 2 readers. A multicenter study is warranted to show the feasibility of measuring the novel parameters. Also, we should validate whether our novel parameters are useful in various arrhythmias. We stratified patients by grading AI obtained at 3 months following LVAD implantation but did not consider the trend of AI severity. AI is progressive,[2] and some in the no significant AI group may also have developed significant AI during the study period.

Furthermore, we did not fully identify the mechanism connecting AI and HRAE. Larger scale longitudinal assessments of hemodynamic and echocardiographic parameters focusing particularly on RV failure and angiogenesis biomarkers would further clarify the pathogenesis of AI. AI assessment at the time of each event would also strengthen our findings.

Conclusion

Significant AI, assessed by novel Doppler echocardiographic parameters, was associated with HRAE in patients with LVADs.

Acknowledgments

TI receives financial support from Postdoctoral Fellowship for Research Abroad of the Japan Society for the Promotion of Science; NU receives grant support from Abbott and Medtronic; GS is a consultant for Medtronic; VJ is a consultant for Abbott.

Appendix

Table A1. Calculation of Hemocompatibility Score

Intensity	Clinical Components	Score
Tier I: mild	≤ 2 gastrointestinal or other nonbleeding episodes	1 point each
	Suspected pump thrombosis (medically treated)	
	Nonstroke-related neurologic events	
Tier II: moderate	> 2 gastrointestinal or other nonbleeding episodes	2 points each
	Nondisabling stroke	
Tier III		
IIIA: moderate to severe	Pump thrombosis leading to reoperation for removal or replacement	3 points each
IIIB: severe	Disabling stroke	4 points each
	Death attributable to a hemocompatibility etiology or inconclusive	

Table A2. Trends of Antiplatelet and Anticoagulation Therapy

	Significant AI (n = 36)	No significant AI (n = 69)	*P* value
At time of enrollment (N = 101)			
Aspirin	25 (74%)	58 (87%)	0.091
INR	2.34 ± 0.52	2.23 ± 0.54	0.32
At 1 month (n = 99)			
Aspirin	24 (71%)	49 (75%)	0.39
INR	2.31 ± 0.42	2.22 ± 0.41	0.30
At 3 months (n = 84)			
Aspirin	20 (77%)	45 (78%)	0.58
INR	2.19 ± 0.42	2.14 ± 0.36	0.59

AI, aortic insufficiency; INR, international ratio.
Note: Variables were compared by using the unpaired *t* test, Mann-Whitney U test or Fisher exact test, as appropriate.

Table A3. Comparison of Hemodynamic Variables

	Significant AI (n = 23)	No Significant AI (n = 39)	*P* Value
Central venous pressure, mmHg	11 (7, 16)	7 (5, 10)	0.041
Pulmonary capillary wedge pressure, mmHg	15 (12, 22)	11 (10, 16)	0.037
Cardiac index, L/min/m^2	2.6 (2.4, 3.0)	2.8 (2.4, 3.2)	0.15
Pulmonary artery pulsatility index	1.9 (1.1, 3.3)	2.5 (1.8, 3.8)	0.039
Mean arterial pressure, mmHg	84 (79, 98)	90 (80, 98)	0.38

AI, aortic insufficiency.
Note: Variables were compared by using the Mann-Whitney U test.

REFERENCES

1. Jorde UP, Uriel N, Nahumi N, Bejar D, Gonzalez-Costello J, Thomas SS, et al. Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. Circ Heart Fail 2014;7:310–9.
2. Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail 2010;3:668–74.
3. Sayer G, Sarswat N, Kim GH, Adatya S, Medvedofsky D, Rodgers D, et al. The hemodynamic effects of aortic insufficiency in patients supported with continuous-flow left ventricular assist devices. J Card Fail 2017;23:545–51.
4. Aggarwal A, Raghuvir R, Eryazici P, Macaluso G, Sharma P, Blair C, et al. The development of aortic insufficiency in continuous-flow left ventricular assist device-supported patients. Ann Thorac Surg 2013;95:493–8.
5. Hiraoka A, Cohen JE, Shudo Y, MacArthur J.W. Jr., Howard JL, Fairman AS, et al. Evaluation of late aortic insufficiency with continuous flow left ventricular assist devicedagger. Eur J Cardiothorac Surg 2015;48:400–6.
6. Imamura T, Kinugawa K, Fujino T, Inaba T, Maki H, Hatano M, et al. Aortic insufficiency in patients with sustained left ventricular systolic dysfunction after axial flow assist device implantation. Circ J 2015;79:104–11.
7. Holley CT, Fitzpatrick M, Roy SS, Alraies MC, Cogswell R, Souslian L, et al. Aortic insufficiency in continuous-flow left ventricular assist device support patients is common but does not impact long-term mortality. J Heart Lung Transplant 2017;36:91–6.
8. Truby LK, Garan AR, Givens RC, Wayda B, Takeda K, Yuzefpolskaya M, et al. Aortic insufficiency during contemporary left ventricular assist device support: analysis of the INTERMACS registry. JACC Heart Fail 2018;6:951–60.
9. Mehra MR. The burden of haemocompatibility with left ventricular assist systems: a complex weave. Eur Heart J 2019;40:673–7.
10. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
12. Grinstein J, Kruse E, Sayer G, Fedson S, Kim GH, Jorde UP, et al. Accurate quantification methods for aortic insufficiency severity in patients with LVAD: role of diastolic flow acceleration and systolic-to-diastolic peak velocity ratio of outflow cannula. JACC Cardiovasc Imaging 2016;9:641–51.
13. Grinstein J, Kruse E, Sayer G, Fedson S, Kim GH, Sarswat N, et al. Novel echocardiographic parameters of aortic insufficiency in continuous-flow left ventricular assist devices and clinical outcome. J Heart Lung Transplant 2016;35:976–85.
14. Uriel N, Colombo PC, Cleveland JC, Long JW, Salerno C, Goldstein DJ, et al. Hemocompatibility-related outcomes in the MOMENTUM 3 Trial at 6 months: a randomized controlled study of a fully magnetically levitated pump in advanced heart failure. Circulation 2017;135:2003–12.
15. Phan K, Haswell JM, Xu J, Assem Y, Mick SL, Kapadia SR, et al. Percutaneous transcatheter interventions for aortic insufficiency in continuous-flow left ventricular assist device patients: a systematic review and meta-analysis. ASAIO J 2017;63:117–22.
16. Imamura T, Nguyen A, Kim G, Raikhelkar J, Sarswat N, Kalantari S, et al. Optimal haemodynamics during left ventricular assist device support are associated with reduced haemocompatibility-related adverse events. Eur J Heart Fail 2019;21:655–62.
17. Sparrow CT, Nassif ME, Raymer DS, Novak E, LaRue SJ, Schilling JD. Pre-operative right ventricular dysfunction is associated with gastrointestinal bleeding in patients supported with continuous-flow left ventricular assist devices. JACC Heart Fail 2015;3:956–64.