Biventricular Pacing Improves the Blunted Force–Frequency Relation Present During Univentricular Pacing in Patients With Heart Failure and Conduction Delay

Dirk Vollmann, MD; Lars Lüthje, MD; Peter Schott, MD; Gerd Hasenfuss, MD; Christina Unterberg-Buchwald, MD

Background—In patients with chronic heart failure (CHF) and conduction delay, biventricular (BiV) and left ventricular (LV) pacing similarly improve systolic function at resting heart rates. We hypothesized that BiV and univentricular pacing differentially affect contractile function at increasing heart rates.

Methods and Results—Twenty-two patients (aged 66±2 years, QRS 179±8 ms, LV ejection fraction 23±1%) underwent cardiac catheterization before device implantation to measure LV hemodynamics at baseline (rate 68±2 bpm; sinus rhythm n=18; atrial fibrillation n=4) and during BiV, LV, and right ventricular (RV) stimulation at 80, 100, 120, and 140 bpm. BiV and LV pacing at 80 bpm equally augmented dP/dt\text{max} as compared with baseline and RV pacing (P<0.001). Stimulation rate significantly interacted with the effect of BiV, LV, and RV pacing on LV end-diastolic pressure (LVEDP), systolic pressure (LVSP), and dP/dt\text{max}. Increasing the rate from 80 to 140 bpm enhanced dP/dt\text{max} from 913±28 to 1119±50 mm Hg/s during BiV stimulation (P<0.001) but had no significant effect on contractility during single-site LV (951±47 versus 1002±54 mm Hg/s) or RV (800±46 versus 881±49 mm Hg/s) pacing. At 140 bpm, LVEDP was lower and LVSP higher during BiV pacing than during RV and LV pacing (LVEDP 12±1 versus 17±1 and 16±1 mm Hg, P<0.001; LVSP 112±5 versus 106±5 and 108±6 mm Hg, P<0.01 and P=0.09; BiV versus RV and LV pacing, respectively).

Conclusions—Different modes of ventricular stimulation alter the in vivo force–frequency relation of CHF patients. In contrast to single-site LV and RV pacing, contractile function improves with increasing heart rates during BiV stimulation. This effect may contribute to the enhanced exercise capacity during BiV pacing and could provide a functional benefit over LV-only pacing in patients for whom resynchronization therapy is indicated. (Circulation. 2006;113:953-959.)

Key Words: ventricular pacing ▪ cardiac resynchronization ▪ heart rate ▪ hemodynamics ▪ heart failure

Clinical trials demonstrated that biventricular (BiV) pacing improves cardiac function and exercise capacity in patients with heart failure and ventricular conduction delay.1 The underlying mechanisms are not completely elucidated. It is believed that mechanical resynchronization of left ventricular (LV) activation and consecutive improvement in systolic function play a crucial role.2,3 At baseline heart rates, BiV and single-site LV pacing produce similar improvements in mechanical asynchrony4,5 and systolic function4–7; however, clinical investigations that compared functional parameters during BiV and LV-only pacing produced controversial results.8–10 Furthermore, recent studies reported differences in systolic and diastolic time intervals between single-site and BiV pacing.5,11 and this disparity could significantly influence hemodynamic function during different modes of ventricular pacing at elevated heart rates. Thus, the discussion about whether or not BiV and single-site LV pacing may provide similar hemodynamic and functional effectiveness continues.

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Increasing heart rates have long been recognized as a potential modulator of systolic function.12 In the normal heart, a positive force–frequency relationship provides intrinsic augmentation of cardiac contractility at elevated heart rates. In failing hearts, alterations in the force–frequency relation have been identified that potentially contribute to an impaired exercise capacity.13 In the present study, we hypothesized that the force–frequency relationship of selected heart failure patients may be influenced by different modes of ventricular pacing. Specifically, we assumed that BiV stimulation may provide beneficial effects on systolic function at increasing heart rates. To test this hypothesis, we measured LV end-diastolic and systolic pressures and determined the maximum rate of LV pressure rise (dP/dt\text{max}) at increasing heart rates...
Methods

Study Group
Twenty-two consecutive patients indicated for cardiac resynchronization therapy (CRT) were included after their written informed consent was obtained and before a CRT device was implanted. Patient selection was based on established criteria for CRT: moderate to severe heart failure despite optimal medical therapy, severely depressed LV ejection fraction (≤35%), and a QRS complex that exhibited left bundle-branch block configuration with a duration >120 ms or >150 ms in patients with atrial fibrillation (AF). Patients were excluded if the baseline heart rate was >75 bpm, if they had unstable angina, if they had acute myocardial infarction within 6 to 12 months before the study, or if they were receiving intravenous inotropic support. Patients with ischemic cardiomyopathy had a coronary angiography within the last 6 months before the procedure to exclude the need for revascularization.

Study Protocol
The study complied with the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee. Catheterization was performed in the fasting state via the femoral vein and artery. Baseline medications were withheld for 6 to 12 hours, and heparin (2500 to 5000 U) was given intravenously at the beginning of the procedure. Quadripolar 5F catheters (Supreme, model 401443, St. Jude Medical) were placed into the RV apex and in the high right atrium if sinus rhythm was present. After coronary vein angiography, a 2.5F mapping catheter (Pathfinder 16, model 01-161003, Cardima) was advanced through a 7F guiding catheter (Amplatzer AL2, model 778-040-00, Cordis) introduced into the coronary sinus. The LV pacing electrode was positioned in a lateral or posterolateral cardiac vein, midway between the base and apex. For LV pressure measurements, a 6F micromanometer catheter (Micro-Tip, model SPC-464D, Millar Instruments) was placed into the LV cavity.

A Medtronic Programmer/Analyzer (model 2090/2290, Medtronic) was used for cardiac pacing at different rates. For BiV stimulation, the RV and LV electrodes were connected with a Y adapter. Patients in sinus rhythm were paced in the DDD mode with an atrioventricular (AV) delay of 80 to 140 ms. In each patient, the longest AV delay that still produced full preexcitation during RV and LV stimulation at 80 bpm was determined and used for the complete pacing protocol. Subjects in AF were paced in the VVI mode. Baseline LV pressure measurements were recorded ~15 minutes after all catheters had been positioned and pacing thresholds had been determined. Thereafter, RV, LV, and BiV pacing was performed in random order at a rate of 80 bpm. LV pressures were determined during each ventricular stimulation mode after 3 minutes of continued pacing. Thereafter, the stimulation frequency was increased to 100, 120, and 140 bpm. At each heart rate, LV pressures were again measured after 3 minutes of RV, LV, and BiV pacing, respectively. A 12-lead ECG tracing was monitored continuously to confirm appropriate cardiac pacing.

Data Analysis
Hemodynamic data were analyzed with a commercial heart catheter measuring system with hemodynamic evaluation software (Cardis, Schwarzer GmbH). The analog signal from the Millar system was digitized at 1000 Hz. Individual hemodynamic data were derived from an average of at least 10 consecutive cardiac cycles. Statistical analysis was performed with commercial software (SigmaStat 3.11). Unless otherwise noted, all data are reported as mean±SEM. Differences in hemodynamic data and QRS duration between baseline and RV, LV, or BiV pacing at 80 bpm were evaluated by use of 1-way repeated-measures ANOVA followed by Tukey test. Comparison of hemodynamic data measured during RV, LV, and BiV pacing at various heart rates was performed by use of a 2-way repeated-measures ANOVA followed by Tukey test. Multiple regression analysis was used to determine predictors of the contractile response to pacing tachycardia. A 2-tailed probability value <0.05 was considered statistically significant.

Results

Patients
Baseline characteristics of the 22 patients are summarized in Table 1. In patients with sinus rhythm, an average AV delay of 109±3 ms was programmed to provide full electrical preexcitation of the ventricles during DDD pacing. Four patients with permanent AF, a QRS duration of 179±5 ms, and an average ventricular rate of 69±2 bpm were included. Three patients described New York Heart Association class II symptoms at the time of inclusion but had experienced severe cardiac decompensation in the preceding 6 months despite optimal medical therapy. Complete data sets for repeated-measures analysis were obtained from 17 subjects (77%). In 2 patients, pacing at 80 bpm was not possible because of a higher intrinsic heart rate at the time of the investigation. In 3 patients, pacing at 140 bpm had to be aborted owing to symptoms (dyspnea or dizziness). None of the subjects reported chest pain as a potential indicator for myocardial ischemia during pacing tachycardia.

Effects of RV, LV, and BiV Pacing at 80 bpm
QRS duration shortened from 179±8 ms during baseline to 145±5 ms during BiV pacing (P<0.001). During single-site RV and LV pacing, QRS width increased to 197±6 and 213±6 ms, respectively (P<0.01 versus baseline).

Hemodynamic data at baseline and during RV, LV, and BiV pacing at 80 bpm are summarized in Table 2. There was

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Patient Characteristics (n=22)</th>
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<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
</tr>
<tr>
<td>Duration of heart failure, y</td>
</tr>
<tr>
<td>NYHA functional class</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Use of heart failure medication</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>ACE inhibitor/AT blocker</td>
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<tr>
<td>Diuretics</td>
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<tr>
<td>Spironolactone</td>
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<tr>
<td>Digitalis</td>
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<td>ECG characteristics</td>
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<tr>
<td>Intrinsic heart rate, bpm</td>
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<tr>
<td>Sinus rhythm</td>
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<tr>
<td>Intrinsic QRS duration, ms</td>
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<tr>
<td>Echocardiographic characteristics</td>
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<tr>
<td>LV ejection fraction, %</td>
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<tr>
<td>LV end-diastolic diameter, mm</td>
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</tbody>
</table>

NYHA indicates New York Heart Association; AT, angiotensin. Values are mean±SD (range) or n (%).
Table 2. LV Hemodynamics

<table>
<thead>
<tr>
<th>Rate, bpm</th>
<th>dP/dtmax, mm Hg/s</th>
<th>LVEDP, mm Hg</th>
<th>LVSP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>68±2</td>
<td>818±39</td>
<td>115±4</td>
</tr>
<tr>
<td>RV pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>800±46</td>
<td>12±1</td>
<td>108±5</td>
</tr>
<tr>
<td>100</td>
<td>859±51</td>
<td>13±1</td>
<td>109±5</td>
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<tr>
<td>120</td>
<td>888±51</td>
<td>14±1</td>
<td>107±5</td>
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<tr>
<td>140</td>
<td>881±49</td>
<td>17±1</td>
<td>106±5</td>
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<tr>
<td>LV pacing</td>
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<tr>
<td>80</td>
<td>951±47</td>
<td>13±1</td>
<td>115±6</td>
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<tr>
<td>100</td>
<td>953±57</td>
<td>12±1</td>
<td>111±5</td>
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<tr>
<td>120</td>
<td>1004±68</td>
<td>13±1</td>
<td>110±5</td>
</tr>
<tr>
<td>140</td>
<td>1002±54</td>
<td>16±1</td>
<td>108±6</td>
</tr>
<tr>
<td>BiV pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>913±28</td>
<td>10±1</td>
<td>112±4</td>
</tr>
<tr>
<td>100</td>
<td>980±35</td>
<td>11±1</td>
<td>113±4</td>
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<tr>
<td>120</td>
<td>1057±46</td>
<td>11±1</td>
<td>113±4</td>
</tr>
<tr>
<td>140</td>
<td>1119±50</td>
<td>12±1</td>
<td>112±5</td>
</tr>
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</table>

2P<0.001 vs baseline; 3P<0.05; 4P<0.01; 5P<0.001 vs RV 80 bpm; 6P<0.05; 7P<0.001 vs LV 80 bpm; 8P<0.05; 9P<0.001 vs RV 100 bpm; 10P<0.05; 11P<0.01; 12P<0.001 vs RV 120 bpm; 13P<0.05 vs LV 120 bpm; 14P<0.01 vs RLV 140 bpm; 15P<0.001 vs RV and LV 140 bpm; 16P<0.001 vs RV and BiV 140 bpm.

an increase in dP/dtmax from 818±39 mm Hg/s at baseline to 951±47 and 913±28 mm Hg/s during LV and BiV pacing, respectively (P<0.001). The difference in dP/dtmax between baseline and RV pacing (800±46 mm Hg/s) was not significant.

LV end-diastolic pressure (LVEDP) during RV, LV, and BiV pacing at 80 bpm was lower than during baseline rhythm (P<0.001; Table 2). BiV pacing was associated with a lower LVEDP than single-site RV or LV pacing, but this difference was not statistically significant. As shown in Table 2, LV systolic pressure (LVSP) during RV pacing was lower than during baseline, LV stimulation, or BiV pacing.

Systolic Function During RV, LV, and BiV Pacing Tachycardia
Contractile performance at increasing heart rates and during different modes of ventricular stimulation is illustrated in Figure 1. Table 2 summarizes all hemodynamic data. Overall, a significant interaction was found between rate of stimulation and effect of RV, LV, and BiV pacing on dP/dtmax (P<0.001), LVEDP (P<0.01), and LVSP (P<0.05). As shown in Figure 1, dP/dtmax increased with the pacing rate during BiV stimulation. In contrast, no significant change in contractile function was observed at increasing heart rates during single-site RV and LV pacing. Thus, both LV and BiV pacing enhanced dP/dtmax as compared with baseline and RV stimulation, but augmentation of cardiac contractility by higher heart rates only occurred during BiV stimulation. Figure 2 shows examples of the hemodynamic response to increasing rates during BiV pacing. Individual patient data for percent change in dP/dtmax during pacing tachycardia are summarized in Figure 3. Baseline parameters and changes in QRS width or dP/dtmax induced by pacing at 80 bpm did not predict the effect of pacing tachycardia.

The differential effect of univentricular pacing and BiV pacing on the force–frequency relation was similar in AF patients and in subjects with normal sinus rhythm. Within the subgroup of 4 AF patients, dP/dtmax at 80 and 140 bpm, respectively, was 748±16 and 768±38 mm Hg/s during RV pacing (P=0.9), 908±32 and 905±105 mm Hg/s during LV pacing (P=0.5), and 864±11 and 1189±66 mm Hg/s during BiV pacing (P<0.05).

During all 3 modes of ventricular stimulation, the increase in pacing rate from 80 to 140 bpm was associated with a significant elevation of the LVEDP (Figure 4). This rate-dependent increase in LVEDP was greater during single-site RV and LV pacing than during BiV pacing. Accordingly, LVEDP at 120 and 140 bpm was significantly lower during BiV pacing than during RV- and LV-only pacing (Figure 4). Of note, the significant increase in dP/dtmax during BiV pacing at 120 bpm occurred without a significant change in LVSP.

As illustrated in Figure 5, LVSP decreased during LV pacing at higher heart rates. No significant change was observed during RV pacing and BiV stimulation at increasing frequencies. At 140 bpm, LVSP was significantly higher during BiV pacing than during RV pacing and somewhat higher (P=0.09) than during LV-only stimulation.

Discussion
This study compared the acute effects of RV, LV, and BiV pacing on the relationship between heart rate and systolic function in patients with heart failure and ventricular conduc-
Our main new finding is that increasing heart rates enhance cardiac contractility during BiV pacing, whereas this effect is absent during single-site RV or LV stimulation. This finding is exciting for the following reasons: First, we identify site and mode of ventricular activation as an important modulator of the force–frequency relationship in selected heart failure patients. Second, the in vivo demonstration of a positive force–frequency relationship in heart failure is remarkable per se, because it contrasts prior experimental studies and resulting clinical expectations. Third, the present data help to understand the beneficial effect of BiV pacing on exercise capacity in heart failure patients and provide evidence for the preferential use of BiV stimulation over LV-only pacing in patients indicated for CRT. In addition, the present study confirms prior investigations4–7 that demonstrated that at baseline heart rates, both BiV and single-site LV pacing improve dP/dt\text{max} as compared with intrinsic activation or RV stimulation.

**Mode of Ventricular Activation and Force–Frequency Relation in Heart Failure**

It has long been recognized that increasing heart rates augment ventricular contractility in the normal, nonfailing heart.12 This phenomenon, termed “positive force–frequency relation” or “Treppe” (staircase) phenomenon, can be considered an important intrinsic mechanism of the heart for adapting to the hemodynamic changes that occur during exercise.13 In isolated human myocardium, the force–frequency relationship is positive in nonfailing hearts and negative in failing myocardium.14 Only a few clinical investigations performed an in vivo evaluation of the force–frequency relationship in human heart failure,15–17 and these studies did not consider the potential role of stimulation site and sequence of ventricular activation. Hasenfuss et al16 evaluated the force–frequency relationship in 9 heart failure patients during RV pacing. Similar to the present findings, no significant increase in dP/dt\text{max} was observed with increasing RV pacing frequencies. Feldman et al15 found that even with atrial pacing, increasing stimulation rates did not augment dP/dt\text{max} in 7 heart failure patients; however, 2 subjects in that study group had a ventricular conduction delay at baseline, and no information was given on the incidence of conduction disturbances at higher rates. Similarly, Cotton and colleagues17 observed a blunted force–frequency relation during atrial pacing in 11 patients with dilated cardiomyopathy; the incidence of ventricular conduction disturbances was not reported in that study either. Thus, it remains unknown whether atrial pacing in heart failure patients may produce a positive force–frequency relation-

**Figure 2.** Improvement in contractile function during BiV pacing at increasing rates. Top, Tracings from a 66-year-old patient with a dilated cardiomyopathy and an LV ejection fraction of 20%. Bottom, Recordings from a 63-year-old male with an ischemic cardiomyopathy and an ejection fraction of 32%. In each subject, BiV pacing at increasing rates augments dP/dt\text{max} by 19% and 30%, respectively. LVP indicates LV pressure.
ship (similar to that seen during BiV pacing) if normal intrinsic AV conduction and synchronous ventricular activation are preserved at baseline and at higher rates.

Potential Mechanisms of the Positive Force–Frequency Relation During BiV Pacing

Rate-dependent augmentation of dP/dt\textsubscript{max} during acute BiV pacing occurred without major changes in preload and afterload and did not depend on supraventricular timing or effect of atrial systole, as evidenced by the subgroup of AF patients. In contrast, single-site LV and RV pacing produced no significant change in contractile function but resulted in a rate-dependent increase in LVEDP and decrease in LVSP. Prior investigations related the altered force–frequency relationship in heart failure to changes in the level of myocardial calcium cycling proteins\textsuperscript{13,14}; however, the rapid hemodynamic response we observed on changes in ventricular pacing mode suggests that alterations in protein expression do not underlie our findings. Thus, switching between acute RV, LV, and BiV pacing at increasing rates appears to modulate primarily the interplay of chronically diseased myocytes, thereby influencing the mechanical function of the failing ventricle. Alterations in myocardial structure and calcium cycling could additionally influence the force–frequency relation during chronic pacing, but this remains to be determined.

It has been recognized that acute BiV and LV pacing similarly improve intraventricular (LV) mechanical dysynchrony in patients with heart failure, left bundle-branch block–type conduction delay and impaired systolic function. Only BiV pacing, however, reduces the interventricular (RV-LV) dyssynchrony and the LV electromechanical delay.\textsuperscript{4,5,11} Accordingly, single-site LV\textsuperscript{5,11} and RV\textsuperscript{11} pacing each produce longer systolic and shorter diastolic intervals than BiV pacing. This difference appears to be irrelevant for hemodynamic function at resting heart rates but may become important at increasing frequencies, when diastolic intervals and time for ventricular filling are further reduced. Hay and colleagues\textsuperscript{11} for example, found that an increase in pacing frequency from 80 to 120 bpm reduced the relative diastolic

Figure 3. Individual patient data for percent change in dP/dt\textsubscript{max} during pacing tachycardia (80 to 140 bpm). Lines indicate mean values. Overall, the contractile response is significantly higher during BiV pacing than during single-site RV or LV stimulation. **P<0.01 (BiV vs LV and RV).

Figure 4. LVEDP during different modes of ventricular pacing at varying stimulation frequencies. LVEDP is higher during single-site RV and LV pacing than during BiV pacing, and increasing rates worsen this disparity. *P<0.05; **P<0.001 (140 vs 80 bpm); §§§P<0.001 (BiV vs LV and RV at 140 bpm).

Figure 5. Effect of BiV, LV, and RV pacing at increasing rates on LVSP. With higher pacing rates, LVSP decreases significantly during LV pacing. At 140 bpm, BiV stimulation produces higher LVSP than single-site RV or LV pacing. ***P<0.001; ns, not significant (140 vs 80 bpm); **P<0.01 (BiV vs RV at 140 bpm).
period by 55% and 60% during RV and LV pacing as compared with only 47% during BiV stimulation. This rate-dependent impairment of ventricular relaxation and filling could underlie the increase in LVEDP and contribute to the blunted force–frequency relation we observed during single-site RV and LV pacing as compared with BiV stimulation.

Another factor to be considered in this context is the programmable AV delay. Auricchio et al demonstrated that optimal systolic function during RV, LV, and BiV pacing occurs at a site- and patient-specific AV delay. Furthermore, a recent study found that the optimal AV delay is longer at higher rates than at baseline rates during BiV stimulation. The present study aimed to compare the effect of different modes of ventricular activation on systolic function at increasing heart rates. We selected AV delays that ensured full ventricular preexcitement, thereby avoiding fusion with intrinsic activation and ensuring true single-site LV and RV stimulation. We cannot exclude that individual optimization of the AV delay during different modes and rates of ventricular pacing could have influenced our results. Nevertheless, the subanalysis of AF patients convincingly demonstrates that the preferential effect of BiV stimulation on the force–frequency relation is independent of supraventricular timing or effect of atrial contraction. In fact, given the findings by Scharf et al, one may speculate that BiV stimulation at increasing rates enhances systolic function to an even greater extent if the AV delay is prolonged.

Clinical Implications

Multiple trials demonstrated that BiV pacing improves the exercise capacity of selected patients with heart failure and ventricular conduction delay. This clinically important CRT feature has been related to pacing-induced improvement of LV function at rest, reverse LV remodeling, and normalization of neurohumoral parameters. The positive force–frequency relation during long-term RV, LV, or BiV pacing has been associated with detrimental ventricular remodeling, whereas chronic BiV stimulation can cause reverse LV remodeling. These changes may influence the force–frequency relation during long-term RV, LV, or BiV pacing.

Conclusions

This is the first study demonstrating that different modes of ventricular pacing can modulate the relationship between heart rate and systolic function in selected heart failure patients. Contrary to single-site LV or RV pacing, cardiac contractility is augmented by increasing heart rates during BiV stimulation. This positive force–frequency relation may contribute significantly to the enhanced exercise capacity during BiV pacing and could provide a functional benefit over LV-only pacing in patients for whom CRT is indicated.

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Disclosures

None.

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