ORIGINAL RESEARCH

# Decoupling Between Diastolic Pulmonary Artery and Pulmonary Capillary Wedge Pressures Is Associated With Right Ventricular Dysfunction and Hemocompatibility-Related Adverse Events in Patients With Left Ventricular Assist Devices

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***Background*—**Decoupling between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure is an index of pulmonary vascular damage. This study assessed the impact of decoupling on right heart function and hemocompatibility-related adverse events.

***Methods and Results*—**In this prospective study, patients underwent invasive hemodynamic tests following left ventricular assist device implantation. Decoupling was defined as a difference of >5 mm Hg between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure. Among 92 patients with left ventricular assist devices (median age, 61 years; 57% male), 44 patients (48%) had decoupling. Right heart function and size by echocardiographic assessment worsened during a 1-year observational period in the decoupling group as compared with the control group ($P<0.05$). The decoupling group had significantly lower 1-year freedom from any hemocompatibility-related adverse events (49% versus 79%; $P=0.005$), as well as a higher hemocompatibility score (2.14 versus 0.67; $P=0.004$). The scoring system depicts the severity of hemocompatibility-related adverse events using 4 escalating tiers. Increased tier I scores (1–2 gastrointestinal bleedings or medically managed pump thrombosis; $P=0.027$) and tier IIIB scores (disabling stroke or hemocompatibility-related adverse event–related death; $P=0.041$) occurred more frequently in the decoupling group.

***Conclusions*—**The presence of decoupling between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure was associated with worsening of right heart function and hemocompatibility-related adverse events in patients with left ventricular assist devices. **(*J Am Heart Assoc*. 2020;9:e014801. DOI: 10.1161/JAHA.119.014801.)**

**Key Words:** bleeding • hemodynamics • pulmonary hypertension • unloading

Group 2 pulmonary hypertension is a significant and common clinical condition in patients with advanced heart failure (HF).[1] Following left ventricular assist device (LVAD) implantation with subsequent left ventricular unloading, pulmonary hypertension attributable to left heart disease (Group 2 pulmonary hypertension) often reverses.[2,3] "Decoupling" between the diastolic pulmonary artery pressure (dPAP) and the pulmonary capillary wedge pressure (PCWP), which represents combined precapillary and postcapillary pulmonary hypertension, is present in nearly half of LVAD patients and strongly predicts post-LVAD HF recurrence.[4] However, the impact of decoupling on right heart function and other comorbid conditions has not been fully investigated.

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## Clinical Perspective

### What Is New?

- Decoupling of pressure between diastolic pulmonary artery and pulmonary capillary wedge pressure was associated with hemocompatibility-related adverse events during left ventricular assist device support, potentially attributable to worsening right heart function.

### What Are the Clinical Implications?

- These findings should alert clinicians to evaluate for the presence of decoupling between diastolic pulmonary artery and pulmonary capillary wedge pressure in patients supported with left ventricular assist devices. Future studies are needed to assess potential therapeutic strategies for decoupling.

Although the mechanism remains unclear, the existence of decoupling may have a potential negative impact by increasing right ventricular afterload.[5] Furthermore, nonoptimized hemodynamics reflected by persistently elevated central venous pressure is associated with a higher incidence of hemocompatibility-related adverse events (HRAEs) in patients with LVADs.[6] Given these prior findings, we further investigated the impact of decoupling on HRAEs in patients with LVADs.

## Methods

### Patient Selection

The data that support the findings of this study are available from the corresponding author upon reasonable request. We prospectively collected data on clinically stable consecutive outpatients with LVADs who underwent invasive hemodynamic assessments as part of our routine protocol. Those with any active comorbidities, including decompensated HF requiring in-hospital intravenous diuretics and HRAEs requiring hospitalization at the time of hemodynamic assessments, were excluded. All patients were followed at our institute for 1 year with implementation of guideline-directed medical therapies for HF. No patients were started on pulmonary hypertension–specific therapies following hemodynamic assessment. The study protocol was approved by the Institutional Review Board at the University of Chicago beforehand. Informed consents were obtained from all participants before the enrollment.

### Right Heart Catheterization for Hemodynamic Assessments

All patients underwent right heart catheterization via the right jugular vein using a 7 French Swan-Ganz catheter, and standard hemodynamic assessments were performed. All hemodynamic parameters were obtained at end expiration and manually inspected by 2 attending HF cardiologists. PCWP was measured as a mean of the a-wave pressure waveform. Decoupling was defined as >5 mm Hg difference between dPAP and PCWP, given its prognostic impact demonstrated in our previous study.[4]

### Echocardiographic Assessment of Right Heart Size and Function

Transthoracic echocardiography was performed at the time of hemodynamic assessment (baseline) and 1 year later following the current American Society of Echocardiography guidelines.[7] 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 apical 4-chamber 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.

We also investigated the occurrence of the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support)–defined right HF of any grade, satisfying both documentation and manifestation of elevated central venous pressures during the observational period.

### Hemocompatibility-Related Adverse Events

Clinical adverse events attributable to LVAD-related bleeding or thrombosis were classified as HRAEs.[8] Data of deaths and hospital readmissions due to HRAEs were collected and validated by 2 independent researchers (T.I. and D.R.). As a therapeutic parameter, aspirin dose and international normalized ratio were obtained at baseline (baseline) and 1, 3, and 6 months following the hemodynamic assessment. Time of therapeutic range for international normalized ratio was also calculated.

### Hemocompatibility Score

A tiered hierarchal score (hemocompatibility score) was calculated for each patient by weighing each event considering its escalating clinical relevance to determine the aggregate net burden of HRAEs (Table S1).[9]

### Statistical Analyses

Statistical analyses were performed using SPSS Statistics 22 (IBM, Armonk, NY). A 2-tailed $P<0.05$ was considered significant. The primary end point of this study was the risk

**Table 1.** Baseline Characteristics

| | Total (N=92) | Decoupling (N=44) | Control (N=48) | *P* Value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, y | 61 (54–70) | 61 (54–66) | 65 (52–72) | 0.11 |
| Male, n (%) | 57 (6%) | 23 (52) | 34 (71) | 0.053 |
| White, n (%) | 45 (49) | 19 (43) | 26 (54) | 0.53 |
| Body mass index | 29.8 (24.0–34.2) | 29.5 (23.5–33.9) | 28.4 (24.8–35.7) | 0.69 |
| Ischemic etiology, n (%) | 38 (41) | 17 (39) | 21 (44) | 0.32 |
| Destination therapy, n (%) | 71 (77) | 38 (86) | 33 (69) | 0.12 |
| LVAD duration before day 0, mo | 10 (4–21) | 9 (3–21) | 10 (4–26) | 0.68 |
| HeartMate II LVAD, n (%) | 53 (58) | 26 (59) | 27 (56) | 0.48 |
| HVAD LVAD, n (%) | 39 (42) | 18 (41) | 21 (44) | … |
| Comorbidity, n (%) | | | | |
| Diabetes mellitus | 32 (35) | 12 (27) | 20 (42) | 0.13 |
| Atrial fibrillation | 37 (40) | 20 (45) | 17 (35) | 0.27 |
| History of stroke | 13 (14) | 6 (14) | 7 (15) | 0.54 |
| History of ventricular tachyarrhythmia | 22 (24) | 12 (27) | 10 (21) | 0.36 |
| Chronic kidney disease | 20 (22) | 10 (23) | 10 (21) | 0.56 |
| Hemodynamics parameters at baseline | | | | |
| Central venous pressure, mm Hg | 8 (5–12) | 9 (5–11) | 8 (4–12) | 0.19 |
| Systolic pulmonary artery pressure, mm Hg | 37.2±10.1 | 41.2±9.8 | 33.5±9.1 | <0.001* |
| Mean pulmonary artery pressure, mm Hg | 25.1±7.1 | 28.2±6.3 | 22.2±6.6 | <0.001* |
| Diastolic pulmonary artery pressure, mm Hg | 18.8±6.3 | 22.0±5.5 | 15.9±5.7 | <0.001* |
| Pulmonary capillary wedge pressure, mm Hg | 13.1±5.1 | 12.5±4.5 | 13.7±5.6 | 0.28 |
| Pulmonary capillary wedge pressure ≥15 mm Hg, n (%) | 30 (33) | 11 (25) | 19 (40) | 0.10 |
| Cardiac index, L/min per $m^2$ | 2.7 (2.3–3.0) | 2.6 (2.2–3.0) | 2.7 (2.3–3.0) | 0.53 |
| Pulmonary vascular resistance, WU | 2.1 (1.5–2.8) | 2.8 (2.4–4.0) | 1.6 (1.2–2.0) | <0.001* |
| Echocardiographic parameters at baseline | | | | |
| Left ventricular end-diastolic diameter, cm | 5.8±1.2 | 5.9±1.2 | 5.7±1.2 | 0.57 |
| Aortic insufficiency, degree | 0 (0–1) | 0 (0–1) | 0 (0–0) | 0.079 |
| Mitral regurgitation, degree | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0.75 |
| Laboratory parameters at baseline | | | | |
| Serum total bilirubin, mg/dL | 0.84±0.32 | 0.88±0.33 | 0.81±0.31 | 0.32 |
| Serum creatinine, mg/dL | 0.78±0.30 | 0.81±0.33 | 0.75±0.27 | 0.39 |
| Therapeutic parameters | | | | |
| Aspirin administration, n (%) | 69 (75) | 33 (75) | 36 (75) | 0.40 |
| INR | 2.1±0.6 | 2.2±0.6 | 2.0±0.5 | 0.16 |
| Anti–pulmonary hypertension agent, n (%) | 7 (8) | 4 (9) | 3 (6) | 0.61 |

INR indicates international normalized ratio; LVAD, left ventricular assist device.

*$P<0.05$. Normally distributed continuous variables were compared by using unpaired t test; nonnormally distributed continuous variables were compared by using the Mann–Whitney U test; categorical variables were compared by using Fisher's exact test. The degree of valvular regurgitation was graded as 0, none; 1, trace; 2, mild; 3, mild to moderate; 4, moderate; 5, severe.

of any HRAEs from the time of hemodynamic assessment (baseline) through 1-year follow-up. Continuous variables were expressed as mean and standard deviation and compared between the groups using the unpaired t test when normally distributed. Nonnormally distributed continuous variables were expressed as median with interquartile ranges, and compared between the groups by using the Mann–Whitney U test. Categorical variables were compared between the groups using Fisher's exact test.

Echocardiographic parameters at the time of hemodynamic assessment (baseline) and 1 year later were compared by using the Wilcoxon signed-rank test. Risk of any HRAEs was assessed by using Kaplan–Meier analyses and compared between the groups using the log-rank test. Event rate was expressed as events per year and compared between the groups using negative binomial regression analyses to assess multiple individual events. Cox proportional hazard ratio regression analyses were performed to investigate the impact of variables including decoupling on HRAEs. Variables with $P<0.05$ in the univariate analyses were included in the multivariate analyses after confirmation of their variant inflation factors <5.0. Sex was also included in the multivariate model given its significant impact on HRAE. Hemocompatibility scores were expressed as a mean value for applicability, although they were nonnormally distributed.

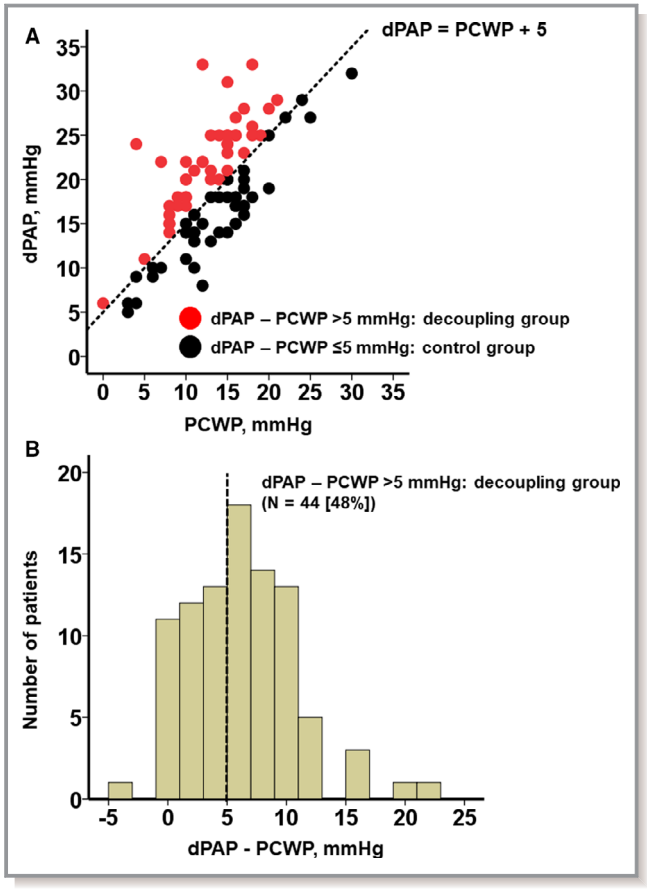


**Figure 1.** Relationship between dPAP and PCWP (**A**) and distribution of decoupling (**B**). Red dot indicates decoupling between dPAP and PCWP (>5 mm Hg). dPAP indicates diastolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

## Results

### Baseline Characteristics

A total of 92 patients (61 years old, 57 males) were enrolled and received hemodynamic assessment at a median 10 months (baseline) following LVAD implantation (Table 1). Patients received HeartMate II (58%) or HVAD (42%), and most of them (77%) were implanted as destination therapy.

### Decoupling and Background Comparison

The association between dPAP and PCWP is shown in Figure 1A. Decoupling patients (red dots) were observed over a wide range of PCWP and dPAP. Sixty-four percent of patients with decoupling had elevated mean PAP (>25 mm Hg), and 36% had normal mean pulmonary artery pressure (PAP; ≤25 mm Hg). Distribution of dPAP minus PCWP ranged widely, with 44 patients (48%) showing evidence of decoupling (Figure 1B). There were no statistical differences in background characteristics between the decoupling group and the control group ($P>0.05$ for all; Table 1). Among 71 patients who had pre-LVAD hemodynamics data, 33 had post-LVAD decoupling. Of them, 13/33 (39%) had persistent decoupling before and after LVAD implantation and 20/33 (61%) experienced de novo decoupling.

Aspirin dose and international normalized ratio were not statistically different between the 2 groups during the observational period ($P>0.05$ for all; Table S2). Time of therapeutic range for international normalized ratio did not significantly differ between the decoupling group and the control group (55.4±14.4% versus 58.2±15.8%; $P=0.32$).

### Impact of Decoupling on Right Heart Function

Overall, 69 patients completed right heart–specific echocardiographic assessments at the time of hemodynamic assessment (baseline) and 1 year later (Figure 2).

At baseline, 3 parameters of right heart function (tricuspid annular plane systolic excursion, annular systolic motion velocity, and RV fractional area change) were lower in the decoupling group (N=33) compared with the control group (N=36), although changes in annular systolic motion velocity did not reach statistical significance. Both right atrial and RV areas were enlarged in the decoupling group ($P<0.05$ for both). The grades of tricuspid regurgitation did not significantly differ between the groups.

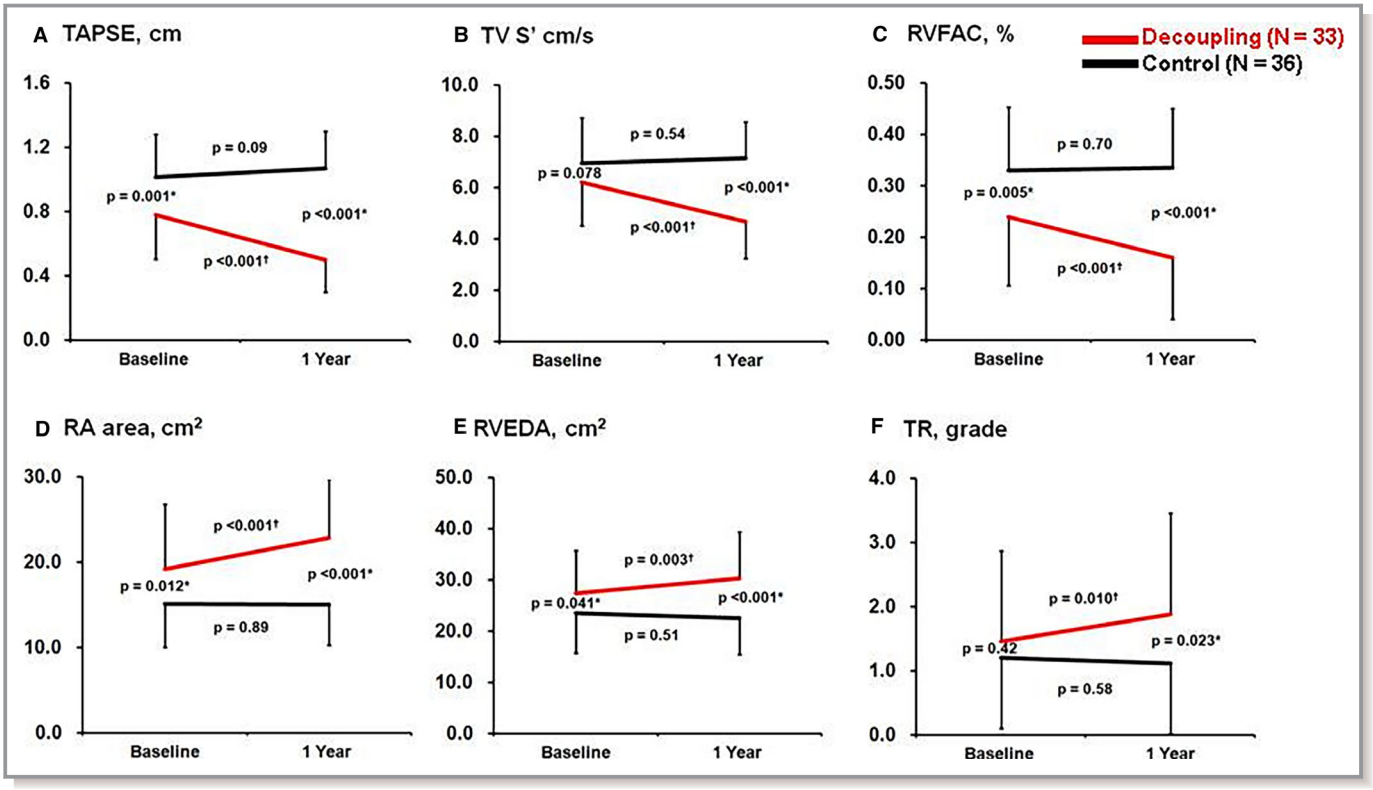


**Figure 2.** Trends of echocardiographic right heart parameters in the decoupling group and the control group. **A–F**, Right ventricular function worsened and right ventricular size enlarged in the decoupling group. RA indicates right atrium; RVEDA, right ventricular end-diastolic area; RVFAC, right ventricular fraction area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV S′, lateral tricuspid annular systolic motion velocity. **P*<0.05 by unpaired t test; †*P*<0.05 by paired t test.

During the 1-year observational period, all 6 parameters of right heart size and function significantly worsened (ie, increase in chamber size and reduction in function) in the decoupling group compared with the control group (*P*<0.05 for all). At 1 year, inferior vena cava maximum diameter was also significantly larger in the decoupling group compared with the control group (18.1±5.9 mm versus 14.4±4.6 mm; *P*=0.010). There were, however, no significant differences between the 2 groups at baseline (16.4±4.8 mm versus 15.2±4.1 mm; *P*=0.64). Seven patients (16%) in the decoupling group and 2 (5%) in the control group had INTERMACS-defined right heart failure (*P*=0.058).

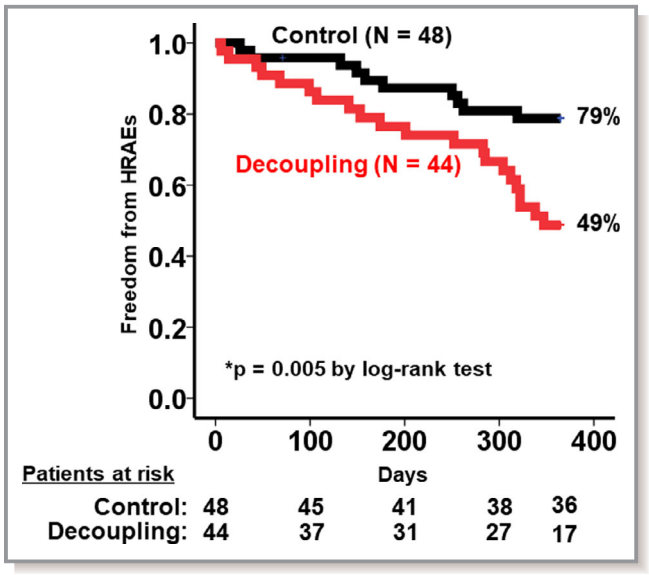


**Figure 3.** Freedom from HRAEs in the decoupling group and the control group. **P*<0.05 by the log-rank test. HRAEs indicates hemocompatibility-related adverse events.

## Impact of Decoupling on the Development of HRAEs

During the 1-year observational period from initial hemodynamic assessment, 21 patients had HRAEs in the decoupling group, while 10 patients experienced HRAEs in the control group. Median time duration free from HRAEs for them was 177 (99, 304) days. One-year freedom from HRAEs was significantly lower in the decoupling group compared with the control group (49% versus 79%; *P*=0.005; Figure 3). We examined the incidence of HRAEs in patients with and without decoupling when stratified by a PCWP cut point of 15 mm Hg. Among those with PCWP ≥15 mm Hg, those with decoupling (N=11) tended to have lower freedom from HRAE compared

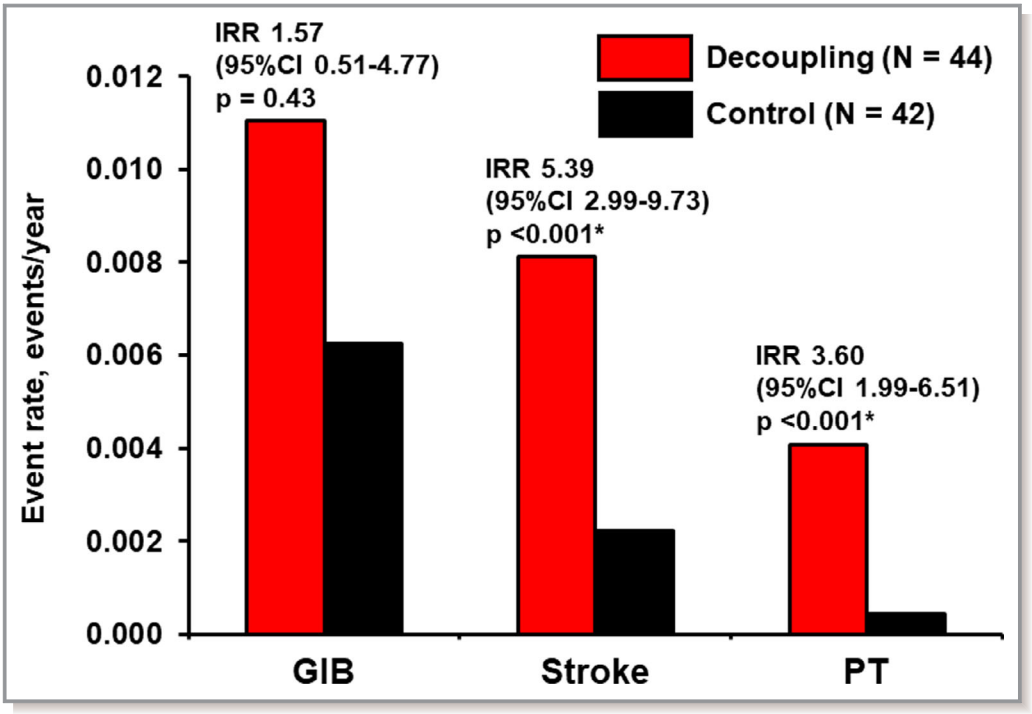


**Figure 4.** Comparisons in the event rates between the decoupling group and the control group. *$P$<0.05 by the negative binomial regression analyses. GIB indicates gastrointestinal bleeding; ORR, odds rate ratio; PT, pump thrombosis.

with those without decoupling (N=19) (42% versus 74%; $P$=0.069). Among those with PCWP <15 mm Hg, those with decoupling (N=33) had lower freedom from HRAE compared with those without decoupling (N=29) (51% versus 82%; $P$=0.020).

Regarding the observed incidence of HRAEs by subgroup, the decoupling group had significantly higher event rates of stroke and pump thrombosis compared with the control group ($P$<0.001 for both), whereas those of gastrointestinal bleeding did not significantly differ between the 2 groups ($P$=0.43; Figure 4).

Univariate and multivariate Cox proportional hazard ratio analyses demonstrated that decoupling (hazard ratio, 2.73; 95% CI, 1.24–5.97) was independently associated with development of future HRAEs (Table 2).

## Impact of Decoupling on Hemocompatibility Score

Among the 4 tiers of the hemocompatibility score, the mean scores of tier I (0.32 versus 0.08 points; $P$=0.027) and tier IIIB (0.32 versus 0.08 points; $P$=0.041) were significantly higher in the decoupling group (Figure 5). Mean scores of tier II (0.20 versus 0.08 points; $P$=0.24) and tier IIIA (0.05 versus 0.02 points; $P$=0.51) did not significantly differ between the groups. As a result, net hemocompatibility score averaged 2.14 points in the decoupling group versus 0.67 points in the control group ($P$=0.009).

## Discussion

In this prospective study, we investigated the impact of decoupling between dPAP and PCWP on HRAEs during 1 year of LVAD support. The main findings are follows: (1) In clinically stable patients with LVADs, almost half had decoupling irrespective of the PCWP; (2) decoupling was associated with worsening of right heart function and a higher incidence of right heart failure; and (3) higher rates of HRAEs were observed in patients with decoupling.

## Impact of Decoupling on Right Heart Function

Decoupling was associated with worse right heart function, which was assessed by 3 functional parameters (tricuspid annular plane systolic excursion, annular systolic motion velocity, and RV fractional area change) and 2 size parameters (right atrial and RV area),[7] as well as occurrence of right heart failure. Decoupling may therefore be an important risk factor for the development of late RV failure, which additionally is associated with worse clinical outcomes, as observed in this study.

It has been postulated that PAP normalizes in response to the left ventricular unloading in most patients with LVADs. We demonstrated again that some patients had decoupling between dPAP and PCWP with persistently elevated dPAP despite a sufficient decrease in PCWP, which may represent adverse pulmonary vasculature remodeling.[4,10] Continuously

**Table 2.** Cox Proportional Hazard Ratio Analyses for Any HRAEs

| | Univariate Analyses | | Multivariate Analyses | |
|---|---|---|---|---|
| | Hazard Ratio (95% CI) | *P* Value | Hazard Ratio (95% CI) | *P* Value |
| Age, y | 1.00 (0.97–1.04) | 0.87 | | |
| Male | 0.96 (0.47–1.98) | 0.91 | 0.73 (0.33–1.60) | 0.43 |
| White | 1.19 (0.79–1.80) | 0.4 | | |
| Body mass index | 0.96 (0.91–1.02) | 0.18 | | |
| Ischemic etiology | 0.94 (0.45–1.93) | 0.86 | | |
| Destination therapy | 2.89 (0.88–9.50) | 0.081 | | |
| Prior LVAD duration, mo | 1.00 (0.98–1.02) | 0.85 | | |
| HeartMate II LVAD | 1.25 (0.60–2.56) | 0.55 | | |
| Diabetes mellitus | 0.87 (0.41–1.85) | 0.71 | | |
| Atrial fibrillation | 0.81 (0.39–1.70) | 0.58 | | |
| History of stroke | 1.46 (0.60–3.56) | 0.41 | | |
| History of ventricular tachyarrhythmia | 1.65 (0.78–3.51) | 0.19 | | |
| Chronic kidney disease | 0.57 (0.22–1.47) | 0.24 | | |
| Central venous pressure, mm Hg | 1.05 (0.97–1.13) | 0.23 | | |
| Pulmonary capillary wedge pressure, mm Hg | 1.01 (0.94–1.08) | 0.77 | | |
| Cardiac index, L/min per $m^2$ | 0.65 (0.33–1.29) | 0.22 | | |
| Pulmonary vascular resistance | 1.33 (0.87–1.71) | 0.087 | | |
| Decoupling | 2.83 (1.33–6.01) | 0.007* | 2.73 (1.24–5.97) | 0.012* |
| Left ventricular end-diastolic diameter, cm | 0.91 (0.67–1.24) | 0.55 | | |
| Mitral regurgitation, degree | 0.98 (0.49–1.95) | 0.95 | | |
| Aortic insufficiency, degree | 0.81 (0.37–1.79) | 0.61 | | |
| Aspirin administration | 0.88 0.36–2.16) | 0.79 | | |
| INR | 0.57 (0.30–1.08) | 0.086 | | |
| INR <2.0 | 2.18 (1.08–4.42) | 0.030* | 2.03 (0.70–5.93) | 0.20 |

INR indicates international normalized ratio; LVAD, left ventricular assist device.
*$P<0.05$ by Cox proportional hazard ratio analyses. Variables with $P<0.05$ in the univariate analyses were enrolled into the multivariate analysis.

elevated PAP increases RV afterload and results in right heart chamber enlargement and reduction in function.[5,11] Coaptation of the tricuspid valve attributable to the remodeling of the RV leads to progression of tricuspid regurgitation, increasing RV preload.[12] Of note, decoupling can exist in patients with a normal mean PAP, and thus measurement of PAP alone may be insufficient to assess for pulmonary vasculature damage. Furthermore, it may be possible that decoupling in the absence of other obvious clinical factors may unmask RV failure that is early in its clinical course.

## Decoupling and HRAEs

As reported, decoupling was associated with worsening right heart failure, which may contribute to the development of HRAEs. Right heart failure reduces LVAD filling, lowers LVAD flow, and may lead to pump stasis. Adequate laminar flow across the blood-washed inflow bearing of the pump is critical for heat transfer. If this is not maintained, bearing thrombus formation may occur and potentially lead to systemic thrombosis.[13] Tier IIIA HRAEs, which consists of surgically managed pump thrombosis, were not statistically different irrespective of the presence of decoupling. The mechanisms underpinning the development of pump thrombosis are clearly multifactorial with contributions from device positioning, presence of antiplatelet and anticoagulation therapies and device type.

Decoupling-derived right heart failure may increase the risk of LVAD-associated bleeding events. Right heart failure may contribute to the development of hepatic congestion and subsequently lead to increased coagulopathy. Inflammatory and angiogenesis signal cascades are also associated with the development of arteriovenous malformations,[14] though the relationship between decoupling and these contributing factors remains unclear.[15] Nevertheless, event rates of bleeding were

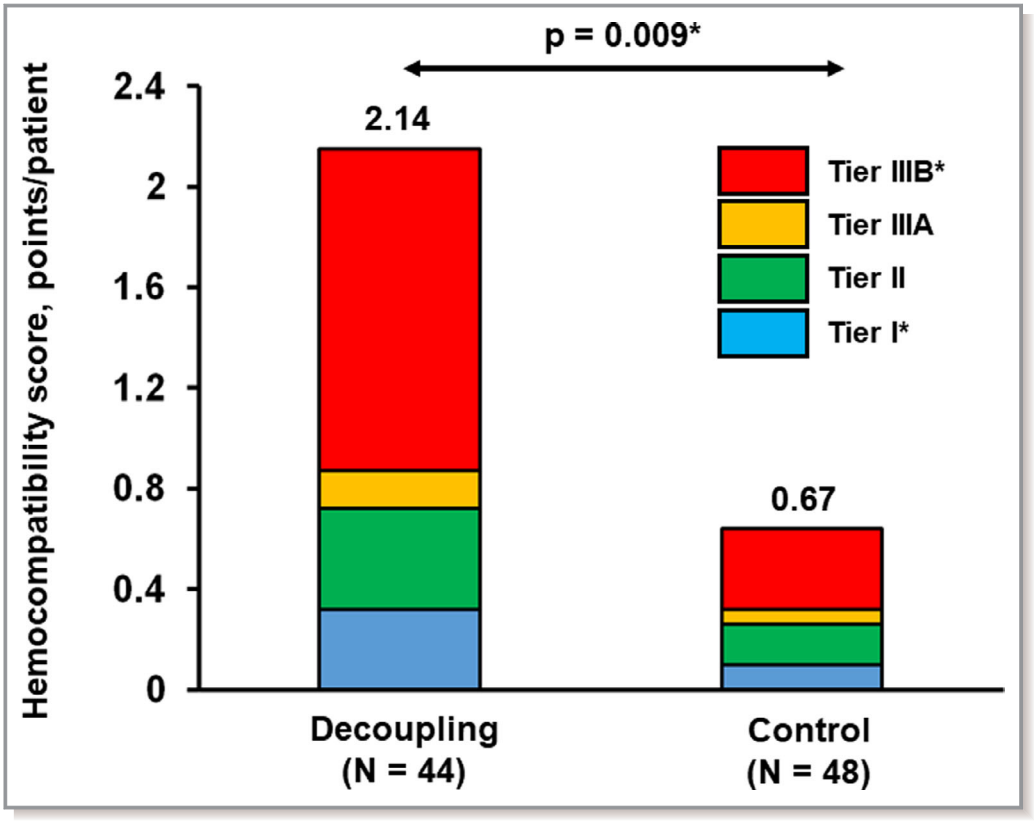


**Figure 5.** Comparison in the hemocompatibility score between the decoupling group and the control group. *$P$<0.05 by Mann–Whitney U test.

not statistically different irrespective of the existence of decoupling. Multifactorial mechanisms certainly contribute to the cumulative risk for bleeding events. Longer observational periods are needed for assessment of longitudinal bleeding risk.

## Study Limitations and Future Directions

This is a single-center study composed of a moderate-sized cohort with a 1-year observational period. Longer observational periods may better clarify the impact of decoupling on the development of HRAEs. We performed hemodynamic assessments for clinically stable outpatients only limiting the generaliziability of the results to all subsets of patients with LVADs. Further investigation is also needed to understand the implications of potential medical therapies in response to decoupling. The incidence of decoupling during HeartMate 3 support remains uncertain. The incidence of pump thrombosis is low, whereas bleeding risk with HeartMate 3 support is still nonnegligible.[16] Decoupling still may be a factor in the occurrence of HRAEs in the era of HeartMate 3. We showed the clinical relationship between decoupling and HRAEs, but the biological and pathophysiologic mechanisms of decoupling remain unclear. Right heart failure may contribute to the development of HRAEs, though it is clear that other factors are important to consider. Decoupling was an independent risk factor for HRAEs, but we cannot completely exclude other unknown confounders or risk factors such as sex difference, given moderate sample size with small number of events.

## Conclusions

The presence of decoupling between dPAP and PCWP was associated with worsening of right heart function and HRAEs in patients with LVADs. Therapeutic strategies to address decoupling are needed.

## Disclosures

Dr Uriel receives grant support from Abbott and Medtronic, and serves as a consultant to Leviticus Cardio; Dr Jeevanandam receives consultant fee from Abbott. Dr Sayer has received consulting fees from Medtronic. The remaining authors have no disclosures to report.

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# Supplemental Material

**Table S1. 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) | |
| Tier II: moderate | >2 gastrointestinal or other nonbleeding episodes | 2 points each |
| | Nondisabling stroke | |
| Tier III | | |
| IIIA: moderate to severe | Pump malfunction attributable to 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 S2. Trends of therapeutic parameters.**

| | Decoupling (N = 44) | Control (N = 48) | p value |
|---|---|---|---|
| *Baseline* | | | |
| Aspirin dose, mg | 81 (81, 264) | 81 (81, 244) | 0.41 |
| INR | 2.2 (1.9, 2.4) | 2.1 (1.6, 2.5) | 0.4 |
| *At 1 month later* | | | |
| Aspirin dose, mg | 81 (81, 325) | 81 (81, 162) | 0.38 |
| INR | 2.3 (1.9, 2.6) | 2.1 (1.9, 2.4) | 0.29 |
| *At 3 month later* | | | |
| Aspirin dose, mg | 81 (0, 162) | 81 (81, 162) | 0.99 |
| INR | 2.3 (2.1, 2.6) | 2.2 (1.9, 2.5) | 0.14 |
| *At 6 month later* | | | |
| Aspirin dose, mg | 81 (81, 325) | 81 (0, 101) | 0.28 |
| INR | 2.1 (1.9, 2.4) | 2.1 (1.8, 2.4) | 0.65 |

INR, international normalized ratio. Variables were compared by Mann-Whitney U test.