Journal of Cardiac Failure Vol. 00 No. 00 2020

Longitudinal Trajectories of Hemodynamics Following Left Ventricular Assist Device Implantation

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ABSTRACT

Background: Continuous-flow left ventricular assist devices (LVADs) improve the hemodynamics of patients with advanced heart failure. However, the longitudinal trajectories of hemodynamics in patients after LVAD implantation remain unknown. The aim of this study was to investigate the trends of hemodynamic parameters following LVAD implantation.

Methods and Results: We retrospectively reviewed patients who underwent LVAD implantation between April 2014 and August 2018. We collected hemodynamic parameters from right heart catheterizations. Of 199 consecutive patients, we enrolled 150 patients who had both pre- and postimplant right heart catheterizations. They had 3 (2, 4) postimplant right heart catheterizations during a follow-up of 2.3 (1.3, 3.1) years. The mean age was 57 ± 13 years, and 102 patients (68%) were male. Following LVAD implantation, pulmonary arterial pressure and pulmonary capillary wedge pressure decreased, and cardiac index increased significantly, then remained unchanged throughout follow-up. Right atrial pressure decreased initially and then gradually increased to preimplant values. The pulmonary artery pulsatility index decreased initially and returned to preimplant values, then progressively decreased over longer follow-up. Subgroup analysis showed significant differences in the trajectories of the pulmonary artery pulsatility index based on gender.

Conclusions: Despite improvement in left-side filling pressures and cardiac index following LVAD implantation, right atrial pressure increased and the pulmonary artery pulsatility index decreased over time, suggesting progressive right ventricular dysfunction. (*J Cardiac Fail 2020;00:1−8*)

Key Words: Left ventricular assist device, heart failure, hemodynamics.

Introduction

Continuous-flow left ventricular assist devices (LVADs) have become the mainstay therapy for patients with advanced heart failure (HF), both as a bridge to transplantation and as destination therapy.[1] LVADs improve clinical outcomes in patients with HF by improving hemodynamics.[2,3] However, some patients develop symptoms of HF following LVAD implantation, due mainly to right ventricular failure (RVF), a significant early postoperative complication following LVAD implantation.[4,5] Late-onset RVF can also occur during long-term LVAD support and is associated with increased morbidity and mortality.[6,7]

We have recently reported that almost half of clinically stable patients have abnormal hemodynamics after LVAD implantation.[3] We have also shown that abnormal hemodynamics are related to worse clinical outcomes, which underscores how the optimization of hemodynamics during long-term LVAD support is critical.[8−11] However, the longitudinal trajectories of hemodynamics following LVAD implantation are unknown. The aim of this study was to describe the longitudinal trajectories of hemodynamic parameters obtained from right heart catheterizations (RHCs) following LVAD implantation.

Methods

Patient Selection

We retrospectively reviewed the electronic medical records of patients who underwent LVAD implantation at our

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Manuscript received August 2, 2019; revised manuscript received January 15, 2020; revised manuscript accepted January 28, 2020.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2020.01.020

institution between April 2014 and August 2018. We enrolled patients who had RHCs at least once following LVAD implantation. Patients underwent RHCs after LVAD implantation according to institutional protocol (hemodynamic ramp study at 1 to 3 months following implantation) and when clinically indicated according to the physicians' discretion. All patients had an RHC before LVAD implantation, and this ensured that we had a minimum of 2 RHCs per patient for longitudinal analysis. All patients were followed until November 2018. Follow-up was ceased at death, heart transplantation, pump exchange, or pump explantation. The study protocol was approved by the Institutional Review Board at the University of Chicago.

Variables

Demographic data. Patients' preoperative background characteristics, including age, race, gender, causes of HF, indications for LVAD implantation and device types, and patients' physical data, were recorded.

Hemodynamic data. Hemodynamic data were extracted from the most recent RHC performed within 3 months prior to LVAD implantation. We also obtained data from all RHCs following LVAD implantation. All hemodynamic data were obtained at end-expiration and were manually reviewed by the attending cardiologist. Hemodynamic parameters were calculated as follows: transpulmonary gradient (TPG) (mmHg) = mean pulmonary arterial pressure (mPAP) (mmHg) − pulmonary capillary wedge pressure (PCWP) (mmHg); pulmonary vascular resistance (PVR) (Wood units) = (mPAP − PCWP) / cardiac output (L/min); systemic vascular resistance (SVR) (dyne*sec/cm^5) = (mean blood pressure (mmHg) − right arterial pressure (RAP) (mmHg) × 80 / cardiac output; pulmonary arterial pulsatility index (PAPi) = (systolic PAP) (sPAP) (mmHg) − diastolic PAP (dPAP) (mmHg) / RAP; RAP/PCWP ratio = RAP / PCWP; right ventricular stroke work index (RVSWI) (mmHg*mL/m^2) = (mPAP − RAP) × stroke volume (SV) index (mL/m^2); effective pulmonary arterial elastance (PEa) (mmHg/mL) = sPAP / SV (mL); and pulmonary arterial compliance (PAC) (mL/mmHg) = SV / (sPAP − dPAP).[12]

Statistical Methods

Descriptive statistics. Categorical variables were expressed as percentages. Continuous variables were expressed as a mean ± standard deviation or median (interquartile range) as appropriate. To investigate the time-dependent changes in each hemodynamic parameter, we performed a paired comparison for each parameter between the time periods of 0 to 6 months and greater than 1 year following LVAD implantation. We used Wilcoxon signed-rank test for this paired analysis. We also performed a sensitivity analysis that included only patients followed for more than 3 years. The longitudinal trends of RAP and PAPi were compared using hierarchical linear modeling (HLM). If there were several tests in 1 time period, we averaged the values in each period.

Inferential statistics. We used nonparametric (locally weighted error sum of squares) (loess) regression to guide our choice of the functional form of the longitudinal trends and then analyzed the longitudinal trends statistically by using multilevel modeling techniques. Loess models are particularly useful when the data are nonlinear. Each value of time defines a window of data (a small percentage of the timepoints around the focal point), and a local polynomial regression line is fit to the data in each span. The width of the span and the type of polynomial function (linear or quadratic) are specified. The regression lines are then connected to make a smooth curve. For each hemodynamic parameter, statistical analysis of change over time was performed by HLM.[13] HLM models fit a polynomial regression line describing the relationship between the dependent variable (hemodynamic parameter) and time to each patient's data. The coefficients from the individual models are then compared to describe average growth in the cohort. Thus, HLM models incorporate both fixed effects (sample averages) and random effects (individual variability around the sample average). Using the best form of loess curve as a guideline, we created HLM models with 3 terms: intercept, linear time and quadratic time^2 as both fixed and random effects.

Subgroup analysis. We created subgroups based on demographics (gender, age, race, ischemic etiology, body surface area [BSA], and pump type). For age and BSA, patients were divided into 2 subgroups based on median values of enrolled patients. Then we compared the trend of PAPi between the subgroups using HLM.

All statistical analyses were performed using SPSS Statistics 23 (SPSS, Chicago, IL, USA) and HLM 7 (Scientific Software International, Lincolnwood, IL, USA). A 2-tailed P value of < 0.05 was considered significant.

Results

Study Cohort

Among 199 consecutive LVAD patients in the study period, 150 patients who had both pre- and postimplant RHCs were included. The time between presurgery RHC and LVAD implantation was 8 (4, 15) days. There was a median of 3 (2, 4) RHCs after LVAD implantation during follow-up of 2.3 (1.3, 3.1) years. Patients' demographics and echocardiographic parameters prior to LVAD implantation and at the time of discharge are shown in Table 1. Mean age at implant was 57 ± 13 years, and 102 patients (68%) were male. Forty-eight (32%) patients had an ischemic HF etiology. The indication for LVAD was destination therapy in 112 (75%) patients.

Descriptive Longitudinal Trends in Hemodynamic Parameters

Fig. 1 shows the descriptive longitudinal trends (loess curves) of hemodynamic parameters following LVAD implantation. RAP decreased initially and then gradually

Table 1. Demographic and Clinical Characteristics of Patients Prior to LVAD Implantation and at the Time of Discharge

	N = 150
Age at implant, years	57 ± 13
Male, n	102 (68%)
Race, n	
African-American	72 (48%)
White	65 (43%)
Others	13 (9%)
Ischemic etiology, n	48 (32%)
Destination therapy, n	112 (75%)
Device type, n	
Centrifugal pump	85 (57%)
Axial pump	65 (43%)
Body height, cm	172 ± 10
Body weight, kg	88 ± 25
Body surface area, m^2	2.0 ± 0.3
Heart rate, beats per minute	88 ± 19
Mean blood pressure, mmHg	82 ± 12
Preimplant echocardiographic parameters	
LVEDD, mm	70 ± 10
LVEF, %	20 ± 7
E, cm/s	102 ± 31
A, cm/s	52 ± 21
E/A	2.2 ± 1.0
Deceleration time, msec	171 ± 58
TRPG, mmHg	37 ± 13
TAPSE, mm	13 ± 7
Echocardiographic parameters at discharge	
LVEDD, mm	58 ± 12
LVEF, %	23 ± 11
E, cm/s	83 ± 23
A, cm/s	52 ± 24
Deceleration time, msec	1.9 ± 0.9
TRPG, mmHg	20 ± 10
TAPSE, mm	10 ± 3
Interventricular septal position, n	
Midline	103 (69%)
Rightward shift	27 (18%)
Leftward shift	20 (13%)
Aortic valve opening, n	55 (39%)

LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annual plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

increased to preimplant values (Fig. 1A). PAP and PCWP decreased and remained lower throughout follow-up (Fig. 1B). Cardiac index increased and remained higher (Fig. 1C). TPG decreased initially and increased slightly with time (Fig. 1D). PVR and SVR decreased with LVAD implantation and remained lower throughout follow-up (Fig. 1E, 1F). PAPi decreased slightly and returned to preimplant values within 6 months, and then progressively decreased over longer follow-up periods (Fig. 1G).

The overall survivals at 1 and 2 years following LVAD implantation were 85% and 78%, respectively (Supplementary Fig. 1). Changes in pump speed, physical data and medications during LVAD support are shown in Supplementary Table 1. Of the patients, 26% were on inotropes at 0−1 month post-LVAD implantation, and less than 10% in the other time periods. Between 19% and 29% of patients were on a pulmonary vasodilator at each time period. Beta-blocker use increased over time, increasing from 55% at 1−3 months to 83% after more than 2 years of support. At 1−3 months post-LVAD implantation, PAPi was 2.2 (1.3, 3.5) in patients taking beta-blockers and 1.9 (1.2, 2.9) in those not taking beta-blockers ($P = 0.65$).

Changes in Hemodynamics Following LVAD Implantation

We performed paired comparisons for each parameter between the time periods of 0−6 months and greater than 1 year following LVAD implantation (Fig. 2). Hemodynamic values were averaged in 12 patients for the 0−6 month-period and in 17 patients for the > 1-year period. There was a significant increase of RAP (8 [6, 14] to 11 [8, 14] mmHg, $P = 0.039$) (Fig. 2A) and a significant decrease of PAPi (2.2 [1.4, 3.8] to 1.5 [1.2, 2.0], $P = 0.005$) (Fig. 2H) between the periods. PCWP increased slightly with time but was not statistically significant (14 [10, 18] to 16 [13, 20]) mmHg, $P = 0.077$) (Fig. 2C). We also performed sensitivity analysis using patients who were followed for more than 3 years (n = 22) (Table 2). In the sensitivity analysis, we averaged hemodynamic values in 3 patients for the 0−6 month-period and in 6 patients for the > 1-year period. The trend of RAP (Pre, 8 [4, 17] mmHg; 0−6 months, 6 [3, 13] mmHg; > 1 year, 10 [7, 13] mmHg) was similar to the loess curve in Fig. 1. We would not expect that the HLM coefficients would be significantly different from 0 because of low power in the smaller sample. However, we note that the direction and magnitude of the coefficients was similar to those reported for the whole cohort, and we report these in Supplementary Table 2. As in the analysis of the whole cohort, PAPi decreased significantly in the long-term follow-up period (pre, 2.8 [2.2, 5.8]; 0−6 months, 3.7 [2.1, 6.6]; > 1 year, 1.9 [1.2, 2.2]). The coefficient for linear change was −1.042). The trends of the other parameters were also similar to the loess curves in Fig. 1.

Because the loess curves for RAP (Fig. 1A) and PAPi (Fig. 1G) demonstrated ongoing changes during follow-up, we analyzed these trends with HLM. The RAP trajectory showed a positive quadratic or U-shape (P value for quadratic trajectory < 0.001) over the course of 2 years following LVAD implantation. The PAPi trajectory showed a linear decline (P value for linear trajectory = 0.001). The coefficients and P values of the HLM models are shown in Supplementary Table 3.

The RAP/PCWP ratio increased immediately following LVAD implantation, then decreased for a short period, followed by a gradual increase in the long term (Fig. 3A). In contrast, RVSWI did not change during the course of follow-up (Fig. 3B). PEa decreased with LVAD implantation and remained lower (Fig. 3C), whereas PAC increased and remained higher throughout follow-up (Fig. 3D). In sensitivity analysis, the trends of RAP/PCWP ratio and RVSWI were similar to those of the whole cohort (Table 2).

Comparison of PAPi Trends in Subgroups

We created subgroups based on gender, age, race, ischemic etiology, BSA, and pump type, and we compared the PAPi trend among the subgroups (Fig. 4). There were

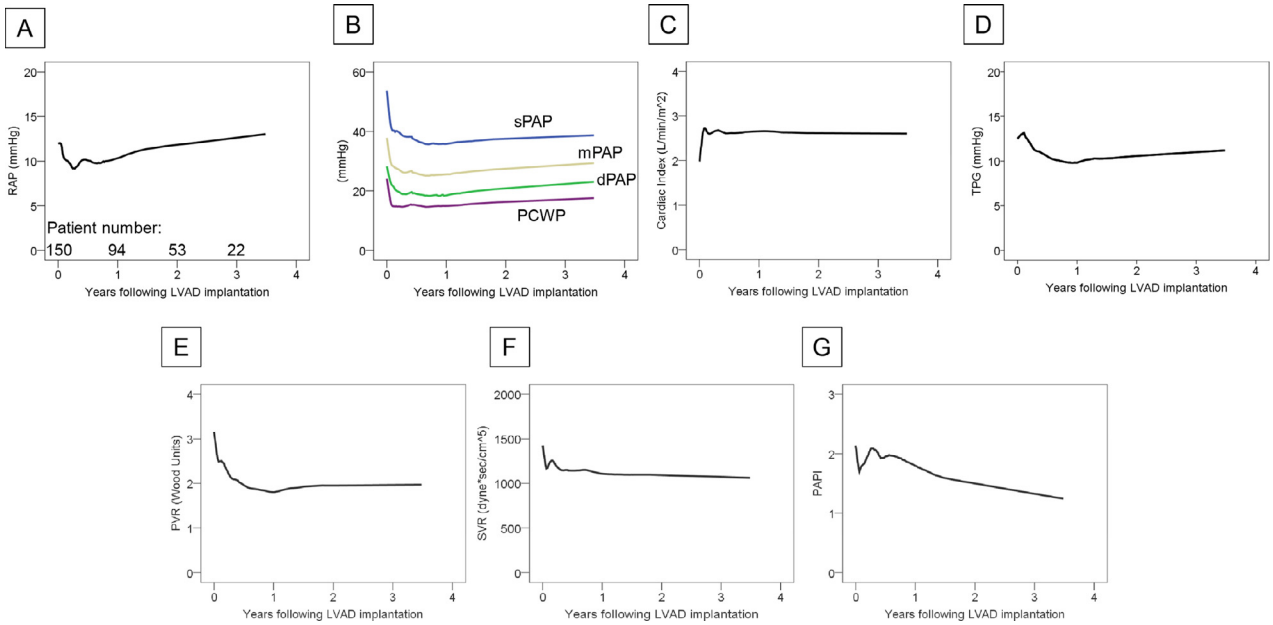

Fig. 1. Loess curves of RAP (A), PAP and PCWP (B), cardiac index (C), TPG (D), PVR (E), SVR (F), and PAPi (G). dPAP, diastolic pulmonary arterial pressure; LVAD, left ventricular assist device; mPAP, mean pulmonary arterial pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SVR, systemic vascular resistance; TPG, transpulmonary pressure gradient.

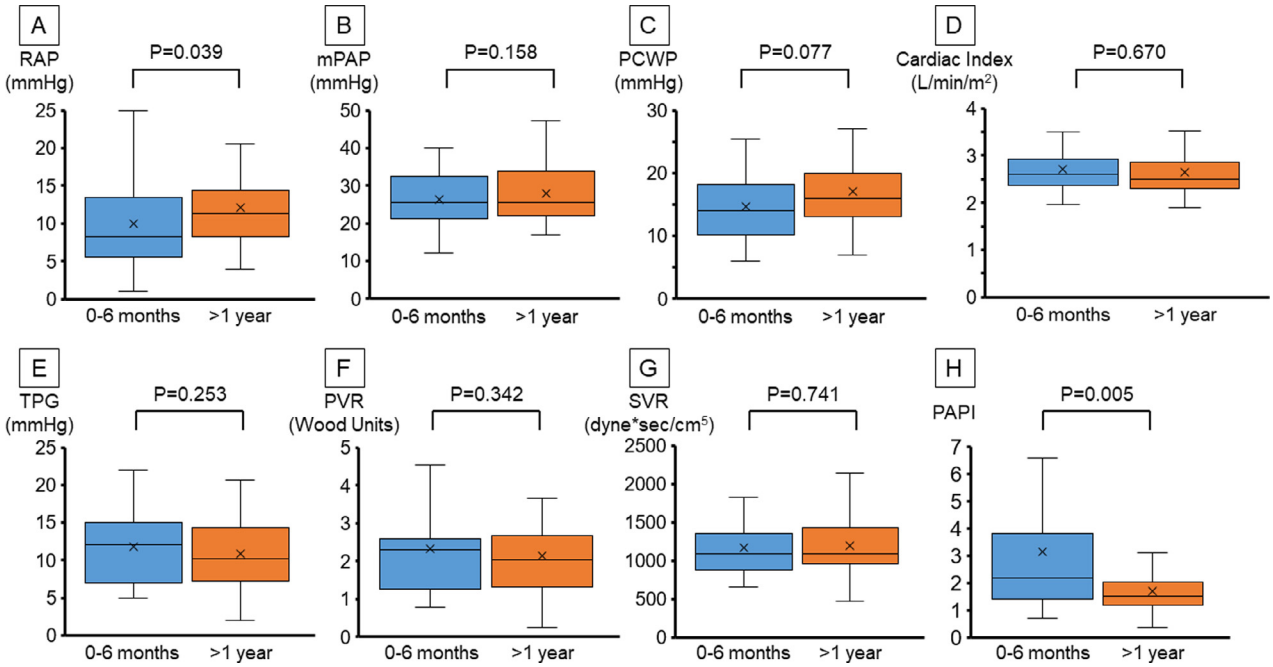

Fig. 2. Paired comparison of consecutive change of RAP (A), mPAP (B), cardiac index (C), TPG (D), PVR (E), SVR (F), and PAPi (G). mPAP, mean pulmonary arterial pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance; TPG, transpulmonary pressure gradient.

significant gender differences in the trajectories (P value for quadratic trajectories = 0.025) (Fig. 4A). PAPi increased in the short term but gradually decreased in the long term in female patients as compared to males. Baseline PAPi prior to LVAD implantation was significantly higher in patients ≥ 59 years of age (P value for intercepts = 0.012) (Fig. 4B); ischemic etiology (P value for intercepts = 0.001) (Fig. 4D); and BSA < 2.0 m^2 (P value for intercepts = 0.030) (Fig. 4E), but the longitudinal trends following LVAD implantation were not significantly different in these groups. The coefficients and P values of HLM models for differences among subgroups are shown in Supplementary Table 4. Longitudinal trends of PAPi were not significantly different when patients

Table 2. Longitudinal Change of Hemodynamic Parameters in Patients Followed for More Than 3 years (N = 22)

	Pre	0−6 months	< 1 year
RAP, mmHg	8 (4, 17)	6 (3, 13)	10 (7, 13)
mPAP, mmHg	33 (23, 41)	23 (17, 27)	24 (20, 29)
PCWP, mmHg	21 (18, 28)	10 (8, 15)	15 (12, 18)
Cardiac index, L/min/m^2	2.0 (1.3, 2.4)	2.7 (2.4, 2.9)	2.6 (2.3, 3.1)
TPG, mmHg	10 (8, 16)	12 (6, 13)	9 (7, 13)
PVR, Wood units	2.9 (2.2, 4.8)	2.3 (1.4, 2.9)	1.6 (1.3, 2.7)
SVR, dyne*sec/cm^5	1600 (1182, 2012)	1268 (1028, 1574)	1106 (963, 1406)
PAPi	2.8 (2.2, 5.8)	3.7 (2.1, 6.6)	1.9 (1.2, 2.2)
RVSWI, mmHg*mL/m^2	451 (303, 729)	458 (353. 662)	432 (311, 678)
RAP/PCWP ratio	0.46 (0.24, 0.58)	0.50 (0.33, 1.00)	0.65 (0.54, 0.89)

mPAP, mean pulmonary arterial pressure; PAPi, pulmonary arterial pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SVR, systemic vascular resistance; TPG, transpulmonary gradient.

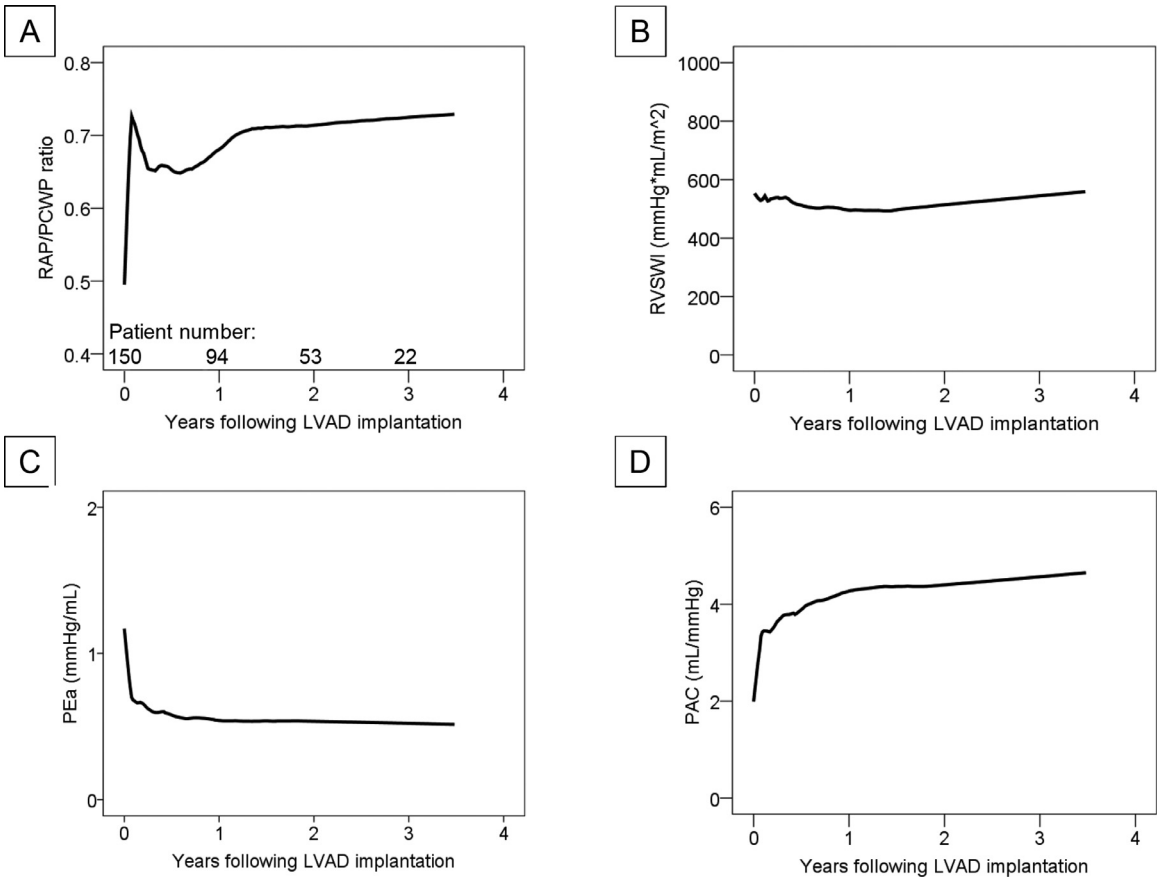

Fig. 3. Loess curves of RAP/PCWP ratio (A), RVSWI (B), PEa (C), and PAC (D). LVAD, left ventricular assist device; PAC, pulmonary arterial compliance; PCWP, pulmonary capillary wedge pressure; PEa, effective pulmonary arterial elastance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index.

were grouped based on preimplant tricuspid annual plane systolic excursion, blood product transfusion during surgery, aortic valve opening at the time of discharge, or leftward shift of the interventricular septum at the time of discharge (Supplementary Figure 2).

Discussion

We described, for the first time, the longitudinal trajectories of hemodynamic parameters following LVAD implantation by using inferential statistics. Despite improvements in left-side filling pressures and CO following LVAD implantation, RAP increased and PAPi decreased over time, suggesting progressive right ventricular (RV) dysfunction. Subgroup analysis showed significant differences in the pattern of change of PAPi based on gender.

Hemodynamics After LVAD Implantation

We have previously demonstrated that hemodynamics are frequently unexpectedly abnormal in otherwise stable patients after LVAD.[3] We have also shown that such

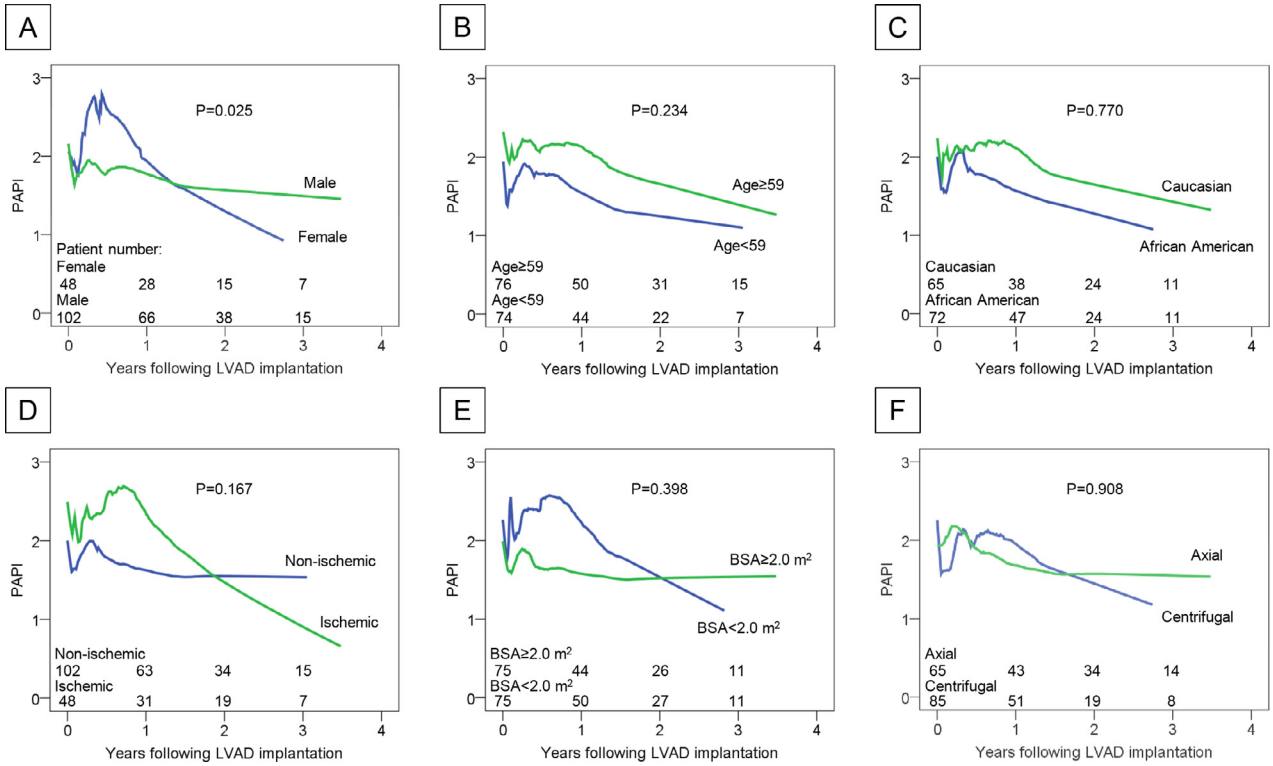

Fig. 4. Loess curves of PAPi in subgroups of gender (A), age (B), race (C), etiology (D), BSA (E) and pump type (F). *P* values represent the difference of quadratic trajectories between the 2 subgroups in each panel. BSA, body surface area; LVAD, left ventricular assist device; PAPi, pulmonary artery pulsatility index.

abnormal hemodynamics were related to worse clinical outcomes.[8–11] However, the trajectories of hemodynamic parameters over time have not been described previously.

The results of this study suggest worsening RV function over time following LVAD implantation. The dominant cause of hemodynamic vulnerability in patients after LVAD is RV dysfunction. RVF is related to poor clinical outcomes and is a major reason for mortality and morbidity. The longitudinal trend of PAPi in this study showed a transient early postoperative decrease and a progressive decline over a long period, which is consistent with previous reports showing that patients with LVADs can suffer from RVF in the late phase as well as in the early postoperative period.[1,6,14] The increase of RAP over a long period also supports the progression of RV dysfunction. The measurements of RV afterload, such as TPG, PVR, PEa, and PAC, were mostly stable over this period, whereas PCWP increased slightly, though not statistically significantly. Therefore, the changes in RAP and PAPi more likely reflect worsening of underlying RV contractile function.

The pathophysiology of RV dysfunction in patients after LVAD can be divided into 3 main etiologies. First, many patients have RV dysfunction prior to device implantation, and that worsens in the context of the increased CO provided by the LVADs. Second, LVAD surgery may be associated with transient trauma to the RV due to RV ischemia, blood product use and inflammation. Finally, the LVAD itself induces septal shift toward the left, reduces septal force generation and reduces left ventricular pressure generation, which contribute to deterioration of RV function. Furthermore, previous studies have also shown that the decrease of left ventricular volume and the leftward shift of the intraventricular septum may reduce tricuspid valve coaptation and cause progressive tricuspid regurgitation, and this could also lead to late-onset RV dysfunction.[15] All these pathophysiologic mechanisms may contribute to the hemodynamic trends we report here; the initial decrease of PAPi may be associated with LVAD surgery; longer-term decrease of PAPi and increase of RAP may be associated with the unfavorable effect of the LVAD itself on RV function. Further investigations into the mechanisms of RV dysfunction are needed.

Interestingly, we did not find significant changes in RVSWI throughout the period of follow-up. In contrast, the trend of the RAP/PCWP ratio, which is also known as a marker of RV dysfunction,[16] was consistent with PAPi. To date, there are no data supporting the use of either RVSWI or PAPi to evaluate RV function after LVAD implantation. However, the calculation of RVSWI incorporates CO and may, therefore, overestimate RV function when CO is being sustained artificially by an LVAD. In contrast, PAPi is a more specific measurement of the reduced pulsatility generated by the RV in this circumstance and may be better at capturing the degree of RV dysfunction independently from overall CO.[17] Whether PAPi or RVSWI predict subsequent admissions for RVF should be investigated in future studies. Taking the trend of PAPi, RAP and RAP/PCWP ratio together, we conclude in this study that there is progressive

RV dysfunction; however, we should point out that it has not been firmly established whether PAPi is a better surrogate for RV dysfunction than RVSWI in this population.

Our findings regarding longitudinal hemodynamic trends in patients with LVADs are different from those of 2 previous studies, which found an overall improvement in RV parameters during long-term follow-up.[18,19] It is important to note that the larger of these 2 studies excluded, by design, patients taking inotropes or pulmonary vasodilators in order to examine RV load independent of medications that might impact the physiology.[18] The smaller study also excluded patients taking inotropes and was limited to a single device (HeartMate II).[19] In contrast, our study did not exclude these patients so as to reduce selection bias and provide a more comprehensive view of the clinical course following LVAD implantation. These differences in study populations may explain the differences in hemodynamic trends.

Subgroup Analyses of PAPi Trends

Some reports have previously shown the predictors of late-onset RVF following LVAD implantation;[6,15] however, the longitudinal trend of PAPi and its predictors were previously unknown. We performed subgroup analyses based on patients' demographics. Our primary subgroup finding was a difference in the PAPi trend based on gender; in women, PAPi rose more initially and then declined to a greater degree in the long term.

This result is consistent with previous reports. Blumer et al reported that female patients with LVADs were at greater risk of RVF.[20] Defilippis et al also showed that female patients with LVADs experienced increased mortality and worse clinical status than male patients.[21] The reasons female patients have greater decreases in PAPi over time remain unclear, but 1 speculation is that women are often referred for LVAD implantation later, when their HF is more advanced. This could potentially explain the increased risk of RVF following LVAD implantation.[20] Another potential reason is that LVAD flow might be too high for female patients and those with small BSAs. This could explain the initial increase of PAPi due to aggressive reduction of RV afterload and the subsequent worsening of RV function associated with high LVAD flow. Further investigations are expected to elucidate the mechanism of significant difference in the PAPi trend based on gender.

Study Limitations

Several potential limitations of this study should be considered. First, this was a retrospective cohort, and the timing and number of RHCs varied across the patient cohort. With a limited number of measurements, we had less power to identify what might have been clinically significant subgroup differences. Further investigations are required to elucidate fully the characteristics that predict the trend of PAPi and the mechanism of significant PAPi reduction in female patients. Second, this was an observational analysis that may be affected by selection bias. Some of the RHCs were performed in response to clinical symptoms, which may influence the findings of this study. In particular, RVF may be more prevalent in this cohort than in the LVAD population as a whole. Third, as noted above, the lack of change in RVSWI could be interpreted to mean that RV function is, in fact, preserved over time. Currently, there are no data to determine whether RVSWI or PAPi is a better measurement of RV function in patients with LVADs. Finally, we did not consider the change of therapeutics during the follow-up period. Optimization of LVAD speed and medical therapy were commonly performed according to each physician's discretion, and this could have affected the trends of hemodynamic parameters. However, we believe it is unlikely that PAPi was influenced by inotrope discontinuation because PAPi continued to decline outside of the perioperative period. We also did not find an association between beta-blocker use and PAPi at the 1−3 months timepoint.

Conclusions

We have described the longitudinal trajectories of hemodynamic parameters following LVAD implantation. Despite improvement in left-side filling pressures and CO and no change in RVSWI, RAP increased and PAPi decreased over time, suggesting progressive RV dysfunction.

Disclosures

Takeo Fujino receives financial support from MSD Life Support Foundation and Mochida Memorial Foundation for Medical and Pharmaceutical Research; Nir Uriel receives grant support from Abbott and Medtronic; Gabriel Sayer is a consultant for Medtronic; Valluvan Jeevanandam is a consultant for Abbott. The other authors report no conflicts.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2020.01.020.

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