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ORIGINAL RESEARCH

Acute Hemodynamic Effects of Cardiac Resynchronization Therapy Versus Alternative Pacing Strategies in Patients With Left Ventricular Assist Devices

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BACKGROUND: The hemodynamic effects of cardiac resynchronization therapy in patients with left ventricular assist devices (LVADs) are uncharacterized. We aimed to quantify the hemodynamic effects of different ventricular pacing configurations in patients with LVADs, focusing on short-term changes in load-independent right ventricular (RV) contractility.

METHODS AND RESULTS: Patients with LVADs underwent right heart catheterization during spontaneous respiration without sedation and with pressures recorded at end expiration. Right heart catheterization was performed at different pacemaker configurations (biventricular pacing, left ventricular pacing, RV pacing, and unpaced conduction) in a randomly generated sequence with >3 minutes between configuration change and hemodynamic assessment. The right heart catheterization operator was blinded to the sequence. RV maximal change in pressure over time normalized to instantaneous pressure was calculated from digitized hemodynamic waveforms, consistent with a previously validated protocol. Fifteen patients with LVADs who were in sinus rhythm were included. Load-independent RV contractility, as assessed by RV maximal change in pressure over time normalized to instantaneous pressure, was higher in biventricular pacing compared with unpaced conduction (15.7±7.6 versus 11.0±4.0 s^{-1}; P=0.003). Thermodilution cardiac output was higher in biventricular pacing compared with unpaced conduction (4.48±0.7 versus 4.38±0.8 L/min; P=0.05). There were no significant differences in heart rate, ventricular filling pressures, or atrioventricular valvular regurgitation across all pacing configurations.

CONCLUSIONS: Biventricular pacing acutely improves load-independent RV contractility in patients with LVADs. Even in these patients with mechanical left ventricular unloading via LVAD who were relative pacing nonresponders (required LVAD support despite cardiac resynchronization therapy), biventricular pacing was acutely beneficial to RV contractility.

Key Words: cardiac resynchronization therapy ■ left ventricular assist device ■ right ventricular contractility

Cardiac resynchronization therapy (CRT) with biventricular pacing improves functional capacity, morbidity, and mortality in select patients with symptomatic left ventricular (LV) heart failure and electrical evidence of mechanical ventricular dyssynchrony.[1-4] Early short-term hemodynamic studies showed an improvement in LV contractility (defined by maximal change in pressure over time [dP/dt_{max}]) within as few as 6 beats after CRT initiation.[5] Long-term clinical studies have further demonstrated improvements in adverse LV remodeling to a degree comparable to common pharmacologic agents routinely used for cardiomyopathy therapy, such as angiotensin-converting enzyme inhibitors and β-blockers.[1,2,6-8]

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CLINICAL PERSPECTIVE

What Is New?

- The hemodynamic role of cardiac resynchronization therapy in patients with left ventricular assist devices is unknown, particularly as right ventricular contractility becomes increasingly important after left ventricular assist device implantation.
- This study found that cardiac resynchronization therapy pacing was associated with short-term improvement in right ventricular load-independent contractility and cardiac output when compared with unpaced conduction.

What Are the Clinical Implications?

- These findings suggest that patients with left ventricular assist devices who are undergoing cardiac resynchronization therapy may benefit from continued biventricular pacing, and call us to more deeply investigate the hemodynamic mechanisms responsible and to explore potential predictors of short- and long-term right ventricular response with cardiac resynchronization therapy pacing.

Nonstandard Abbreviations and Acronyms

CRT	cardiac resynchronization therapy
dP/dt_{max}	maximal change in pressure over time
E_a	effective arterial elastance
PAWP	pulmonary arterial wedge pressure
RAP	right atrial pressure
RHC	right heart catheterization
RVSWI	right ventricular stroke work index

Despite these salubrious effects, up to 30% to 35% of patients who undergo guideline-appropriate CRT implantation are ultimately classified as CRT nonresponders.[1,3,9,10] Although definitions of CRT nonresponse vary in the literature, most incorporate some combination of clinical measures (eg, New York Heart Association class and quality-of-life metrics), reverse LV remodeling assessments, and outcome measures (eg, heart failure hospitalizations and mortality).[1,11,12] Some CRT nonresponders experience progressive worsening of heart failure and ultimately require LV assist device (LVAD) therapy.

Among patients with LVADs, up to 50% have a preexisting CRT device in situ.[13,14] Whether or not deemed a CRT nonresponder, most patients with LVADs who use CRT devices continue receiving biventricular pacing after implantation.[15] The benefit of CRT in the significantly altered physiologic state of LVAD support, and in a population likely enriched for CRT nonresponders, remains unknown. Representation in the literature is primarily composed of retrospective case reports and observational studies, with continuing clinical equipoise.[13,14,16] Accordingly, some centers have adopted a strategy of deactivating LV leads in all patients with LVADs to conserve battery life.

No prior study has closely investigated the short-term load-independent right ventricular (RV) hemodynamic effects of different ventricular pacing configurations in patients with LVADs. Given the complex potential ramifications of different pacing modalities on RV afterload in particular, assessment of RV contractility via a load-independent metric is crucial to elucidate more accurately the physiologic implications of CRT and other pacing modalities for the RV in patients with LVADs. This study aimed to measure short-term changes in invasively measured hemodynamics with different pacing configurations in patients with LVADs, focusing on short-term alterations in a load-independent measure of RV contractility.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. This was a prospective, randomized, cross-sectional study conducted at the Medical University of South Carolina. Pacemaker setting sequence was the randomized variable, as described below. The study was approved by the Medical University of South Carolina Institutional Review Board, and all patients signed informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki. Eligibility included adult patients with LVADs who had a preexisting functional CRT system, referred for a clinically indicated, outpatient right heart catheterization (RHC). Patients with cardiogenic shock, respiratory failure, hypotension, suspected pump thrombosis, ongoing ventricular arrhythmias, and atrial fibrillation were excluded from consideration.

RHC Procedural Methods

All patients underwent standard RHC during spontaneous respiration and without sedation. Vital signs, including heart rate, blood pressure, and arterial oxygenation, were monitored in accordance with catheterization laboratory protocol. RHC was performed by an experienced heart failure physician (B.A.H. or R.J.T.). All patients were in normal sinus rhythm during testing. RHC measurements were performed at each pacemaker configuration (biventricular pacing, LV pacing, RV pacing, and unpaced conduction) in

a randomly generated sequence with at least 3 minutes allowed between each configuration change and subsequent hemodynamic measurements. Pacemaker changes were made by trained device technicians. Pacemaker-dependent patients were excluded from unpaced conduction testing. The RHC operator and interpreter of hemodynamics was blinded to the pacemaker configuration sequence and to QRS morphological characteristics during the case. Concomitant echocardiography was performed with attention to LV size and valvular function at each pacemaker configuration. LVAD parameters (flow, power, and pulsatility index) were recorded at each pacemaker configuration from the patient's respective LVAD monitor. All patients were returned to their original pacemaker setting following the study.

Hemodynamic Measurements

Hemodynamic measurements were recorded at end expiration and included right atrial pressure (RAP), systolic and end-diastolic RV pressures, systolic and diastolic pulmonary artery (PA) pressures, mean PA pressure, PA wedge pressure (PAWP), PA oxygen saturation, and thermodilution cardiac output, averaged in triplicate. RAP and PAWP were recorded by transecting the A-wave, per guideline recommendations.[17] Hemodynamic waveforms were recorded by the MacLAB recording system. RV pressure waveforms were digitized following a previously described protocol found to closely correlate with micromanometrically obtained data in the time domain.[18] Briefly, screen captures from appropriate RV pressure waveforms were printed, redigitized, and then imported into Engauge Digitizer, version 10.6. Digitized traced wave data were exported to Excel (Microsoft Office 365 ProPlus), and time derivative was calculated using a standard numerical differentiation algorithm. Representative beats were chosen at end expiration and were specifically identified as being without ringing or whip artifact. RV dP/dt_{max} was calculated from digitized hemodynamic waveforms (Figure 1). All digitization and derived measurements were performed blinded to the pacing modality.

The primary outcome was RV dP/dt_{max} normalized to instantaneous pressure. Secondary hemodynamic outcomes included RAP, mean PA pressure, PAWP, RAP:PAWP, RV stroke work index (RVSWI), PA pulsatility index, pulmonary effective arterial elastance (E_a), and thermodilution cardiac output. E_a was calculated as the systolic PA pressure divided by the stroke volume. PA pulsatility index was calculated as the pulmonary pulse pressure divided by RAP. Secondary echocardiographic outcomes included LV end-diastolic diameter, mitral regurgitation, and tricuspid regurgitation. Tricuspid regurgitation and mitral regurgitation were graded (0 indicates none; 1, mild; 2, moderate; and 3, severe) and then grouped on the basis of valvular significance (none-mild and moderate-severe) for comparison purposes.

Statistical Analysis

Continuous parameters are expressed as mean±SD. Comparisons across conditions were performed using repeated-measures ANOVA with 4 levels (ie, 1 for each pacing condition). Post hoc pairwise comparisons were performed by means of paired Student *t* test or Wilcoxon signed-rank test, as appropriate. Between-group analyses were conducted using independent-sample *t*-tests. A nominal 2-sided $P \leq 0.05$ defined statistical significance.

RESULTS

A total of 15 patients (10 men and 5 women) with LVADs, including HeartMate 2 (Abbott, Chicago, IL) ($n=6$), HeartMate 3 ($n=6$), and heartware ventricular assist device (HVAD) ($n=3$) (Medtronic, Minneapolis, MN), participated. All patients had underlying left bundle-branch block (LBBB) as their original indication for CRT. Table 1 features baseline patient demographic and clinical characteristics.

Across subjects, RV dP/dt_{max} normalized to instantaneous pressure was 36% higher with biventricular pacing compared with unpaced conduction (15.7±7.6 versus 11.0±4.0 s^{-1}; $P=0.003$) (Figure 2). There was no significant difference in RV dP/dt_{max} normalized to instantaneous pressure when comparing RV pacing with unpaced conduction ($P=0.13$) or LV pacing with unpaced conduction ($P=0.28$). A per-patient comparison of the primary outcome comparing unpaced conduction with biventricular pacing is shown in Figure 3. Both nonnormalized RV dP/dt_{max} and RV dP/dt_{max} normalized for peak (instead of instantaneous) pressure demonstrated similar differences between unpaced conduction and biventricular pacing ($P=0.014$ and $P=0.009$, respectively) (Figure S1). Three patients were pacemaker dependent, obviating comparison with the unpaced conduction condition. Group and per-patient comparisons in the remaining 12 patients were performed, and results were consistent with the effects observed in the total cohort (Figure S2).

The hemodynamic, echocardiographic, and LVAD parameters during RHC at each pacemaker configuration are shown in Table 2. Thermodilution cardiac output was higher for biventricular pacing than unpaced conduction ($P=0.05$), with no difference when comparing either LV or RV pacing with unpaced conduction. PAWP was lower for LV pacing compared with all other pacing parameters. No significant differences were appreciated in other hemodynamic (RAP, PAWP,

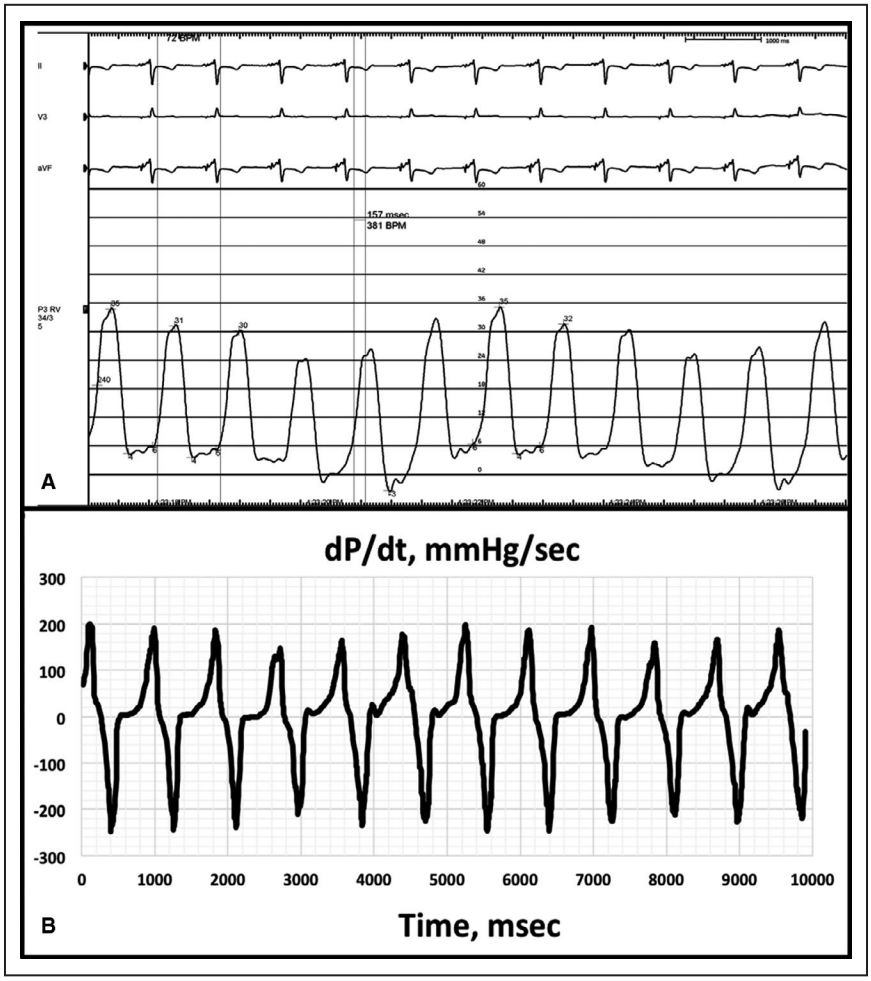

Figure 1. Representative hemodynamic waveform (A) and corresponding change in pressure over time (dP/dt) waveform (B).
BPM indicates beats per minute; and RV, right ventricle.

RVSWI, E_a, and PA pulsatility index), LVAD, or echocardiographic (LV end-diastolic diameter, mitral regurgitation, and tricuspid regurgitation) variables compared between pacemaker configurations.

To explore potential predictors of relative RV contractile response to biventricular pacing, patients were stratified relative to median percentage change of RV dP/dt_{max} normalized to instantaneous pressure (median, 36.4%) into CRT-major (% response>median; *n*=6) and CRT-minor (%response<median; *n*=6) responder groups. Comparison between CRT-major and CRT-minor responder groups is shown in Table 3. There were no differences in age, sex, New York Heart Association class, LVAD type, or duration between the groups. The CRT-major responder group had significantly lower baseline RAP (5.2±0.4 versus 14.2±8.1 mm Hg; *P*<0.02), mean PA pressure (19.5±4.7 versus 29.0±5.0 mm Hg; *P*<0.007), and PAWP (9.3±3.3 versus 17.3±7.1 mm Hg; *P*<0.03) compared with the CRT-minor group. CRT-major responders also had lower overall RV load, as evidenced by lower E_a (0.50±0.15 versus 0.83±0.27 mm Hg /mL; *P*=0.03). Although unpaced and biventricular paced QRS durations were not different between major and minor responders, there was a trend toward greater relative QRS duration reduction in CRT-major responders when assessed by percentage change in QRS duration (–19%+16% versus –6.05%+27%; *P*=0.08). No other significant differences were observed with other hemodynamic parameters, including pulmonary vascular resistance, RVSWI, or echocardiographic variables.

DISCUSSION

In this prospective study, we found that biventricular pacing acutely improves load-independent RV contractility versus unpaced conduction in patients with LVADs. Furthermore, in our analysis, cardiac output was higher during biventricular pacing when compared with unpaced conduction.

Table 1. Demographics and Baseline Characteristics

Variable	Value
Age, y	58±8
Male sex, n (%)	10 (66)
Height, cm	176.4±12.3
Weight, kg	97.2±24.4
BMI, kg/m^2	31.2±7.32
Device type, n (%)	
HeartMate 2	6 (40)
HeartMate 3	6 (40)
HVAD	3 (20)
LVAD duration, d	564±530
LVAD indication, n (%)	
Destination therapy	11 (73)
Bridge to transplant	4 (27)
Nonischemic cardiomyopathy	9 (60)
Sinus rhythm	15 (100)
NYHA classification, n (%)	
II	7 (47)
III	8 (53)
Unpaced QRS duration, ms	137±27
LV end-diastolic diameter, cm	6.03±0.83
LV ejection fraction, %	25.7±10.0

Data are given as mean±SD unless otherwise indicated. BMI indicates body mass index; HVAD, heartware ventricular assist device; LV, left ventricular; LVAD, LV assist device; and NYHA, New York Heart Association.

In the absence of definitive guidelines on CRT management post-LVAD implantation, the individualized decision to continue CRT versus adopting alternate pacing strategies remains controversial.[19] Several factors are involved in this decision, including intrinsic CRT utility in this population, balancing ventricular arrhythmias, and limiting generator replacements. Prior single-center studies suggested reduced arrhythmias with CRT in patients with LVADs, but showed no survival benefit.[13,16] A recent large multicenter study of 488 patients with LVADs suggested no survival benefit and significantly more pulse generator replacement procedures with CRT compared with implantable cardioverters-defibrillators alone.[14] However, these studies examined outcomes in intrinsically different patient populations by comparing patients with CRT indications and biventricular pacing with patients without CRT indications.[20] Our study compared short-term hemodynamic changes within patients all having an indication for CRT. Notably, our study findings stand in some contrast to a recent prospective study that found no improvement in RVSWI with different pacing modalities.[21] Although RVSWI has shown pre-LVAD predictive power for RV failure, it is known to be load dependent and therefore is a suboptimal physiologic descriptor of RV contractility.[22] By using pressure-normalized RV dP/dt$_{max}$, a load-independent metric, we believe our study serves to describe better the differences in the RV contractile state with differing pacemaker configurations. This emphasis on load-independent contractility measurement is important given the increased RV sensitivity to afterload post-LVAD implantation.[21]

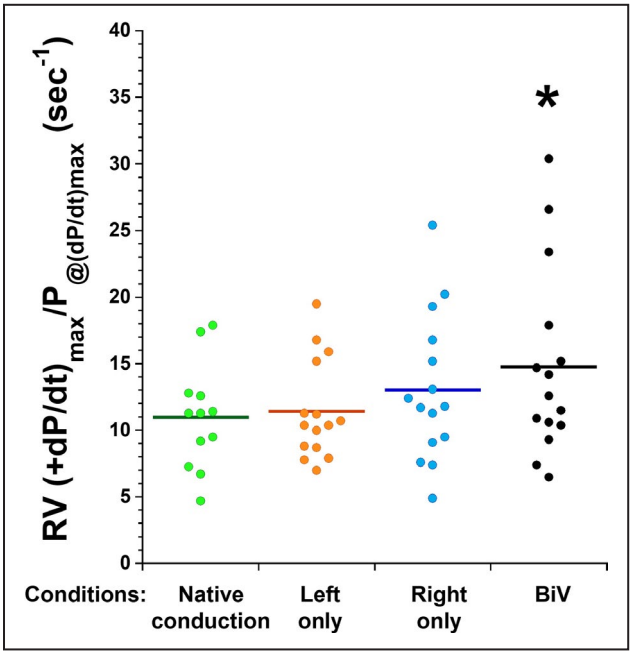

Figure 2. Right ventricular maximal change in pressure over time normalized to instantaneous pressure (RV dP/dt$_{max}$/P) comparison between pacemaker settings.
BiV indicates biventricular.

The potential explanation for our observation that biventricular pacing is associated with improved RV contractility, despite near full LV circulatory support,

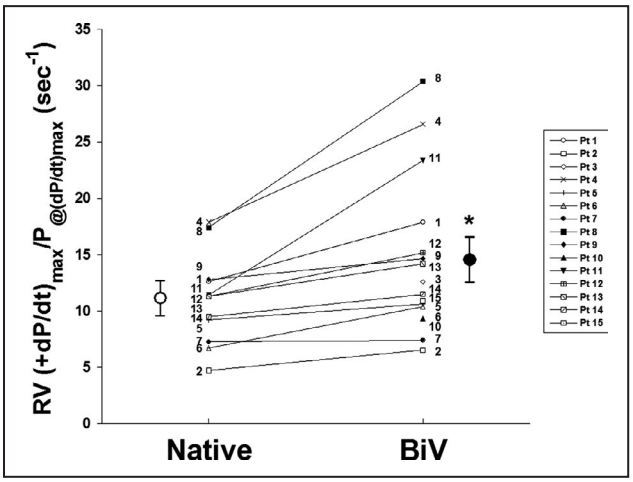

Figure 3. Individual right ventricular maximal change in pressure over time normalized to instantaneous pressure (RV dP/dt$_{max}$/P) values during native conduction (unpaced) and biventricular (BiV) conduction.
Pt indicates patient.

Table 2. Hemodynamic, Echocardiographic, and LVAD Parameters Across All Pacemaker Settings

Variable	Biventricular Pacing (n=15)	RV Pacing (n=15)	LV Pacing (n=15)	Unpaced (n=12)	*P* Value
HR, bpm	76 (13)	76 (14)	76 (14)	71 (12)	0.29
MAP, mm Hg	95 (26)	87 (15)	88 (18)	84 (16)	0.12
RAP, mm Hg	8.7 (4.2)	8.8 (3.6)	8.9 (4.2)	9.7 (7.2)	0.50
mPAP, mm Hg	25.6 (7.05)	26.6 (7.36)	25.3 (6.68)	24.3 (6.80)*	0.04*
PAWP, mm Hg	14.5 (6.96)	15.0 (7.12)	12.4 (5.82)*	13.3 (6.76)	0.02*
RAP:PAWP	0.63 (0.23)	0.64 (0.22)	0.76 (0.27)	0.73 (0.29)	0.24
TDCO, L/min	4.48 (0.73)*	4.4 (0.84)	4.35 (0.95)	4.38 (0.81)	0.05*
PA saturation, %	64.2 (8.8)	62.9 (7.9)	63.8 (9.2)	63.7 (9.0)	0.18
QRS, ms	146 (43)	167 (43)	156 (52)	148 (52)	0.21
LVAD PI	4.9 (1.4)	4.8 (1.5)	4.8 (1.6)	4.8 (1.4)	0.68
LVAD power, Watts	4.4 (0.8)	4.3 (0.7)	4.2 (0.7)	4.2 (0.6)	0.25
LVAD flow, L/min	4.3 (0.6)	4.2 (0.7)	4.2 (0.6)	4.2 (0.7)	0.90
RVSWI, g/m^2 per beat	6.5 (2.3)	6.6 (2.3)	5.9 (1.9)	5.5 (2.9)	0.06
PAPi	3.0 (1.8)	2.8 (1.2)	2.9 (1.6)	2.9 (1.5)	0.78
E_a, mm Hg/mL	0.71 (0.28)	0.74 (0.28)	0.74 (0.28)	0.67 (0.27)	0.17
LVEDD, cm	6.05 (0.63)	6.12 (0.79)	6.04 (0.88)	5.96 (0.89)	0.75
TR grade	13:2	12:3	12:3	9:3	0.39
MR grade	13:2	11:4	15:0	8:4	0.06

Continuous parameters are expressed as mean (SD). Comparisons across conditions were performed using repeated-measures ANOVA with 4 levels (ie, 1 for each pacing condition). Post hoc pairwise comparisons were performed by means of paired Student *t* test or Wilcoxon signed-rank test, as appropriate. Between-group analyses were conducted using independent-sample *t* tests. Bpm indicates beats per minute; E_a, effective arterial elastance; HR, heart rate; LV, left ventricular; LVAD, LV assist device; LVEDD, LV end-diastolic diameter; MAP, mean arterial pressure; MR, mitral regurgitation; mPAP, mean PA pressure; PA, pulmonary artery; PAPi, PA pulsatility index; PAWP, PA wedge pressure; PI, pulsatility index; RV, right ventricular; RVSWI, RV stroke work index; RAP, right atrial pressure; TDCO, thermodilution cardiac output; and TR, tricuspid regurgitation.

*$p<0.05$.

may lie in the ability of CRT to synchronize biventricular systolic interaction. RV contractility is inextricably linked to LV contractility through septal interaction.[23] Animal models demonstrate that the LV contributes as much as 50% to RV pressure generation in normal functioning hearts.[24] Even in patients with LVADs without aortic valve opening, these studies suggest that LV pressure generation may augment RV pressure generation. Allowing LV and RV pressure generation to occur simultaneously with CRT (instead of temporally offset, as occurs with LBBB) may augment RV contractility. This temporal contractile synergy may become increasingly important in the compromised RV state post-LVAD. Specifically, the deleterious geometrical changes and augmented load sensitivity post-LVAD[23] may leave the RV more reliant on LV pressure generation than in its native state.

Concurrent with augmented load-independent RV contractility, our analyses demonstrated an increase in thermodilution cardiac output with biventricular pacing compared with unpaced conduction, suggesting that the observed increase in RV contractility carried meaningful hemodynamic benefit, at least at rest. We did not witness changes in relative RV or LV filling pressures, although our period of observation may have been too brief for this observation.

In an exploratory analysis, we observed that patients with better baseline ventricular unloading and/or RV function had more RV contractility augmentation with CRT. Patients with lower PAWP, RAP, and E_a and numerically (although not statistically significantly) higher PA pulsatility index had better relative response to biventricular pacing. A potential explanation for this finding may again rely on alterations in the LV's relative contribution to RV contractility on the basis of septal geometry. In the native heart, the septum drives RV contractility through twist, generating a longitudinal contractile motion.[25,26] The generation of septal twist relies on a specific myofibrillar orientation within the septum.[27-29] In states of RV failure and worsening congestion, the septum is progressively shifted leftward, disrupting this myofibrillar orientation and diminishing septal twist.[23] In our patients, those with worse RV failure may have had more deleterious septal shift, and therefore may not have gained as great an advantage from the synchronous LV and RV contraction afforded by CRT. This potentially represents a clinical conundrum in that biventricular pacing may acutely improve RV contractility, at least for those who need it most (ie, those with the greatest degree of native RV dysfunction). Notably, however, even patients with lower baseline RV function did realize improved RV contractility

Table 3. Comparison of Baseline Characteristics During Unpaced Conduction Between CRT-Major and CRT-Minor Response Groups

Unpaced Conduction	CRT-Major Response ($\%dP/dt_{max}$/P>Median)	CRT-Minor Response ($\%dP/dt_{max}$/P<Median)	*P* Value
RAP, mm Hg	5.2 (0.4)	14.2 (8.1)	0.02*
mPAP, mm Hg	19.5 (4.7)	29.0 (5.0)	0.007*
PAWP, mm Hg	9.3 (3.3)	17.3 (7.1)	0.03*
RAP:PAWP	0.63 (0.26)	0.83 (0.31)	0.49
TDCO, L/min	4.6 (1.0)	4.1 (0.6)	0.35
PVR, Wood units	2.2 (0.4)	2.9 (1.8)	0.42
RVSWI, g/m^2 per beat	5.6 (2.1)	5.5 (3.8)	0.94
PAPi	3.6 (1.2)	2.2 (1.5)	0.12
E_a, mm Hg/mL	0.50 (0.15)	0.83 (0.27)	0.03*
LVEDD, cm	5.82 (1.01)	6.10 (0.82)	0.62
Age, y	58 (6.5)	56 (9.5)	0.56
Sex, men:women	5:1	2:4	0.08
LVAD indication, DT:BTT	4:2	5:1	0.51
Cardiomyopathy cause, NICM:ICM	5:1	4:2	0.51
Unpaced QRS duration, ms	158 (59)	138 (48)	0.79
Biventricular-paced QRS duration, ms	127 (18)	138 (36)	0.13
Change in QRS, ms	38 (44)	−0.67 (37)	0.14
% Change in QRS	−19 (16)	−6.05 (27)	0.08
LVAD duration, d	656 (619)	426 (491)	0.25

Continuous parameters are expressed as mean (SD). Comparisons across conditions were performed using repeated-measures ANOVA with 4 levels (ie, 1 for each pacing condition). Post hoc pairwise comparisons were performed by means of paired Student *t* test or Wilcoxon signed-rank test, as appropriate. Between-group analyses were conducted using independent-sample *t* tests. BTT indicates bridge to transplant; CRT, cardiac resynchronization therapy; $dP/dt_{max}/P$, maximal change in pressure over time normalized to instantaneous pressure; DT, destination therapy; E_a, effective arterial elastance; ICM, ischemic cardiomyopathy; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; mPAP, mean pulmonary artery pressure; NICM, nonischemic cardiomyopathy; PAPi, pulmonary artery pulsatility index; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; and TDCO, thermodilution cardiac output.

*$p \leq 0.05$.-

with biventricular pacing, albeit to a lesser degree. This bears further exploration. It is also notable that we observed RV contractility augmentation with CRT even in this group, who were presumably pre-LVAD CRT nonresponders. This may be caused by biventricular mechanical[29] or electrical[30] reverse remodeling after LVAD, although this correlation has not been explored.

To date, CRT therapy has solely focused on augmentation of LV contractility, function, and remodeling. Our study did not investigate subtleties of pacing, such as atrio-ventricular (A-V) delays, LV-RV offset, and site of LV activation, which may make meaningful differences in relative RV contractility. Earlier work has demonstrated that AV delays for optimal RV contractility tended to be shorter than those used for optimal LV contractility.[31] Furthermore, multisite RV pacing afforded greater RV contractility than single-site RV pacing.[31] Notably, although biventricular pacing (and not RV or LV pacing) was the only modality that led to improved RV contractility when compared with unpaced conduction, there was no statistical difference between the primary outcome comparing biventricular with RV pacing (14.8+7 versus 13+5.5 s^{-1}; *P*=0.23). Our prior work in patients with right bundle-branch block[32] suggests that pacing site plays a significant role in RV contractility response to pacing. It may be that patients who responded favorably to RV pacing alone had a more advantageous pacing site. We were unable to assign RV lead locations (apex, free wall, and septum) on the basis of available information in this cohort. Future studies should explore the RV contractile effects of alterations in pacing configurations beyond changing which ventricle is stimulated in patients with LVADs. It is noteworthy that LV-only pacing did not achieve hemodynamic benefits similar to biventricular pacing in this study. In non-LVAD heart failure patients with LBBB, LV pacing provides similar LV hemodynamic effects as biventricular pacing.[32] Its use is becoming more common given its lower battery consumption and similar outcomes to CRT in patients with LBBB. This is of particular import in patients with LVADs given the potential advantages of prolonging battery life and reducing pulse generator replacements. The observation that RV hemodynamics were not improved with LV-only pacing is consistent with previous studies.[33]

The findings of this study should be interpreted in the context of certain limitations. First, this study was purely descriptive in nature, and we only assessed short-term hemodynamic changes. The historical lessons of CRT

research teach that its long-term benefits are gained through mechanisms beyond those responsible for the short-term improvement in ventricular contractility.[34] Second, our sample was relatively small, given the limited population; however, it was both randomized and blinded in data acquisition and analysis, enhancing the validity of its results. Third, we neither addressed clinical outcomes nor evaluated long-term hemodynamic follow-up. Future studies should focus on both long-term hemodynamic and clinical outcomes (eg, New York Heart Association class and quality-of-life metrics) to determine the clinical significance of these short-term hemodynamic findings. The findings in this study solely reflect a population in sinus rhythm and with CRT for the indication of underlying LBBB. Thus, these results should not be extrapolated to patients with alternative rhythm or conduction patterns before further study

Despite these caveats, this study suggests that biventricular pacing leads to increased load-independent RV contractility in patients with LVAD. These findings should give pause to the bedside clinician considering empiric deactivation of CRT in patients with LVADs who have any clinical RV failure. More pressingly, these findings call us to more deeply investigate the hemodynamic mechanisms responsible and to explore potential predictors of short- and long-term RV response with CRT pacing. With new LVAD and pacing technology on the horizon, further investigation into individualized CRT optimization could provide another layer of investigation into this field of research.

ARTICLE INFORMATION

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Supplementary Material

Figures S1–S2

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SUPPLEMENTAL MATERIAL

Figure S1. Comparison of non-normalized dP/dt_{max} and RV dP/dtmax normalized for peak RV pressure at different pacing modalities only in non-pacemaker dependent patients.

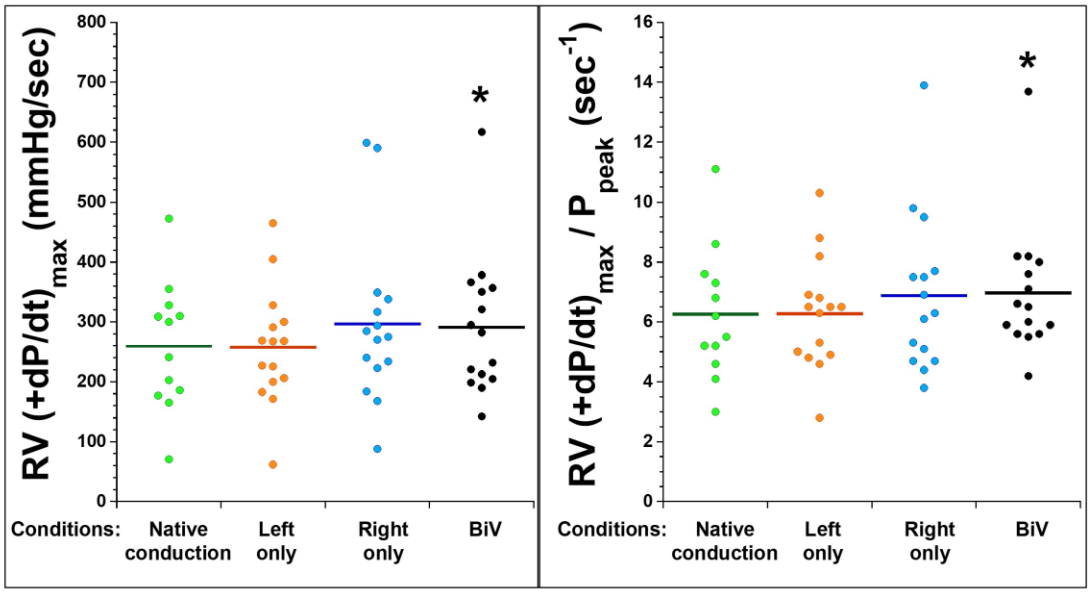

Figure S2. Comparison of non-normalized dP/dt_{max}, dP/dt_{max} normalized for instantaneous pressure, and RV dP/dt_{max} normalized for peak RV pressure at different pacing modalities.