

# Decoupling Between Diastolic Pulmonary Artery Pressure and Pulmonary Capillary Wedge Pressure as a Prognostic Factor After Continuous Flow Ventricular Assist Device Implantation

**BACKGROUND:** A cohort of heart failure (HF) patients receiving left ventricular assist devices (LVADs) has decoupling of their diastolic pulmonary artery pressure and pulmonary capillary wedge pressure. However, the clinical implications of this decoupling remain unclear.

**METHODS AND RESULTS:** In this prospective study, patients with LVADs underwent routine invasive hemodynamic ramp testing with right heart catheterization, during which LVAD speeds were adjusted. Inappropriate decoupling was defined as a >5 mm Hg difference between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure. The primary outcomes of survival and heart failure readmission rates after ramp testing were assessed. Among 63 LVAD patients (60±12 years old and 25 female [40%]), 27 patients (43%) had inappropriate decoupling at their baseline speed. After adjustment of their rotation speed during ramp testing, 30 patients (48%) had inappropriate decoupling. Uni/multivariable Cox analyses demonstrated that decoupling was the only significant predictor for the composite end point of death and heart failure readmission during the 1 year following the ramp study (total of 18 events; hazards ratio, 1.09; 95% confidence interval, 1.04–1.24;  $P<0.05$ ). Furthermore, normalization of decoupling ( $n=8$ ) during ramp testing was significantly associated with higher 1-year heart failure readmission-free survival rate compared with the non-normalized group ( $n=19$ , 100% versus 53%;  $P=0.035$ ).

**CONCLUSIONS:** The presence of inappropriate decoupling was associated with worse outcomes in patients with LVADs. Prospective, large-scale multicenter studies to validate the result are warranted.

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### WHAT IS NEW?

- Assessment of the pulmonary vascular system is an established practice in durable left ventricular assist device therapy and pulmonary vascular abnormalities can be quantified in a number of ways.
- Inappropriate decoupling, defined as difference  $>5$  mmHg between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure, e.g. the diastolic pulmonary pressure gradient (DPG), was a strong prognostic predictor of death and HF readmission rates in left ventricular assist device (LVAD) patients when assessed at the time of ramp testing.
- Many asymptomatic outpatients with LVAD had inappropriate decoupling despite no pre-LVAD pulmonary hypertension.
- Furthermore, the degree of decoupling often changed during ramp testing, and these changes also had a prognostic impact.

### WHAT ARE THE CLINICAL IMPLICATIONS?

- Inappropriate decoupling, defined as an increased DPG, in severe heart failure may be an important hemodynamic variable of the pulmonary vascular system in patients undergoing LVAD support, regardless of patient symptoms.
- The adjustment of LVAD speed during ramp testing to optimize coupling may be an important strategy to improve patient outcomes following LVAD implantation but will require validation in a prospective randomized study.
- Therapies targeting the pulmonary vasculature in patients exhibiting decoupling after VAD implantation warrant further investigation.

Left ventricular assist device (LVAD) therapy significantly improves long-term survival rates in patients with stage D heart failure (HF), particularly in the era of modern devices such as HVAD (HeartWare International, Framingham, MA) and HeartMate II (Abbott, Pleasanton, CA).<sup>1,2</sup> Improved optimization of patient selection and sophisticated management strategies for complications have further improved postimplantation quality of life and survival rates.<sup>3,4</sup> However, recurrent decompensated HF remains a common cause of hospitalization in these patients.

Recently, several institutions have implemented LVAD speed optimization using right heart catheterization to adjust LVAD speed and patient medical therapy.<sup>5</sup> A portion of these patients exhibit an excessive difference between diastolic pulmonary artery pressure (dPAP) and pulmonary capillary wedge pressure (PCWP). Such decoupling, defined as an excessive increase of dPAP gradient, provides an index of precapillary pulmonary hypertension (PH) which may be superimposed on postcapillary PH in patients with left heart disease.<sup>6</sup>

There is a paucity of data on the mechanism and prognostic implications of decoupling in LVAD patients, particularly on the recurrence of HF. Furthermore, the clinical impact of changes in the degree of decoupling during rotation speed change is unknown. In this study, we investigated the clinical significance of decoupling and its reversibility in patients who undergo ramp testing while on LVAD support.

## METHODS

### Patient Selection

We prospectively collected data on clinically stable outpatients with LVADs (HVAD or HeartMate II) followed at our institution who were evaluated with a hemodynamic ramp testing. All patients received guideline-directed medical therapy before testing.<sup>7</sup> Patients with suspicion for LVAD thrombosis or device malfunction were excluded. Written informed consent was obtained from all participants before ramp testing. The study protocol was approved by the Ethics Committee at our institution.

### Ramp Testing Protocol

Ramp tests evaluated hemodynamics by right heart catheterization in combination with transthoracic echocardiography. Serial measurements were performed starting with the patient's baseline speed and then again after the devices were turned down to a minimal acceptable speed; subsequently, measurements were taken at progressively increasing speeds to a maximal value.<sup>5</sup> Cardiac output and cardiac index were calculated by the indirect Fick method. At the conclusion of each test, an attending cardiologist reviewed the data, and LVAD speed was adjusted to the final speed to achieve hemodynamic optimization. Primary goals were central venous pressure  $<12$  mmHg and PCWP  $<18$  mmHg, with secondary goals of intermittent aortic valve opening and minimal mitral regurgitation.

### Variables Evaluated

Patients' preoperative background characteristics, including demographic, echocardiographic, and hemodynamic data, were obtained within the 1-month period preceding LVAD implantation. During ramp testing, hemodynamic and echocardiographic data were obtained per protocol. All hemodynamic data were reviewed by the attending cardiologist, who was blinded to the study results to ensure accuracy of measurements. Inappropriate decoupling was defined as  $dPAP-PCWP$ , difference of  $>5$  mmHg. Pulmonary artery pulsatility index was calculated according to  $(\text{systolic PAP}-dPAP)/\text{central venous pressure}$ . Pulmonary artery compliance was calculated according to  $\text{stroke volume}/(\text{systolic PAP}-dPAP)$ . All patients were followed at our institution at the final speed determined according to the results of the ramp test.

### Statistical Analyses

Baseline data were expressed as mean $\pm$ SD, unless otherwise indicated. Continuous variables were compared between groups using the unpaired *t* test or Mann-Whitney *U* test as appropriate, and categorical variables were compared between groups using the  $\chi^2$  test or Fisher exact test as appropriate.

Correlation between decoupling and other hemodynamic variables was assessed by Pearson correlation coefficient.

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 zero) through 1-year follow-up. Patients were censored at the termination of LVAD therapy because of explantation or heart transplantation. The prognostic impact of hemodynamic variables at the final speed setting was analyzed by Cox hazards ratio analysis. Variables with  $P < 0.05$  of significance in univariable analyses were entered into multivariable analyses after the confirmation that there was no significant multicollinearity among them (variance inflation factor  $< 5$  was considered nonsignificant). Cutoff values of variables predicting prognosis were calculated by using receiver operating characteristic analysis. Patients' prognosis stratified by the existence of inappropriate decoupling was assessed by Kaplan–Meier analyses and compared by log-rank test. All statistical analyses were performed using SPSS Statistics 22 (SPSS Inc, Chicago, IL).

## RESULTS

### Baseline Characteristics

Sixty-three LVAD patients (19 HVAD and 44 HeartMate II) were enrolled (Table 1). Patients were  $59.9 \pm 11.5$  years old, and 25 (40%) were female. The majority of patients were implanted as destination therapy (79%), and 33 (52%) had an ischemic cause of their cardiomyopathy. The median duration between time of LVAD implantation and ramp testing was 280 days (13–1954 days).

### Decoupling and Other Clinical Variables

At the baseline speed, there was a significant correlation between dPAP and PCWP (Figure 1A). Decoupling was normally distributed ( $P = 0.290$  by Shapiro–Wilk test) and averaged  $4.7 \pm 5.2$  mmHg, ranging between  $-5$  and  $18$  mmHg. Twenty-seven patients (43%) had inappropriate decoupling at their baseline speed (Figure 1B).

At the final speed setting, 30 patients (48%) had inappropriate decoupling. Comparison of preoperative background characteristics demonstrated that more patients with inappropriate decoupling received LVAD as destination therapy than those without. Otherwise, there were no significant differences in baseline characteristics between these 2 groups (Table 1). At the baseline speed setting, the decoupling group had higher PAP and pulmonary vascular resistance (PVR) compared with the nondecoupling group (Table 2;  $P < 0.05$  for all). Pulmonary artery pulsatility index and pulmonary artery compliance were comparable irrespective of inappropriate decoupling.

### Decoupling and Patient Prognosis

The group of patients with inappropriate decoupling experienced 6 deaths and 8 HF readmissions. In comparison, the group of patients without inappropriate decoupling experienced 1 death and 3 HF readmissions. In univariable

Cox regression analysis of hemodynamic characteristics at the final speed setting, mean PAP, dPAP, and decoupling were significant predictors of death or HF readmission during the 1-year study period (Table 3;  $P < 0.05$  for all analyses). PVR was not a significant predictor of the outcome ( $P = 0.094$ ). Multivariable analysis revealed that decoupling was the only significant predictor of death or HF readmission (Table 3;  $P = 0.046$ ; hazards ratio, 1.09; 95% confidential interval, 1.04–1.24). Variance inflation factors of decoupling, dPAP, and mean PAP were 1.482, 13.52, and 13.35, respectively, and dPAP was not included in the multivariable analysis because of its high collinearity with mean PAP. By receiver operating characteristic analysis, the cutoff level for decoupling was found to be values  $> 5$  mmHg (Appendix Figure I in the Data Supplement).

Kaplan–Meier analysis showed that patients with inappropriate decoupling had significantly lower HF readmission–free survival compared with those without inappropriate decoupling during the 1-year study period (Figure 2A; 47% versus 87%;  $P = 0.002$ ). Overall mortality was also significantly higher in the group with inappropriate decoupling (Figure 2B;  $P = 0.026$ ).

Among 19 HVAD patients, 10 patients with inappropriate decoupling had a trend toward lower HF readmission–free survival compared with 9 without inappropriate decoupling (47% versus 80%;  $P = 0.16$ ). Among 44 HeartMate II patients, 20 patients with inappropriate decoupling had significantly lower HF readmission–free survival compared with 24 without inappropriate decoupling (48% versus 91%;  $P = 0.005$ ).

### Changes in Decoupling During Ramp Testing and Patients' Prognosis

During ramp testing, 49 patients (78%) had increasing degrees of decoupling at incremental rotation speed. The relationship between decoupling and rotation speed (expressed as speed steps) is shown in Figure 3A. Eventually, the change in decoupling between baseline and final speed averaged  $0.95 \pm 3.97$  mmHg (range,  $-9$  to  $15$  mmHg), and 26 patients (41%) experienced an increase in decoupling between baseline and final speed settings (Figure 3B).

Among 27 patients with inappropriate decoupling at baseline speed, 8 (30%) achieved normalization of decoupling at the final speed (Figure 4A). This cohort had higher HF readmission–free survival rates than the non-normalized group (Figure 4B; 100% versus 53%;  $P = 0.035$ ). There were no significant differences in preoperative background characteristics between the normalized and non-normalized groups (data not shown). Patients in the normalized group had comparable LVAD duration to those in the non-normalized group ( $530.1 \pm 757.1$  versus  $347.2 \pm 341.3$  days;  $P = 0.87$ ).

Among 36 patients without inappropriate decoupling at their baseline speed, 11 (31%) experienced de

**Table 1. Comparison of Background Characteristics Stratified by the Existence of Decoupling at the Final Speed**

	Total (n=63)	Inappropriate Decoupling (n=30)	Noninappropriate Decoupling (n=33)	P Value
Demographics				
Age, y	59.9±11.5	57.9±10.4	61.7±12.3	0.20
Sex (female)	25 (40)	15 (50)	10 (30)	0.09
Race (white)	32 (51)	12 (40)	20 (61)	0.31
Nonischemic cause	33 (52)	17(57)	16 (48)	0.35
Body height, cm	170±19	173±10	173±11	0.84
Body weight, kg	89.0±23.2	85.6±21.8	92.1±24.4	0.27
HeartMate II	44 (70)	20 (66)	24 (73)	0.60
HVAD	19 (30)	10 (33)	19 (58)	0.60
Destination therapy	50 (79)	27 (90)	23 (70)	0.045*
Diabetes mellitus	23 (37)	9 (30)	14 (42)	0.22
Hypertension	35 (56)	14 (47)	21 (64)	0.14
Peripheral artery disease	2 (3)	0 (0)	2 (6)	0.17
Atrial fibrillation	24 (38)	13 (43)	11 (33)	0.29
History of ventricular tachyarrhythmia	14 (22)	7 (23)	7 (21)	0.54
Chronic obstructive pulmonary disease	11 (17)	8 (27)	3 (9)	0.066
LVAD duration before ramp testing, d	507±534	443±447	565±604	0.39
Echocardiography				
LVDd, cm	7.50±1.09	7.54±0.76	7.47±1.33	0.77
Hemodynamics				
PCWP, mm Hg	24.0±9.6	25.5±10.1	22.7±9.1	0.34
CI, L min <sup>-1</sup> m <sup>-2</sup>	1.86±0.58	1.88±0.50	1.84±0.65	0.81
mPAP, mm Hg	36.4±12.0	36.7±11.9	36.1±12.3	0.87
dPAP, mm Hg	27.7±11.2	29.9±12.2	25.8±10.0	0.21
CVP, mm Hg	11.9±7.5	11.9±8.7	11.8±6.5	0.96
PVR, WU	3.65±2.79	3.28±2.65	4.02±2.95	0.39

CI indicates cardiac index; CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; LVAD, left ventricular assist device; LVDd, left ventricular diastolic diameter; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and PVR, pulmonary vascular resistance.

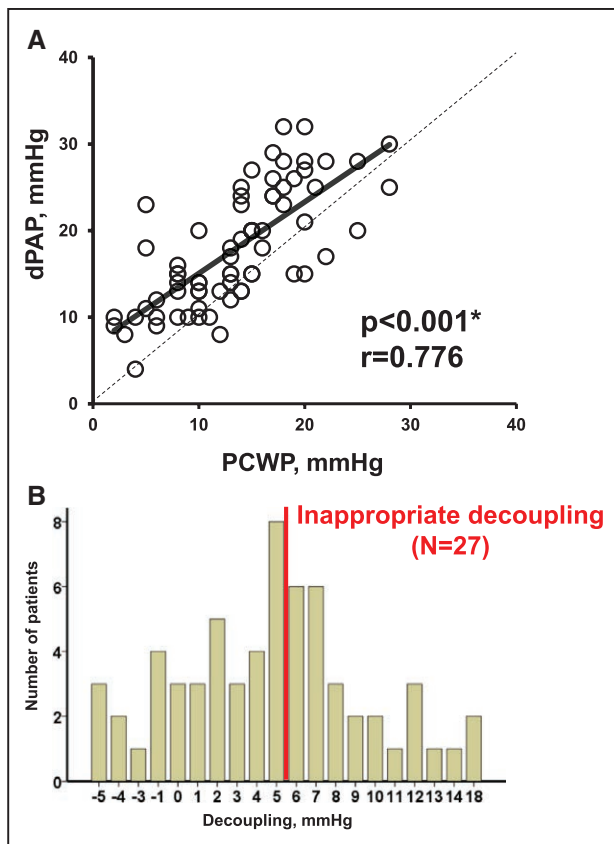
\* $P < 0.05$  by  $\chi^2$  test.

novo inappropriate decoupling at their final speed (Figure 4A). This cohort had significantly lower HF readmission-free survival compared with the persistent normal group (Figure 4C; 35% versus 83%;  $P=0.010$ ). There were no significant differences in preoperative background variables between these groups (data are not shown).

These trends were similar for HVAD and HeartMate II subgroups. Among 19 HVAD patients, normalization of decoupling was associated with a trend toward higher HF readmission-free survival compared with the persistent decoupling group (100% versus 54%;  $P=0.14$ ). Among 44 HeartMate II patients, normalization of decoupling was associated with a trend toward higher HF readmission-free survival compared with the persistent decoupling group (100% versus 53%;  $P=0.16$ ). De novo decoupling was associated with lower HF read-

mission-free survival compared with the persistent normal group (38% versus 89%;  $P=0.010$ ).

Several differences were noted in hemodynamic characteristics between the baseline and final speed settings (Table 4). Among patients with inappropriate decoupling at baseline speed, PCWP tended to increase in the normalized group (LVAD speed was increased in 3 patients, decreased in 4 patients, and unchanged in 1 patient), whereas PCWP tended to decrease at incremental rotation speed in the persistent decoupling group. Among patients without inappropriate decoupling at baseline speed, dPAP and PVR increased significantly accompanied by a trend toward decrease in PCWP in the de novo decoupling group (LVAD speed was increased in 4 patients, decreased in 4 patients, and unchanged in 3 patients). Rotation speed could be increased without the development of decoupling in the persistent normal group.



**Figure 1.** Relationship between diastolic pulmonary artery pressure (dPAP) and pulmonary capillary wedge pressure (PCWP; A) and distribution of the decoupling (B).

\* $P < 0.05$  by Pearson correlation coefficient.

## DISCUSSION

In this prospective study, we analyzed the prognostic implications of decoupling during LVAD support. The main finding is that inappropriate decoupling is common in clinically stable outpatients with LVAD and a strong predictor of the composite end point of death or HF readmission. More than 40% of stable outpatients with LVAD had inappropriate decoupling without a trend toward PH in preoperative hemodynamics. In addition, the degree of decoupling often changed during ramp testing, and this change also had prognostic implications: those whose decoupling normalized as a result of ramp test–guided speed adjustment had a better prognosis compared with those that did not.

### Inappropriate Decoupling During LVAD Therapy

We quantified the degree of decoupling in clinically stable LVAD patients irrespective of the existence of PH; as a result, the decoupling group included many patients without PH. Considering that patients with inappropriate decoupling had higher PVR, inappropriate decou-

**Table 2.** Postoperative Echocardiographic and Hemodynamic Data Stratified by the Existence of Inappropriate Decoupling at Final Speed

	Inappropriate Decoupling Group (n=30)	Noninappropriate Decoupling Group (n=33)	P Value
Echocardiography			
LVDd, cm	6.08±1.00	6.10±1.22	0.96
Hemodynamics			
PCWP, mmHg	14.1±5.9	13.8±6.8	0.84
CI, L min <sup>-1</sup> m <sup>-2</sup>	2.52±0.38	2.89±0.84	0.062
mPAP, mmHg	27.6±7.3	21.8±6.7	0.003*
dPAP, mmHg	20.9±6.4	16.2±6.3	0.007*
Heart rate, beats per minute	84.5±11.7	82.4±11.0	0.49
RVSWI, g/m <sup>2</sup>	7.38±2.65	6.43±3.31	0.25
CVP, mmHg	10.3±4.6	8.2±5.9	0.15
PVR, WU	2.84±1.35	1.51±0.84	<0.001*
PAPi	2.74±2.21	3.09±2.01	0.51
PAC, mL/mmHg	3.64±1.37	4.17±1.36	0.38

CI indicates cardiac index; CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; LVDd, left ventricular diastolic diameter; mPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; and RVSWI, right ventricular stroke work index.

\* $P < 0.05$  by unpaired *t* test.

pling may indicate damage to the pulmonary vasculature. Pathological studies may provide further insight into the mechanism underlying the current results.

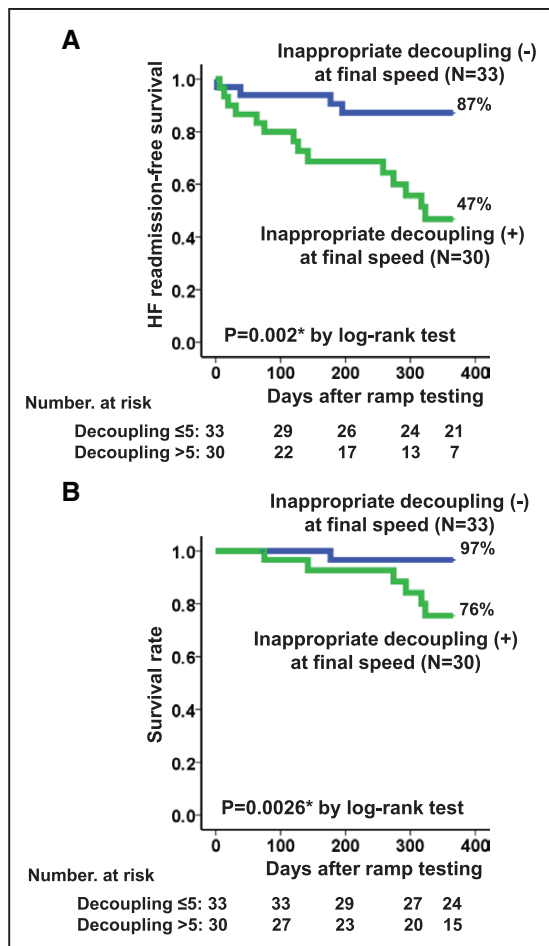
### Prognostic Impact of Decoupling in LVAD Population

Decoupling was the strongest predictor of the composite of HF readmission and mortality among all considered hemodynamic parameters. This easily calculable variable is unique because inappropriate decoupling can exist irrespective of PH. PVR was not a significant

**Table 3.** Univariable/Multivariable Cox Hazard Ratio Analysis for the Prediction of Death or Heart Failure Readmission Among Hemodynamics at Final Speed

	Univariable		Multivariable	
	P Value	Hazards Ratio (95% CI)	P Value	Hazards Ratio (95% CI)
mPAP, mmHg	0.005*	1.10 (1.03–1.17)	0.22	1.05 (0.97–1.15)
dPAP, mmHg	0.002*	1.13 (1.05–1.22)		
PVR, WU	0.094	1.33 (0.95–1.86)		
Decoupling, mmHg	0.003*	1.16 (1.05–1.27)	0.046*	1.09 (1.04–1.24)

CI indicates confidence interval; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; and PVR, pulmonary vascular resistance. \* $P < 0.05$  by Cox hazard ratio analysis.



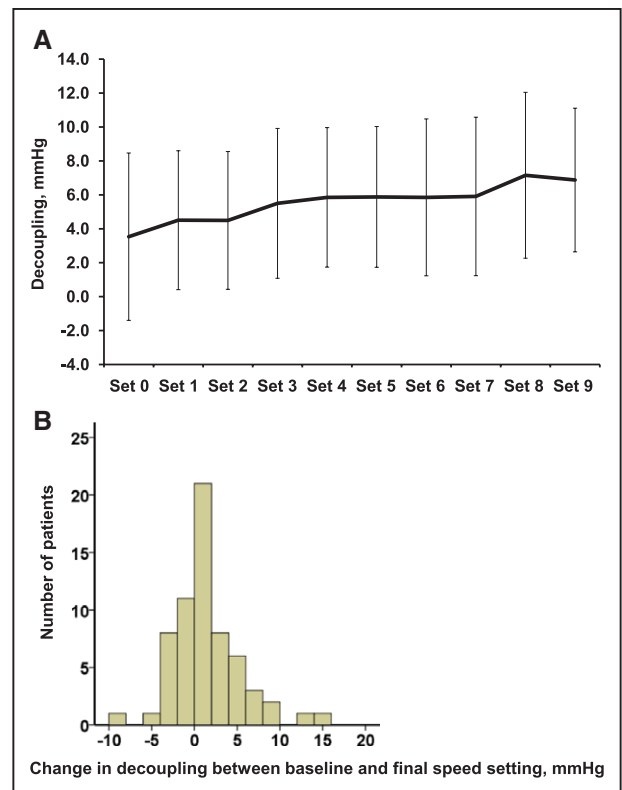
**Figure 2.** Comparison of heart failure (HF) readmission-free survival rate (A) and survival rate (B) stratified by the existence of inappropriate decoupling at the final speed setting.

\* $P < 0.05$  by the log-rank test.

predictor in univariable analysis, probably because of the dependency of mean PAP and cardiac output on volume and flow.<sup>8</sup>

There are no prior studies evaluating the prognostic implications of decoupling in LVAD patients. However, prior research has been conducted on decoupling in other clinical settings. Tedford et al<sup>9</sup> showed that preoperative decoupling had no effect on postheart transplant survival in patients with reactive PH. However, in this study, preoperative decoupling may be diminished after drastic improvement in hemodynamics by heart transplantation. In contrast, among HF patients with reactive PH, Gerges et al<sup>10</sup> demonstrated that decoupling identified those with significant pulmonary vascular disease and increased mortality. They enrolled only patients with reactive PH, whereas we expanded the research population to include all LVAD patients, including those without PH.

Patients with inappropriate decoupling were more likely to have an HF readmission during the study period. Pulmonary vascular damage, as indicated by the



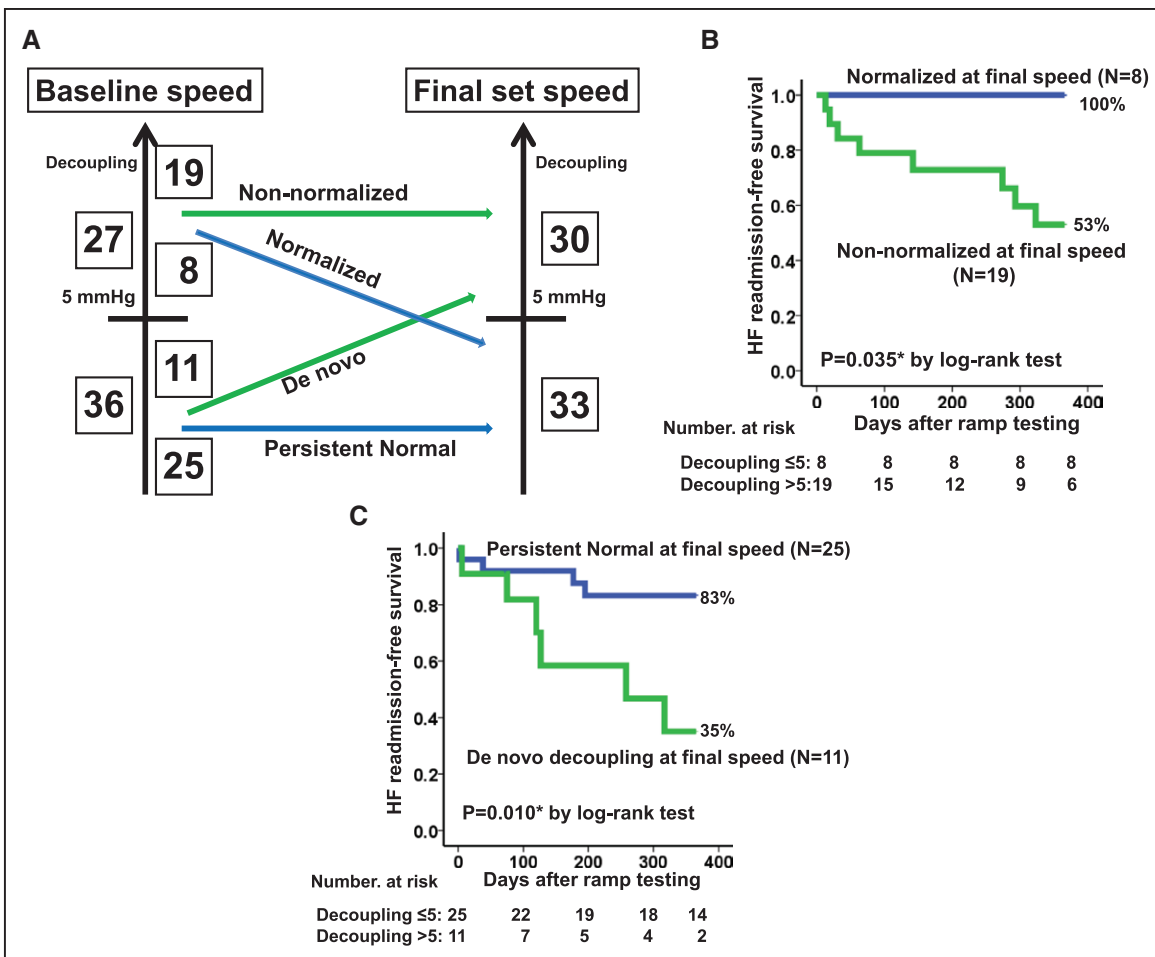
**Figure 3.** Trend of decoupling during speed ramp testing (A) and distribution of change in decoupling between baseline and the final speed setting (B).

presence of decoupling, may present a greater hemodynamic load on the right ventricle, leading to subsequent right ventricular failure and hospitalizations. Although there was no association between decoupling and other hemodynamic variables associated with right ventricular failure, repeated hemodynamic and echocardiographic studies may demonstrate worsening of right ventricular function over time.<sup>6</sup>

### Changes in Decoupling by Ramp Testing and Its Prognostic Impact

Normalization of decoupling was associated with improvement in overall patient prognosis, whereas patients with de novo decoupling had a worse overall prognosis. Considering these results, decoupling may be a novel therapeutic target during LVAD therapy, although this should be validated in a larger-scale study. Anti-PH medications such as phosphodiesterase inhibitors and endothelin receptor antagonists may have potential benefit in decreasing decoupling.<sup>11</sup> Very limited data exist on their efficacy in LVAD recipients with residual PH, likely because of their side effects including liver and renal dysfunction.<sup>12,13</sup>

No background factors were identified in association with changes in decoupling during speed changes. Longer duration of LVAD support before the ramp



**Figure 4.** Changes in the proportion of inappropriate decoupling during ramp test and its prognostic impact.

Changes in the patients number with/without inappropriate decoupling between baseline and the final speed setting (A) and comparison of heart failure (HF) readmission-free survival rate stratified by the changes in decoupling during the ramp testing (B, decoupling >5 mmHg at baseline speed setting; C, decoupling ≤5 mmHg at baseline speed setting). \*P<0.05 by the log-rank test.

testing was not associated with changes in decoupling during the ramp test. Duration of preoperative HF to LVAD implant may be associated with reversibility of decoupling; however, these data were not available in this study. Patients experiencing long-term HF may be more likely to develop de novo decoupling during LVAD speed changes because of the presence of irreversible damage to the pulmonary vasculature.

Among those with inappropriate decoupling at baseline speed, irreversible pulmonary vasculature damage may exist. In this situation, unnecessarily aggressive reduction of PCWP leads to worsening of decoupling accompanied by persistently elevated dPAP during ramp test (non-normalized group) and may not be recommended. Instead, leaving PCWP unchanged may be recommended to normalize decoupling (normalized group).

Among those without decoupling at baseline speed, some patients may have advanced pulmonary vasculature pathology, and others may not. In patients with

such advanced pulmonary vasculature pathology, reduction in PCWP may lead to the development of decoupling accompanied by persistently elevated dPAP during ramp tests (these are the de novo decoupling group). During hemodynamic ramp testing, decreases in PCWP can occur even when the final speed is reduced compared with the baseline speed, and, therefore, it is more important to give attention to the changes in hemodynamics than the change in speed. In contrast, decreases in PCWP may not necessarily be associated with the development of decoupling in patients without significant pulmonary vascular pathology (these are the persistent normal group).

### Repeated Adjustment of Rotation Speed to Reduce Decoupling

On the basis of the results of the present study, the use of ramp testing to adjust rotation speed to reduce the degree of decoupling may lead to improved out-

**Table 4. Changes in Hemodynamic Variables Between Baseline and the Final Speed Setting Stratified by Changes in Decoupling**

	Baseline Speed	Final Speed	P Value
Normalized group (n=8)			
Rotation speed			
HeartMate II (n=4), rpm	9533±416	9600±600	0.67
HVAD (n=4), rpm	2725±143	2705±175	0.35
PCWP, mmHg	9.6±8.0	12.6±8.4	0.078
CI, L min <sup>-1</sup> m <sup>-2</sup>	2.79±0.68	2.50±0.49	0.16
dPAP, mmHg	17.0±7.7	16.6±8.1	0.56
CVP, mmHg	6.9±6.1	7.1±4.9	0.90
PVR, WU	2.03±0.53	1.79±0.66	0.27
Non-normalized group (n=19)			
Rotation speed			
HeartMate II (n=14), rpm	9015±377	9267±421	0.013*
HVAD (n=5), rpm	2704±182	2792±168	0.28
PCWP, mmHg	13.2±5.7	12.2±5.6	0.20
CI, L min <sup>-1</sup> m <sup>-2</sup>	2.57±0.38	2.70±0.67	0.29
dPAP, mmHg	22.8±6.5	21.8±7.0	0.18
CVP, mmHg	10.4±4.8	9.3±4.1	0.021*
PVR, WU	3.43±1.29	3.40±1.39	0.87
Persistent normal group (n=25)			
Rotation speed			
HeartMate II (n=20), rpm	9219±375	9486±415	0.013*
HVAD (n=5), rpm	2580±86	2644±124	0.040*
PCWP, mmHg	15.0±6.0	14.3±5.8	0.33
CI, L min <sup>-1</sup> m <sup>-2</sup>	2.93±0.89	2.92±0.87	0.99
dPAP, mmHg	15.9±6.0	16.1±6.6	0.84
CVP, mmHg	8.6±5.9	8.9±6.9	0.56
PVR, WU	1.34±0.86	1.54±0.70	0.15
De novo decoupling group (n=11)			
Rotation speed			
HeartMate II (n=8), rpm	9429±214	9486±279	0.36
HVAD (n=3), rpm	2733±181	2780±72	0.75
PCWP, mmHg	15.6±6.2	12.7±4.2	0.10
CI, L min <sup>-1</sup> m <sup>-2</sup>	2.61±0.28	2.68±0.35	0.61
dPAP, mmHg	17.7±5.0	20.8±3.8	0.009*
CVP, mmHg	10.0±4.6	9.1±5.4	0.33
PVR, WU	1.80±0.43	2.34±0.41	0.018*

CI indicates cardiac index; CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and PVR, pulmonary vascular resistance.

\*P<0.05 by paired t test.

comes in LVAD patients, although prospective large-scale study is required to validate our results before such an approach can be recommended. Recently,

pulmonary artery sensors (CardioMEMS, Inc, Atlanta, GA) have become widely used to adjust medical therapies in outpatients with HF or PH.<sup>14,15</sup> Noninvasive technologies such as remote dielectric sensing are also being used to quantify lung fluid content and estimate filling pressures.<sup>16</sup> Although the clinical implication of these technologies in LVAD patients remains uncertain, our study highlights the importance of understanding both the PCWP and PAP in LVAD patients.

### Study Limitations

Several potential limitations of this study should be considered. First, the cohort is a small population from a single center, and the number of events was very low. In particular, the analyses about changes in decoupling during the ramp test included small subgroups, and the strength of statistical precision and power is limited. Furthermore, speed adjustments were performed to optimize central venous pressure and PCWP but not to optimize decoupling. Accordingly, a randomized, multicenter large-scale study would be useful to validate our findings and the implications for clinical practice. 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 decoupling and other clinical parameters vary during long-term LVAD support. Fourth, LVAD duration before the ramp testing varied widely. Eight patients had experienced HF readmission between LVAD implantation and ramp testing. 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 ramp test and such bias may therefore be minimized. Fifth, deceased LVAD patients could not receive ramp testing, and this study has a selection bias. Sixth, although our results showed similar trends in the HVAD and HeartMate II subgroups, some of the comparisons did not reach statistical significance because of the small size of the subgroup. A larger multicenter study could provide more detailed information about differences between the 2 devices.

### Conclusions

The presence of inappropriate decoupling was associated with worse outcomes in patients with LVAD. A prospective, multicenter, large-scale study to validate the results is warranted.



## AFFILIATIONS

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## DISCLOSURES

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## FOOTNOTES

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### **Decoupling Between Diastolic Pulmonary Artery Pressure and Pulmonary Capillary Wedge Pressure as a Prognostic Factor After Continuous Flow Ventricular Assist Device Implantation**

Teruhiko Imamura, Ben Chung, Ann Nguyen, Daniel Rodgers, Gabriel Sayer, Sirtaz Adatya, Nitasha Sarswat, Gene Kim, Jayant Raikhelkar, Takeyohi Ota, Tae Song, Colleen Juricek, Viktoriya Kagan, Valluvan Jeevanandam, Mandeep Mehra, Daniel Burkhoff and Nir Uriel

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# **SUPPLEMENTAL MATERIAL**

**Appendix Figure 1.** The receiver operating characteristic curve of decoupling showed an area under the curve of 0.734 with sensitivity 0.778 and specificity 0.644 at cutoff point of 5 mmHg.

