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Clinical Investigation

Decoupling Between Diastolic Pulmonary Arterial Pressure and Pulmonary Arterial Wedge Pressure at Incremental Left Ventricular Assist Device (LVAD) Speeds Is Associated With Worse Prognosis After LVAD Implantation

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ABSTRACT

Background: Decoupling between diastolic pulmonary arterial pressure (dPAP) and pulmonary arterial wedge pressure (PAWP) is an index of pulmonary vasculature remodeling and provides prognostic information. Furthermore, decoupling may change during incremental left ventricular assist device (LVAD) speed changes.

Methods and Results: In this prospective study, patients underwent an echocardiographic and hemodynamic ramp test after LVAD implantation and were followed for 1 year. The change in decoupling (dPAP − PAWP) between the lowest and highest LVAD speeds during the ramp test was calculated. Survival and heart failure admission rates were assessed by means of Kaplan-Meier analysis. Eighty-seven patients were enrolled in the study: 54 had a Heartmate II LVAD (60.8 ± 9.3 years of age and 34 male) and 33 had an HVAD LVAD (58.6 ± 13.2 years of age and 20 male). Patients who experienced greater changes in decoupling (Δdecoupling >3 mm Hg) had a persistently elevated dPAP at incremental LVAD speed and had worse 1-year heart failure readmission−free survival compared with the group without significant changes in the degree of decoupling (41% vs 75%; $P = .001$).

Conclusions: An increase in decoupling between dPAP and PAWP at incremental LVAD speed changes was associated with worse prognosis in LVAD patients. (*J Cardiac Fail 2018;00:1−8*)

Key Words: Ramp, hemodynamics, unloading, pulmonary hypertension.

Pulmonary hypertension (PH) is one of the critical comorbidities in advanced heart failure (HF).[1,2] Indices of PH such as mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), and transpulmonary arterial pressure gradient improve after left ventricular assist device (LVAD) implantation, mainly owing to left ventricular unloading.[3,4] Several investigators demonstrated in small cohorts that patients whose elevated PVRs were normalized after LVAD implantation had post−heart transplantation survival rates similar to those without PH.[5,6] In contrast, Tsukashita et al recently showed in a moderately large cohort that in-hospital mortality after heart transplantation was higher in patients with a pre-LVAD PVR ≥5 Wood units compared with those with lower PVR, despite the fact that the elevated PVRs were normalized after LVAD implantation.[7] They speculated that unknown indexes of PH might still exist and affect post-transplantation outcome.

Lately, our group demonstrated that "decoupling," which is defined as an excessive separation between the diastolic pulmonary arterial pressure (dPAP) and the pulmonary

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arterial wedge pressure (PAWP)[8] and represents combined pre-capillary and post-capillary PH, is a strong predictor of post-LVAD HF-free survival.[9] The aim of the present study was to assess if the degree of decoupling changes with incremental changes in LVAD speed during a hemodynamic ramp test,[10] and whether changes in the degree of decoupling predict clinical outcomes.

Methods

Patient Selection

We prospectively collected data on clinically stable outpatients with LVADs (HVAD or Heartmate II) who were evaluated with a hemodynamic ramp testing and followed at our institution. All patients received guideline-directed medical therapy during the study period.[11] Patients with suspicion for device malfunction were excluded. Written informed consent was obtained from every participant before the ramp test. The study protocol was approved by the Institutional Review Board at the University of Chicago before starting.

Ramp Test Protocol

Patients underwent an echocardiographic and hemodynamic LVAD speed ramp study in the cardiac catheterization laboratory according to a previously detailed protocol.10 Cardiac output and cardiac index (CI) were calculated by means of the direct Fick method. Two-dimensional echocardiographic parameters, including left ventricular dimension and valve features, were measured as detailed previously.[12]

Pump speeds were lowered to 2300 rpm in patients with HVAD and 8000 rpm in patients with Heartmate II at the initiation of the study. After a 5-minute stabilization period, echocardiographic and hemodynamic values were taken. Then, device speeds were increased in 100-rpm increments for HVAD patients and 400-rpm increments for Heartmate II patients. After a 2-minute stabilization period, the same parameters were recorded. This procedure was repeated up to a maximum speed of 3200 rpm for HVAD patients and 12,000 rpm for Heartmate II patients. Eventually, all echocardiographic and hemodynamic data at each LVAD speed setting (from the lowest to the highest) were completed.

At the conclusion of each test, the attending cardiologist reviewed the results and the device was set at the speed which yielded an optimal hemodynamic profile, as defined by central venous pressure (CVP) <12 mm Hg, PAWP <18 mm Hg, and CI >2.2 $L \cdot min^{-1} \cdot m^{-2}$; secondary goals of speed optimization included intermittent aortic valve opening and minimal mitral regurgitation.[13]

Variables Evaluated

Patient preoperative background characteristics, including demographic, echocardiographic, and hemodynamic data, were obtained within the 1-month period preceding LVAD implantation. During the ramp test, hemodynamic and echocardiographic data were obtained per protocol. All hemodynamic data were obtained at end-expiration and manually reviewed by the attending cardiologist. Decoupling was defined as the difference between dPAP and PAWP.[9] For example, when dPAP is 14 mm Hg and PAWP is 9 mm Hg, decoupling is calculated to be 5 mm Hg.

Echocardiographic and hemodynamic changes at incremental LVAD speeds from the lowest to highest speed setting, including that of decoupling, were calculated. For example, when decoupling is 2 mm Hg at the lowest LVAD speed and 6 mm Hg at the highest LVAD speed, the change in decoupling (Δdecoupling) is calculated to be 4 mm Hg.

All patients were followed at our institution for 1 year at the LVAD speed set according to the results of the ramp test. HF readmission or all-cause death was recorded during the 1-year observational period.

Statistical Analyses

The primary end point of this study was the composite of all-cause mortality and HF readmission from the time of the ramp test (time 0) through 1-year follow-up. Continuous variables were presented as mean and SD unless otherwise described, and were compared between groups with the use of the unpaired *t* test or Mann-Whitney *U* test as appropriate. Continuous data between the lowest LVAD speed and the highest LVAD speed were compared by means of paired *t* test. Categoric variables were compared between groups with the use of the chi-square test or Fisher exact test as appropriate.

A cutoff value of Δdecoupling during ramp test was calculated with the use of receiver operating characteristic analysis with the end point of death or HF admission during 1 year as a point minimizing the distance from the curve to the top left corner of the graph, and patients were divided into 2 groups by this cutoff. Patient prognosis stratified by Δdecoupling during ramp test was assessed with the use of Kaplan-Meier analysis and Cox proportional hazards analysis, and compared by means of log-rank test.

Also in the multivariate Cox proportional hazards analysis, the prognostic impact of Δdecoupling was adjusted by the other clinical variables that were significant in the univariate analyses with $P < .05$ Statistical analyses were performed with the use of SPSS Statistics 22 (SPSS, Chicago, Illinois). A 2-tailed *P* value of <.05 was considered to be significant.

Results

Baseline Characteristics

Eighty-seven LVAD patients (60.0 ± 10.9 years old, 54 male, 54 Heartmate II, and 33 HVAD) were enrolled (Table 1). The majority of patients were implanted as destination therapy (78%), and 37 (43%) had an ischemic etiology for their cardiomyopathy. Ramp tests were performed at a median 307 days after LVAD implantation.

Table 1. Comparison of Baseline Preoperative Characteristics

Characteristic	Total (n = 87)	Δdecoupling >3 mm Hg (n = 48)	Δdecoupling ≤3 mm Hg (n = 39)	*P* Value
Demographics				
Age, y	60.0 ± 10.9	60.3 ± 9.2	59.6 ± 12.8	.77
Sex (male)	54 (62%)	30 (63%)	24 (62%)	.55
Race (white)	51 (59%)	26 (54%)	25 (64%)	.37
Body mass index	29.8 ± 7.2	31.1 ± 8.2	28.1 ± 5.5	.087
Ischemic etiology	37 (43%)	18 (38%)	19 (49%)	.20
Destination therapy	68 (78%)	38 (79%)	30 (77%)	.50
LVAD duration before ramp test, d	494.5 ± 533.1	510.8 ± 563.6	474.5 ± 499.7	.75
Heartmate II	54 (62%)	36 (75%)	18 (46%)	.006*
HVAD	33 (38%)	12 (25%)	21 (54%)	–
Comorbidity				
Hypertension	48 (55%)	27 (56%)	21 (54%)	.50
Diabetes mellitus	33 (38%)	21 (44%)	12 (31%)	.15
Atrial fibrillation	33 (38%)	16 (33%)	17 (44%)	.22
History of ventricular arrhythmia	18 (21%)	9 (19%)	9 (23%)	.41
Chronic obstructive pulmonary disease	16 (18%)	10 (21%)	6 (15%)	.36
Obstructive sleep apnea	15 (17%)	11 (23%)	4 (10%)	.10
Echocardiography				
LVDd, cm	7.35 ± 1.14	7.51 ± 1.22	7.15 ± 1.01	.16
Hemodynamics				
CVP, mm Hg	11.4 ± 7.0	12.8 ± 7.7	9.8 ± 5.8	.063
mPAP, mm Hg	36.1 ± 11.2	37.4 ± 10.9	34.5 ± 11.4	.25
dPAP, mm Hg	27.0 ± 10.1	28.6 ± 9.6	25.1 ± 10.5	.13
PAWP, mm Hg	23.5 ± 9.1	24.4 ± 8.5	22.4 ± 9.8	.34
CI, $L \cdot min^{-1} \cdot m^{-2}$	1.95 ± 0.67	1.85 ± 0.70	2.07 ± 0.62	.16
PVR, WU	3.79 ± 2.94	3.91 ± 2.64	3.64 ± 3.30	.70
PAC, mL/mm Hg	1.84 ± 0.89	1.88 ± 0.89	1.79 ± 0.90	.64
Decoupling, mm Hg	3.5 ± 6.5	4.2 ± 5.3	2.7 ± 7.7	.31

LVAD, left ventricular assist device; LVDd, left ventricular diastolic diameter; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; WU, Woods units; PAC, pulmonary artery compliance.

*$P < .05$ by chi-square test.

Change in Decoupling During LVAD Speed Change

Among all patients, as speed was changed from the lowest to the highest setting, dPAP decreased from 20.8 ± 7.7 to 15.9 ± 5.8 mm Hg, PAWP decreased from 17.4 ± 7.3 to 9.2 ± 5.3 mm Hg, and decoupling increased from 3.4 ± 5.0 to 6.7 ± 4.4 mm Hg ($P < .001$ for all).

Δdecoupling (the change in decoupling from low to high speed) averaged 3.4 ± 0.6 mm Hg, ranging from −7 to +18 mm Hg. Forty-eight patients (55%) had Δdecoupling >3 mm Hg, which means, for example, when decoupling at the lowest speed is 3 mm Hg, decoupling at the highest speed is >6 mm Hg (Fig. 1). This cutoff of Δdecoupling at 3 mm Hg was derived from the receiver operating characteristic analysis with a sensitivity of 0.757 and a specificity of 0.600.

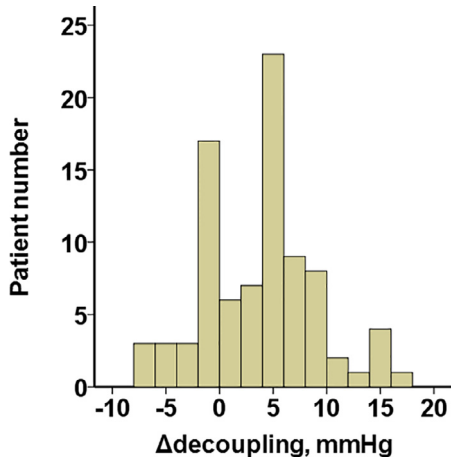

Fig. 1. Distribution of the changes in decoupling between minimum and maximal left ventricular assist device speed.

Comparison Between the Δdecoupling >3 mm Hg Group and the Δdecoupling ≤3 mm Hg Group

A higher proportion of Heartmate II patients than HVAD patients had Δdecoupling >3 mm Hg. All other preoperative background characteristics, including mPAP, showed no significant differences between the Δdecoupling >3 mm Hg group and the Δdecoupling ≤3 mm Hg group (Table 1).

After LVAD implantation, the Δdecoupling >3 mm Hg group had a larger left ventricular diastolic diameter and higher CVP compared with the Δdecoupling ≤3 mm Hg group (Table 2; $P < .05$ for both).

During the ramp test, patients with Δdecoupling >3 mm Hg had less reduction in dPAP (ie, persistently elevated dPAP) and a greater reduction in PAWP compared with patients with Δdecoupling <3 mm Hg (Table 3; $P < .05$ for both). As a result, decoupling increased significantly from 1.0 ± 4.6 to 8.2 ± 4.1 mm Hg in the Δdecoupling

Table 2. Comparison of Post-LVAD Clinical Parameters.

Parameter	Total (n = 87)	Δdecoupling >3 mm Hg (n = 48)	Δdecoupling ≤3 mm Hg (n = 39)	*P* Value
LVAD speed, rpm				
Heartmate II (n = 54)	9179.4 ± 389.1	9175.3 ± 432.1	9187.8 ± 295.6	.91
HVAD (n = 33)	2679.4 ± 146.2	2670.0 ± 155.7	2684.8 ± 144.1	.79
LVDd, cm	6.00 ± 1.16	6.54 ± 1.17	5.94 ± 1.00	.002*
CVP, mm Hg	8.6 ± 5.0	10.7 ± 6.5	8.1 ± 4.7	.041*
mPAP, mm Hg	24.5 ± 7.5	27.6 ± 7.8	26.8 ± 9.2	.59
dPAP, mm Hg	18.4 ± 6.7	20.4 ± 6.8	21.2 ± 8.8	.93
PAWP, mm Hg	13.7 ± 5.9	14.6 ± 5.7	12.5 ± 6.1	.098
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.68 ± 0.63	2.64 ± 0.68	2.73 ± 0.56	.50
PVR, WU	2.19 ± 1.29	2.03 ± 1.19	2.39 ± 1.39	.21
PAC, mL/mm Hg	3.99 ± 1.69	3.88 ± 1.83	4.14 ± 1.49	.49
Decoupling, mm Hg	4.7 ± 4.7	3.8 ± 4.7	5.8 ± 4.4	.10

Abbreviations as in Table 1.
*$P < .05$ by unpaired *t* test or Mann-Whitney *U* test as appropriate.

Table 3. Comparison of Changes in Each Clinical Variable Between the Lowest and Highest LVAD Speeds

Variable	Total (n = 87)	Δdecoupling >3 mm Hg (n = 48)	Δdecoupling ≤3 mm Hg (n = 39)	*P* Value
LVDd, cm	−1.22 ± 1.32	−1.29 ± 1.60	−1.11 ± 0.86	.60
CVP, mm Hg	−1.22 ± 2.74	−1.4 ± 2.9	−1.0 ± 2.5	.51
mPAP, mm Hg	−5.5 ± 7.0	−4.8 ± 7.5	−6.3 ± 6.5	.34
dPAP, mm Hg	−4.6 ± 5.5	−3.3 ± 5.1	−6.4 ± 5.8	.008*
PAWP, mm Hg	−8.0 ± 6.6	−10.2 ± 6.5	−5.2 ± 5.5	<.001*
CI, $L \cdot min^{-1} \cdot m^{-2}$	0.70 ± 0.83	0.81 ± 0.97	0.55 ± 0.60	.14
Decoupling, mm Hg	3.4 ± 5.3	7.2 ± 3.5	−1.2 ± 2.8	<.001*

Abbreviations as in Table 1.
*$P < .05$ by unpaired *t* test or Mann-Whitney *U* test as appropriate.

>3 mm Hg group (Fig. 2A; $P < .001$), whereas decoupling decreased significantly from 6.1 ± 4.2 to 4.9 ± 4.2 mm Hg in the Δdecoupling ≤3 mm Hg group (Fig. 2B; $P = .009$). PAWP at the lowest LVAD speed was higher in the Δdecoupling >3 mm Hg group ($P = .004$), whereas dPAP at the highest LVAD speed was higher in the Δdecoupling >3 mm Hg group ($P = .048$; Appendix Table 1).

At the set LVAD speed, the Δdecoupling >3 mm Hg group had a significantly larger left ventricular diastolic diameter (Table 4; $P = .007$) and a numerically higher CVP

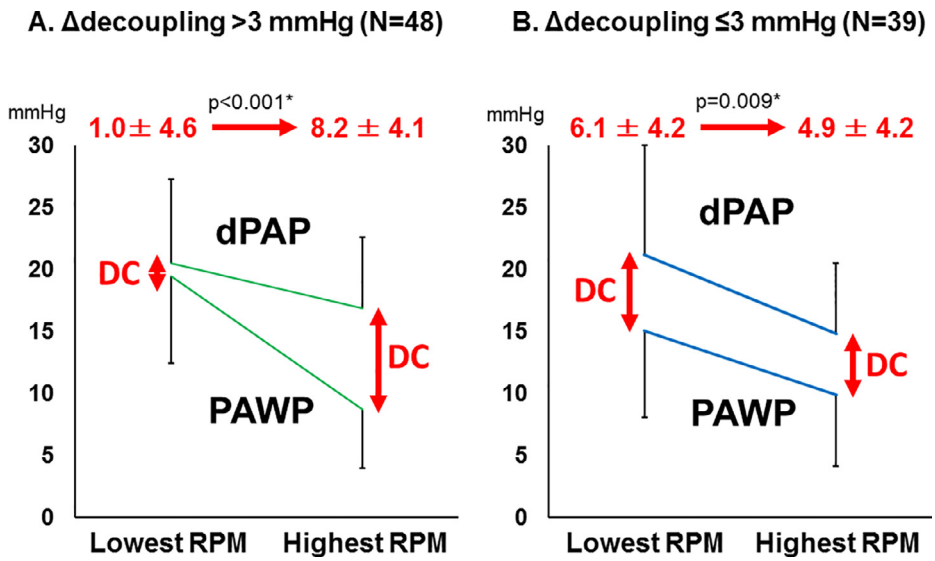

Fig. 2. Changes in diastolic pulmonary arterial pressure (dPAP), pulmonary arterial wedge pressure (PAWP), and decoupling (DC) between minimum and maximal left ventricular assist device speed in (A) Δdecoupling >3 mm Hg group and (B) Δdecoupling ≤3 mm Hg group. *$P < .05$ by paired *t* test.

Table 4. Comparison of Clinical Parameters at Set LVAD Speed

Parameter	Total (n = 87)	Δdecoupling >3 mm Hg (n = 48)	Δdecoupling ≤3 mm Hg (n = 39)	*P* Value
LVAD speed, rpm				
Heartmate II (n = 54)	10,933.3 ± 699.3	11,011.1 ± 761.9	10,777.8 ± 539.7	.25
HVAD (n = 33)	3090.9 ± 158.8	3108.3 ± 173.0	3081.0 ± 153.7	.64
LVDd, cm	5.96 ± 1.20	6.27 ± 1.30	5.59 ± 0.95	.007*
CVP, mm Hg	8.7 ± 5.0	9.8 ± 5.6	7.3 ± 3.8	.068
mPAP, mm Hg	24.8 ± 7.4	25.9 ± 7.9	23.4 ± 6.5	.11
dPAP, mm Hg	18.4 ± 6.5	19.2 ± 6.7	17.5 ± 6.1	.21
PAWP, mm Hg	13.0 ± 5.5	13.9 ± 5.5	11.8 ± 5.4	.074
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.68 ± 0.60	2.72 ± 0.70	2.63 ± 0.46	.51
PVR, WU	1.15 ± 0.93	1.07 ± 1.05	1.24 ± 0.77	.39
PAC, mL/mm Hg	3.87 ± 1.59	3.77 ± 1.54	3.99 ± 1.66	.53
Decoupling, mm Hg	5.5 ± 4.3	5.3 ± 4.5	5.7 ± 3.9	.69

Abbreviations as in Table 1.
*$P < .05$ by unpaired *t* test or Mann-Whitney *U* test as appropriate.

and PAWP compared with patients with the Δdecoupling <3 mm Hg group ($P = .07$ for both).

Prognostic Impact of the Change in Decoupling During Ramp Test

Among the group with Δdecoupling >3 mm Hg, 8 patients (17%) died and 21 (44%) had an HF admission following the ramp test. In the comparison group, 5 patients (13%) died and 7 (18%) had an HF admission.

Patients with Δdecoupling >3 mm Hg had a significantly worse HF readmission−free survival compared with those without during the 1-year study period (Fig. 3; 41% vs 75%; $P = .001$). In the multivariate Cox hazard regression analyses, Δdecoupling >3 mm Hg was a significant predictor of death and HF readmission, with unadjusted hazard ratios of 3.2 (95% confidence interval [CI] 1.5−6.9; $P = .002$) and 2.4 (95% CI 1.1−5.3; $P = .032$), respectively, when adjusted by other

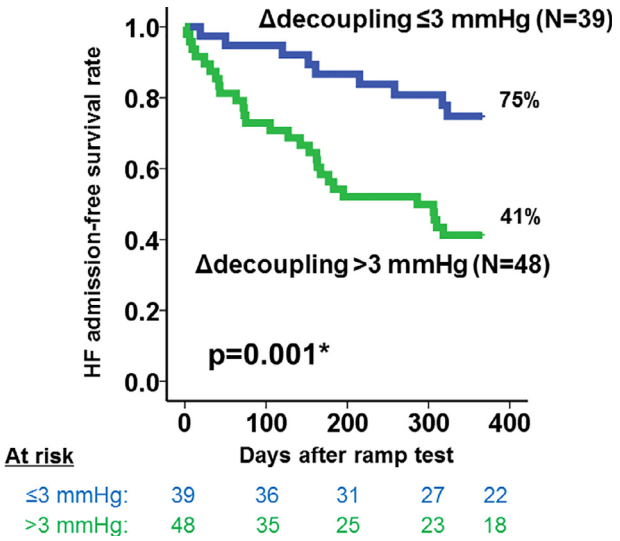

Fig. 3. Heart failure (HF) admission−free survival rate in Δdecoupling >3 mm Hg group and Δdecoupling ≤3 mm Hg group after ramp test. *$P < .05$ by log-rank test.

variables significant in the univariate analyses (CVP, PAWP, and decoupling >5 mm Hg at set LVAD speed; Table 5).

Similar results were found in the subgroup analysis of each device type. In patients with Heartmate II (n = 54), 1-year HF readmission−free survival was lower in Δdecoupling >3 mm Hg compared with Δdecoupling ≤3 mm Hg (42% vs 72%; $P = .028$), with a hazard ratio of 2.9 (95% CI 1.1−7.6; $P = .035$). In patients with HVAD (n = 33) also, 1-year HF readmission-free survival was lower in Δdecoupling >3 mm Hg compared with Δdecoupling ≤3 mm Hg (39% vs 77%; $P = .028$), with a hazard ratio of 3.7 (95% CI 1.1−12.5; $P = .040$).

Discussion

In this prospective study, we analyzed the prognostic implications of a change in the degree of decoupling between the lowest and highest LVAD speeds during a hemodynamic ramp study. Our main findings are: (1) Δdecoupling >3 mm Hg was common in clinically stable outpatients receiving LVAD support regardless of the perioperative existence of PH, (2) The main mechanism of the increase in decoupling at incremental LVAD speeds was persistent elevation of dPAP despite decreases in PAWP, and (3) Δdecoupling >3 mm Hg was a strong predictor of the composite end point of death or HF readmission as demonstrated by multivariate analyses.

Change in the Degree of Decoupling With Incremental LVAD Speed Changes

We previously demonstrated that decoupling between dPAP and PAWP indicates remodeling to the pulmonary vasculature and is associated with a worse prognosis in LVAD patients.[9] In the present study, we focused on the change in the degree of decoupling between the lowest and highest LVAD speeds, which may represent a patient-specific index of decoupling that is independent from the LVAD speed setting.

This technique assesses how dynamic the pulmonary vasculature is, measuring its ability to adapt to decreases in post-capillary (ie, left ventricular [LV]) pressure. In the

Table 5. Cox Proportional Hazards Regression Analyses for Death or Heart Failure Readmission

Factor	Univariate Analysis HR (95% CI)	*P* Value	Multivariate Analysis HR (95% CI)	*P* Value
Age, y	1.0 (1.0−1.0)	.92		
Sex (male)	1.3 (0.7−2.5)	.45		
Race (white)	1.4 (0.9−2.0)	.11		
Body mass index	1.0 (1.0−1.0)	.71		
Ischemic etiology	0.7 (0.4−1.4)	.37		
Destination therapy	1.7 (0.7−4.0)	.26		
LVAD duration before ramp test, d	1.0 (1.0−1.0)	.59		
Heartmate II vs HVAD	1.5 (0.7−3.0)	.26		
Δdecoupling >3 mm Hg	3.2 (1.5−6.9)	.002*	2.4 (1.1−5.3)	.032*
LVDd at set LVAD speed, cm	1.2 (0.9−1.6)	.18		
CVP at set LVAD speed, mm Hg	1.1 (1.0−1.1)	.024*	1.0 (0.9−1.1)	.72
PAWP at set LVAD speed, mm Hg	1.1 (1.0−1.2)	.008*	1.1 (1.0−1.2)	.11
CI at set LVAD speed, $L \cdot min^{-1} \cdot m^{-2}$	1.0 (0.6−1.8)	.97		
PVR at set LVAD speed, WU	0.7 (0.4−1.2)	.25		
PAC at set LVAD speed, mL/mm Hg	1,0 (0.8−1.2)	.86		
Decoupling >5 mm Hg at set LVAD speed	2.9 (1.4−6.2)	.005*	2.2 (1.0−4.8)	.059

HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.
*$P < .05$ by Cox proportional hazards regression analyses.

group of patients whose degree of decoupling increased during the ramp study, the primary hemodynamic finding was a minimal decrease in dPAP despite incremental decreases in PAWP with speed changes. These patients exhibited evidence of pulmonary vascular remodeling that is not responsive to acute decreases in post-capillary pressure through LV unloading.

Importantly, there was no difference in mPAP, PVR, or pulmonary arterial compliance among patients with increases in the degree of decoupling and those without. Therefore, Δdecoupling represents an independent marker of pulmonary vascular disease. By evaluating the response of the pulmonary vasculature to acute decreases in LV pressure, Δdecoupling provides an assessment of whether pulmonary vascular abnormalities are "fixed" or "reversible." Measurement of Δdecoupling during ramp testing may be used to identify pulmonary vascular disease in all LVAD patients, even in patients without evidence of PH with the use of conventional markers. Further studies that incorporate pathologic findings or pulmonary function assessments may provide further insight into the difference between decoupling abnormalities measured at a fixed LVAD speed or during dynamic LVAD speed changes.

Interestingly, the group with increased Δdecoupling had a larger left ventricle and higher CVP after LVAD implantation. The larger left ventricle may reflect a greater degree of LV remodeling in these patients, possibly indicating a longer duration of HF, which may have promoted a greater degree of vascular remodeling. The elevation in CVP reflects the effect of pulmonary vascular remodeling on the right ventricle. Pulmonary vascular disease creates an increase in right ventricular afterload, impairing right ventricular contractile function. It is possible that decreased forward flow from the right ventricle at higher LVAD speeds may have also contributed to the sharper drop in PAWP among the group with increased Δdecoupling.

Prognostic Impact of Δdecoupling

Δdecoupling was a significant predictor of the composite of mortality and HF readmission, even when it was adjusted by clinical variables, including the absolute degree of decoupling at set LVAD speed, and as analyzed separately in each device group. This effect was primarily driven by an increase in HF admissions, reflecting the decremental effect of pulmonary vascular disease on right ventricular function, which was suggested by the higher CVP in the group with increased decoupling during the ramp study. The group with increased Δdecoupling had worse outcomes even though the absolute degree of decoupling at their set speed was similar to the other group, highlighting the value of a dynamic assessment of the pulmonary vasculature.[14]

Future Directions and Study Limitations

It is uncertain whether Δdecoupling may change during long-term LVAD support. Repeated ramp tests may answer this question.[15] We think that Δdecoupling is a patient-specific index of fixed PH, but whether optimization of LVAD speed or introduction of pulmonary vasodilators improves Δdecoupling needs further study. The ongoing SOPRANO study (Clinical Study to

Appendix Table 1. Comparison of PAWP and dPAP at the Lowest LVAD Speed and at the Highest LVAD Speed

Parameter	Δdecoupling >3 mm Hg (n = 48)	Δdecoupling ≤3 mm Hg (n = 39)	*P* Value
Lowest LVAD speed			
PAWP, mm Hg	19.5 ± 7.0	15.0 ± 6.9	.004*
dPAP, mm Hg	20.5 ± 6.8	21.2 ± 8.8	.69
Highest LVAD speed			
PAWP, mm Hg	8.8 ± 4.8	9.9 ± 5.8	.35
dPAP, mm Hg	17.0 ± 5.7	14.8 ± 5.7	.048*

Abbreviations as in Table 1.
*$P < .05$ by unpaired *t* test or Mann-Whitney *U* test as appropriate.

Assess the Efficacy and Safety of Macitentan in Patients With Pulmonary Hypertension After Left Ventricular Assist Device Implantation; ClinicalTrials.gov identifier NCT02554903) will provide further information about the efficacy of pulmonary vasodilator therapy in the LVAD population.

Several potential limitations of this study should be considered. First, this was a single-center study with a moderate-size patient cohort. Second, we did not specify any medication adjustments during the study period; patient management was dependent on the clinical decisions of multiple attending physicians. The physicians were blinded to the data on decoupling, and it seems unlikely to have changed management. Third, we did not show longitudinal data showing how Δdecoupling and other clinical parameters vary during long-term LVAD support. Fourth, LVAD duration before the ramp testing varied widely. This wide variation may set up a time bias, because it relates to subsequent outcome events. However, all participants were clinically stable outpatients until the time of the ramp test, and thus such bias may have been minimized. Consistently, 1-year HF readmission−free survivals were similar regardless of ramp test timing ($P = .65$; 58% in the <1 year group and 53% in the ≥1 year group). Fifth, we included Heartmate II and HVAD patients, and our results may not simply be adopted in patients with other devices, such as Heartmate 3. More Heartmate II patients experienced Δdecoupling >3 mm Hg compared with the HVAD group. The association between device type and decoupling needs further evaluation. Sixth, we can not exclude the possibility of regression to the mean, in which we would expect the group with the high PAWP at low speed (the Δdecoupling >3 mm Hg group) to have a greater change in PAWP during ramp testing as the value returns toward the mean. Seventh, Δdecoupling was negative in several patients. We do not have an appropriate physiologic explanation of this phenomenon and can not completely exclude the effects of catheter whip artifacts. Finally, we used a cutoff of Δdecoupling >3 mm Hg derived from our own dataset, and this value has not undergone external validation, which may lead to exaggeration of the true differences between the 2 groups. A next step would be to confirm the validity of this value in another dataset.

Conclusion

An increase in decoupling between dPAP and PAWP during incremental LVAD speed changes may be a sign of pulmonary vascular remodeling and is associated with worse prognosis in LVAD patients.

Disclosures

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