Biventricular mechanical asynchrony predicts hemodynamic effect of uni- and biventricular pacing

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Biventricular mechanical asynchrony predicts hemodynamic effect of uni- and biventricular pacing. Am J Physiol Heart Circ Physiol 285: H2788–H2796, 2003; 10.1152/ajpheart.00119.2003.—We tested whether biventricular resynchronization explains contractile function changes with univentricular and biventricular pacing in heart failure patients with varying magnitudes of baseline biventricular asynchrony. Thirty patients (New York Hospital Association class ≥ III, QRS duration ≥120 ms) were tested. Contractile function was measured by left ventricular maximum first derivative of pressure over time (dP/dt max). Biventricular mechanical asynchrony was quantified by the normalized pressure-pressure (NPP) loop area formed by the cross-plot of right and left intraventricular pressure curves from each cardiac cycle. Any ventricular pacing increased dP/dt max if it decreased baseline NPP loop area and almost always worsened dP/dt max and asynchrony when baseline NPP loop area <0.3. The quantitative relationship between dP/dt max and NPP loop area change depended on ventricular pacing site and timing relative to intrinsic activation. For similar NPP loop decreases, dP/dt max increased 16% more with left and biventricular pacing compared with right ventricular pacing. In conclusion, right, left, or biventricular pacing can improve contractile function only in patients having sufficient baseline biventricular asynchrony. However, biventricular resynchronization is only one of the improvement mechanisms.

BIVENTRICULAR PACING has been shown to improve the clinical symptoms of severe heart failure patients in normal sinus rhythm with intraventricular conduction delay (1, 20). This clinical benefit is believed to result because atrial-synchronous biventricular pacing significantly improves left ventricular (LV) hemodynamic function without increasing heart rate or myocardial O2 consumption (6, 13, 21). Patients who exhibit hemodynamic improvement with biventricular pacing have abnormal baseline ventricular contraction sequences, inferred from long QRS duration and reduced LV maximum first derivative of pressure over time (dP/dt max) (22) or directly measured by tagged MRI (22), multiple gated equilibrium blood pool sisti-ography (15), or echocardiography (3, 27, 32). Biventricular pacing is increasingly referred to as cardiac resynchronization therapy, because it is widely assumed to restore more synchronized and effective ventricular contractions (18). However, the few direct investigations of the mechanical effects of pacing in heart failure patients (3, 15, 27, 32) have focused on biventricular pacing and have not elucidated the importance of baseline asynchrony magnitude.

Many questions remain about the validity and completeness of the resynchronization theory. It has been proposed that resynchronization is indicated by shortening of the QRS duration with biventricular pacing, because positive clinical outcome was predicted by QRS shortening in some studies (2, 17), but QRS shortening is neither necessary nor sufficient to predict hemodynamic improvement (13, 24) or outcome (3) in other studies. In particular, LV pacing increases systolic function as effectively as biventricular pacing while usually increasing the QRS duration. Experimental studies in normal canine hearts show that LV pacing preexcites the lateral wall and creates a con- traction delay on the right side associated with reduced LV function (23, 24) analogous to the well-known negative hemodynamic effects of right ventricular (RV) pacing in patients with normal ventricular conduction (4, 9, 25). Paradoxically, univentricular left or right pacing can increase contractile function in heart failure patients with intraventricular conduction delay (6, 13). Several nonresynchronization mechanisms have been proposed that might resolve some of these apparent contradictions, including preload improvement and reduction of mitral regurgitation after restoring a more normal atrioventricular (AV) sequence (5, 11).

To test the biventricular resynchronization theory, we measured global biventricular mechanical asyn-chrony by quantifying the synchrony of left and right intraventricular pressure changes during the whole cardiac cycle in severe heart failure patients with pri-marily LV conduction delay and assessed the relationship between LV hemodynamic function and biven-

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tricular asynchrony at baseline and during atrial-synchronous univentricular and biventricular pacing.

**MATERIALS AND METHODS**

**Patient selection.** We analyzed data previously collected during the acute testing phase of the Pacing Therapies for Congestive Heart Failure (PATH-CHF) trial, which was designed to evaluate the effects of pacing on acute hemodynamic function and clinical symptoms in patients with severe heart failure, normal sinus rhythm, LV systolic dysfunction, and intraventricular conduction delay (8). Of the 42 patients enrolled in the study, 30 qualified for our analysis by having simultaneous right and left intraventricular pressure recordings.

**Data collection.** The acute data collection protocol for the PATH-CHF study has been described in detail previously (6). Briefly, each patient was paced in atrial-synchronous ventricular pacing mode at the RV apex (RV pacing), LV freewall (LV pacing), or at both right and left sites simultaneously (biventricular pacing) with five preset AV delays (evenly spaced between 0 and the intrinsic AV interval—30 ms). Each chamber and AV delay pacing combination was randomly repeated five times in a 5 paced beat/15 nonpaced beat episode. Throughout the acute test, high-fidelity pressure recordings (Millar catheters) and intracardiac electrogram recordings from the RV and LV electrodes were stored on tape and later digitized for off-line analysis. The maximum first derivative of LV pressure (LV dP/dt max) was calculated to provide an index of LV contractile function (14).

**Normalized pressure-pressure loop area calculation.** Intraventricular pressure changes are a consequence of the integrated chamber mechanics during the cardiac cycle. Asynchrony of the RV and LV mechanics (i.e., biventricular mechanical asynchrony) thus results in relative differences in the timing and rate of pressure changes in the two ventricles (i.e., phase differences). We quantified biventricular mechanical asynchrony from a Lissajous phase plot (16) of the right and left intraventricular pressures. The digitally sampled intraventricular RV and LV pressure values that were simultaneously recorded during one complete cardiac cycle (defined as the interval between adjacent atrial sense markers) were plotted in two dimensions [LV pressure (LVP) values on the x-axis and RV pressure (RVP) values on the y-axis] to create a pressure-pressure loop (PP loop), as shown in Fig. 1.

In this method, if the two pressure curves are in phase (i.e., covary) during systole and diastole, the PP loop is narrow with small area; otherwise the PP loop has a large area and a clockwise rotation (dextrorotatory) when the right systolic and diastolic pressure changes precede the left or counterclockwise rotation (levorotatory) when the left systolic and diastolic pressure changes precede the right. Thus the PP loop area is a combined measure of biventricular systolic and diastolic mechanical asynchrony. By normalization, we quantified the biventricular synchrony relationships independent of right and left pressure magnitudes, which were variable among beats and patients. The PP loop interior area was calculated for each recorded cycle and normalized PP (NPP loop area) by the maximum possible loop area (a rectangle) for that cycle, as follows (Fig. 1B): NPP loop area = PP loop area/[LVP max − LVP min] × (RVP max − RVP min), where LVP max and LVP min are the maximum and minimum LVP, respectively, and RVP max and RVP min are the maximum and minimum RVP, respectively. The NPP loop area ranges between 0 and 1, with larger values indicating more asynchrony between the RV and LV pressure curves.

**Statistical analysis.** Both LV dP/dt max and NPP loop area were computed for each cardiac cycle. Baseline values for each patient were calculated by averaging all normal sinus beats during the acute protocol. Paced values were calculated by averaging all the beats paced with the same pacing chamber and AV delay. Differences and percent changes of paced values from baseline values were calculated using a local baseline method (6), whereby the average value of the last four paced beats in a pacing episode are compared with the average value of the six nonpaced beats immediately preceding the pacing episode, and the differences (or percent changes) for all episodes with the same pacing chamber and AV delay are averaged. Results for different pacing chambers and AV delays were compared by paired t-test. Data from different patient groups were compared by unpaired t-test. The relationship between changes in NPP loop area and LV dP/dt max was tested by univariate linear regression analysis and ANOVA was used to compare regressions. A P < 0.05 was considered statistically significant. Values in the text are reported as means ± SD.

**RESULTS**

**Study population.** Analyzed patients included 15 males and 15 females with a mean age of 59 ± 6 yr. Their New York Heart Association (NYHA) classifica-

![Fig. 1. Illustration of the pressure-pressure loop (PP loop) method to quantify biventricular (BV) asynchrony.](http://ajpheart.physiology.org/)
tion was 3.1 ± 0.2 with a mean ejection fraction of 21 ± 7%. Origin of the dilated cardiomyopathy was ischemic in 7 patients and idiopathic in 23 patients. Results did not differ between ischemic and idiopathic patients. Left bundle branch block (LBBB) was diagnosed in 28 patients, and the mean QRS duration was 172 ± 28 ms and the mean PR interval was 197 ± 33 ms.

Hemodynamic response to pacing. The hemodynamic response to pacing in the PATH-CHF patients has been classified previously into type I (predominately positive) and type II (predominately negative) (6). A type I response was defined as a positive mean response over a range of short to long AV pacing delays for either LV dP/dt_max or aortic pulse pressure and a type II response was zero or negative for both LV dP/dt_max and aortic pulse pressure. Of the 30 PATH-CHF patients analyzed here, 25 had type I and 5 had type II LV dP/dt_max and aortic pulse pressure responses for the best pacing chamber. Similar to previously reported results (6), most patients with baseline QRS duration >150 ms had a type I response, whereas most patients with a shorter QRS had a type II response (Fig. 2). A QRS threshold of 150 ms had a response type prediction accuracy of 87% (88% sensitivity and 80% specificity). With the use of a previously reported prediction method combining a QRS threshold of 155 ms and baseline LV dP/dt_max threshold of 700 mmHg/s (22), prediction accuracy was 83% (80% sensitivity and 100% specificity). The best pacing chamber was LV in 20 patients, biventricular in eight patients, and RV in two patients. On average, RV pacing increased LV dP/dt_max by 8% and aortic pulse pressure by 5%, whereas both LV and biventricular pacing increased LV dP/dt_max and pulse pressure by more than twice as much at the best AV delay (Table 1).

Baseline biventricular pressure synchrony. Baseline NPP loop area ranged from 0.03 to 0.66 and was bimodally distributed, with two groups separated by a threshold of 0.3 (Fig. 3). The 22 patients with NPP loop areas >0.3 were designated as group 1 and the 8 patients <0.3 as group 2. Typical examples of baseline PP loops from group 1 and group 2 patients are compared in Fig. 4A and B. All group 1 PP loops were large and dextrorotatory resulting from a right-to-left ventricular contraction sequence. All group 2 PP loops were small because RV and LV pressure curves started and ended together. As shown in Table 2, group 1 and group 2 patients did not differ in baseline NYHA class, Minnesota Living with Heart Failure Questionnaire score, 6-min walk distance, peak O2 consumption on

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Values are means ± SD; n, no. of patients. NPP, normalized pressure-pressure; LV, left ventricular; RV, right ventricular; dP/dt_max, maximum first derivative of pressure over time; AV, atrioventricular; BV, biventricular. The RV, LV, and BV paced NPP loop areas refer to the shortest AV delay. P values compare group 1 and group 2 values by unpaired t-test.
maximum exercise test, or LV ejection fraction (20 ± 5% vs. 22 ± 9%). However, consistent with differences previously reported between type I and II patients (6), the group 1 and group 2 patients differed in average baseline QRS duration and baseline LV dP/dt\text{max} and differed significantly in the magnitude of LV dP/dt\text{max} response to pacing and the AV delay required for best response (Table 1). All group 1 patient responses were type I, and 5 of 8 group 2 patient responses were type II (Fig. 3), resulting in a response type prediction accuracy of 90% (88% sensitivity and 100% specificity) for baseline NPP loop area. Baseline NPP loop area was positively correlated with the mean ($R^2 = 0.42, P < 0.001$) and maximum ($R^2 = 0.35, P < 0.001$) LV dP/dt\text{max} response for the best pacing chamber in each individual. In group 1 patients, the peak LV dP/dt\text{max} response with RV pacing was significantly less than with LV and biventricular pacing ($P < 0.001$), and the 7.6% larger peak response (1.8 percentage points) with LV pacing compared with biventricular pacing was also significant ($P = 0.011$).

**Clinical effects of pacing.** The positive short- and long-term clinical outcomes of the PATH-CHF patients have been reported previously (8). Table 2 compares clinical changes of the group 1 and group 2 patients after the first month of continuous pacing in the PATH-CHF study. Each patient was randomized to either biventricular pacing or the best univentricular pacing.

![Fig. 3. Distribution of baseline normalized PP (NPP) loop area in 30 heart failure patients and association with the mean LV dP/dt\text{max} (A) and mean aortic pulse pressure percent change (B) from baseline averaged over all tested atrioventricular (AV) delays when pacing with the best chamber. The NPP loop areas are bimodally distributed and separated by a threshold of 0.3 (dashed line). Group 1 represents patients above and group 2 represents patients below this threshold. Patients with type I, patients with type II hemodynamic response.](http://ajpheart.physiology.org/)

![Fig. 4. Examples of PP loops from two heart failure patients. One patient is from group 1 (A and C) and the other is from group 2 (B and D). A and B are baseline loops and C and D are with LV pacing at a middle AV delay. In each example, the right intraventricular pressure is plotted against the left intraventricular pressure during one complete cardiac cycle. Note different scales for right and left pressures. The dashed line indicates zero transseptal pressure. Diastole ends and systole begins in the bottom left corner, and systole ends and diastole begins in the top right corner of each loop. The sequence of right and left pressure change determines the direction of loop rotation, which is shown by an arrow. When right pressure events precede left pressure events, the loops rotate clockwise and are designated dextrorotatory loops (A), and when the loops rotate counterclockwise, due to left-to-right pressure sequences, they are designated levo-rotatory loops (C and D). Either delay results in a large PP loop area (NPP loop area of 0.51 in A, 0.23 in C and 0.35 in D). When right and left pressure events are synchronized, the PP loop area is minimal (NPP area of 0.07 in B). In C and D, LV pacing created similar PP loops although LV dP/dt\text{max} increased 15% in the group 1 patient (C) and decreased −7% in the group 2 patient (D) because the PP-loop area was decreased from baseline in the group 1 patient (A) and it was increased from baseline in the group 2 patient (B). Note also the small transseptal gradient during baseline systole in the group 1 patient (A) compared with the group 2 patient (B).](http://ajpheart.physiology.org/)
determined by preimplant hemodynamic testing. As shown in Table 2, for all patients combined (group 1 + group 2), all clinical measures significantly improved compared with baseline, similar to results reported for the whole PATH-CHF population (8). The group 1 patients had significant improvements in all clinical measures except the rate of O\textsubscript{s} consumption at anaerobic threshold, whereas group 2 patient changes were significant only for NYHA classification. The mean changes in LV dP/dt\textsubscript{max} and aortic pulse pressure with the chronically programmed pacing mode were significantly larger for group 1 than group 2 patients (Table 2). The 6-min walk distance after 1 mo of pacing was significantly longer in group 1 than group 2 patients.

**Effect of pacing on biventricular pressure synchrony.** The PP loop area decreased when group 1 patients were paced and increased when group 2 patients were paced (Fig. 4, C and D). This is quantified in Table 1, which presents average changes in NPP loop area resulting from RV, LV, and biventricular pacing at a short AV delay that minimized fusion with intrinsic conduction. The average paced NPP loop areas were very similar for group 1 and group 2 patients, although the change from baseline was a decrease for group 1 and an increase for group 2, regardless of whether pacing RV, LV, or biventricular. For example, biventricular pacing had a larger NPP loop area of 0.14 for both group 1 and group 2, but this represented a decrease from baseline of 0.039 for group 1 and an increase from baseline of 0.06 for group 2. LV pacing created the largest increase in NPP loop area over baseline (0.28) in group 2 patients. This was because LV pacing at short AV delays created reversed (levo-toratory) loops due to a left-to-right ventricular contraction sequence in all group 2 patients, as well as in 16 (73%) group 1 patients (Fig. 4, C and D).

The LV dP/dt\textsubscript{max} increased when pacing group 1 patients and decreased when pacing group 2 patients, which was opposite to changes in NPP loop area. This is shown in Fig. 5, which compares the average changes in LV dP/dt\textsubscript{max} and NPP loop area when pac-

**Table 2. Clinical measurements for different patient groups**

| Age, yr  | 58.5 ± 6 | 59.9 ± 6 | 54.6 ± 7 | 0.04 |
| Gender, male/female | 15/15 | 12/10 | 3/5 | 0.41 |
| Etiology, idiopathic/ischemic | 23/7 | 18/4 | 5/3 | 0.27 |
| Paced LV dP/dt\textsubscript{max}, % change | 18.7 ± 15 | 24.5 ± 13 | 2.6 ± 4.4 | <0.01 |
| Paced aortic PP, % change | 10.9 ± 11 | 14.7 ± 10 | 0.4 ± 1.6 | <0.01 |
| NYHA classification | Baseline | 3.1 ± 0.2 | 3.1 ± 0.3 | 3.0 ± 0.0 | 0.24 |
| MLHFQ score | Baseline | 47.2 ± 21 | 48.0 ± 20 | 44.8 ± 27 | 0.72 |
| Six-minute walk distance, m | Baseline | 339 ± 144 | 319 ± 110 | 395 ± 111 | 0.10 |
| Peak V\textsubscript{o}s, ml·min\textsuperscript{-1}·kg\textsuperscript{-1} | Baseline | 12.3 ± 2.9 | 12.4 ± 3.0 | 12.0 ± 2.8 | 0.75 |
| V\textsubscript{o}s AT, ml·min\textsuperscript{-1}·kg\textsuperscript{-1} | Baseline | 9.7 ± 3.4 | 10.4 ± 3.7 | 8.1 ± 2.3 | 0.12 |

Values are means ± SD; n, no. of patients. NYHA, New York Heart Association; MLHFQ, Minnesota Living with Heart Failure questionnaire; AT, anaerobic threshold; V\textsubscript{o}s, rate of O\textsubscript{s} consumption. Percent change of paced LV dP/dt\textsubscript{max} and aortic PP refers to the change from baseline when pacing in the mode programmed for 1 mo of therapy. *P < 0.01, 1-mo change is different from baseline, paired t-test; †P < 0.05, 1-mo change is different from baseline, paired t-test. P values column refers to unpaired t-test comparing group 1 and group 2 data.
ing RV, LV, or biventricular at five different AV delays (normalized to each individual’s intrinsic AV delay) in group 1 and group 2 patients. For group 1 patients (Fig. 5A), each type of pacing at any AV delay decreased the NPP loop area and increased the LV dP/dt\textsubscript{max}, whereas the pattern was opposite for group 2 patients (Fig. 5B). Focusing on group 1, the NPP loop area decreased linearly with increasing LV dP/dt\textsubscript{max} as the AV pacing delay was shortened from near the intrinsic AV interval (a long AV delay) to ~50% of the intrinsic interval (a middle AV delay) (Fig. 5A). This relationship was quantified by correlating the NPP loop area and LV dP/dt\textsubscript{max} changes normalized by the largest NPP loop area decrease and LV dP/dt\textsubscript{max} increase, respectively, in this AV delay range for each group 1 patient. As shown in Fig. 6, decreases in NPP loop area were strongly correlated with increases in LV dP/dt\textsubscript{max} with RV (R\textsuperscript{2} = 0.63), LV (R\textsuperscript{2} = 0.74), and biventricular (R\textsuperscript{2} = 0.77) pacing. The linear regression slopes for these correlations were similar for RV, LV, and biventricular pacing, but the offsets for biventricular (19%) and LV (21%) pacing were significantly larger (P < 0.001) than for RV pacing (4.3%). Thus the LV dP/dt\textsubscript{max} increased nearly the same amount for a given decrease in NPP loop area with LV and biventricular pacing, whereas it increased ~16% less for the same NPP loop area decrease with RV pacing.

When pacing between the middle and shortest AV delays in group 1 patients (Fig. 5A), the average LV dP/dt\textsubscript{max} declined slightly from its peak value, whereas the NPP loop area continued to decrease to an average minimum of 0.29 ± 0.14 at an average AV delay of 29 ± 46 ms with RV pacing and to a minimum of 0.14 ± 0.11 at an AV delay of 21 ± 40 ms with biventricular pacing. With LV pacing, the loops passed through a near-zero minimum area of 0.10 ± 0.06 at an AV delay of 64 ± 52 ms and reversed from dextrorotatory to levorotatory at shorter AV delays (Fig. 5A). With LV pacing, the peak increase in LV dP/dt\textsubscript{max} occurred when the NPP loops were still dextrorotatory in 18 group 1 patients (82%) at an AV delay 26 ± 46 ms longer than the AV delay corresponding to the minimum NPP loop area (P = 0.014).

All group 2 patients decreased LV dP/dt\textsubscript{max} as AV delays were shortened from intrinsic with each type of pacing (Fig. 5B). Correspondingly, the NPP loop area increased as AV delays were shortened, but the magnitude of NPP loop area increases did not correlate to the magnitude of decreases in LV dP/dt\textsubscript{max}. Specifically, the largest increases in NPP loop area occurred with LV pacing, although the largest decreases in LV dP/dt\textsubscript{max} occurred with RV pacing. Also NPP loop area increased only slightly with biventricular pacing, although LV dP/dt\textsubscript{max} decreased to a similar degree with either biventricular or LV pacing.

**DISCUSSION**

It is well known that LBBB is associated with a large delay in LV mechanical events that can cause RV systolic events and LV diastolic events to overlap, which can lead to abnormal transseptal pressure gradients associated with abnormal septal wall motion, reduced ejection fraction, and asymmetric filling patterns (12). We hypothesized that these mechanical abnormalities would desynchronize the pressure changes in the right and left ventricles in proportion to the magnitude of biventricular systolic and diastolic mechanical asynchrony, which we quantified by the NPP loop area in a Lissajous plot of simultaneous RV and LV pressures. The NPP loop area is proportional to the phase difference between RV and LV pressure waveforms through the whole cardiac cycle (systole and diastole). Thus the NPP loop area is an integrated measure of the hemodynamic consequences of LV and RV regional activation sequences and their respective degrees of intra- and interventricular synchrony. We found that larger baseline NPP loop area was associated with a larger QRS duration and lower baseline LV dP/dt\textsubscript{max}, which are known indicators of abnormal ventricular contraction patterns (12, 22, 31). Large baseline NPP loop area predicted hemodynamic benefit with biventricular and univentricular pacing with a 90% accuracy, which exceeded the 87% prediction accuracy using a QRS duration threshold of 150 ms and the 83% accuracy using a previously reported criterion based on a combination of QRS duration and baseline LV dP/dt\textsubscript{max} (22). Thus baseline mechanical asynchrony may be more directly related than electrical asynchrony to the mechanisms by which pacing can improve hemodynamic function in heart failure patients.

**Role of baseline biventricular asynchrony.** All the patients had a QRS duration >120 ms but exhibited a wide variation of biventricular asynchrony, as measured by baseline NPP loop area. The effect of pacing...
on contractile function depended on the magnitude of baseline biventricular asynchrony. PACing was ineffective or even decreased LV dP/dt\textsubscript{max} in patients having little or no asynchrony (group 2). A baseline NPP loop area greater than \( \sim 0.3 \) (group 1) was necessary for univentricular or biventricular pacing to significantly increase LV dP/dt\textsubscript{max}. It is unlikely that these differences are due to pacing having different direct effects in the two types of patients, because with maximal preexcitation (at the shortest AV delays), the paced NPP loop areas were of similar magnitude in all patients, regardless of whether LV dP/dt\textsubscript{max} was improved. Rather, it appears that baseline biventricular asynchrony is a necessary condition for pacing to increase LV dP/dt\textsubscript{max}. The magnitude of LV dP/dt\textsubscript{max} increase with pacing was directly proportional to the decrease in biventricular asynchrony. PACing that did not decrease asynchrony did not increase LV dP/dt\textsubscript{max}. These results support the theory that biventricular resynchronization is an important mechanism by which pacing improves contractile function. With maximal preexcitation, pacing resulted in a biventricular asynchrony index of 0.14–0.27, depending on the pacing chamber. This degree of possible resynchronization is consistent with the baseline NPP loop area threshold of 0.3 that was empirically observed to separate patients by whether pacing is likely to improve (>0.3) or not improve (<0.3) contractile function.

**Effect of RV pacing.** In patients with large baseline asynchrony, even RV apical pacing was able to decrease NPP loop area and increase LV dP/dt\textsubscript{max}. Because RV pacing in normal hearts creates biventricular asynchrony (25), RV pacing in hearts with baseline LV delay must spread preexcitation to the left ventricle quickly enough to advance LV contraction relative to RV contraction. However, resynchronizing with LV and biventricular pacing provides more hemodynamic benefit than with RV pacing. For similar magnitudes of improved NPP-loop area, LV dP/dt\textsubscript{max} improved 16% more with biventricular and LV pacing compared with RV pacing. This indicates the choice of pacing site affects LV dP/dt\textsubscript{max} by means that are not detected by the NPP loop area method and thus may be due to some mechanism in addition to global biventricular resynchronization. One possibility is that different pacing sites create different spatiotemporal activation sequences that cause different LV regional contraction patterns and contraction effectiveness. Prinzen et al. (23) observed asymmetrical effects of RV and LV pacing on ventricular workload in normal canine hearts leading to speculation that RV pacing may activate a disproportionately larger extent of muscle more quickly than LV pacing, creating a larger loss of effective muscle mass. Alternatively, RV pacing creates a right-to-left contraction sequence that generates small or reversed transseptal pressure gradients associated with abnormal septal wall motion that are not generated by LV pacing (19) and that are associated with reduced LV contraction effectiveness (12). A third mechanism is possible in the presence of asymmetrical conduction disorder. For instance, in LBBB, most of the left ventricle will be activated slowly and gradually through intramyocardial conduction (28), although intrafascicular conduction may be partially preserved in the right ventricle, perhaps contributing to interventricular septal activation. In this situation, LV pacing also spreads activation by intramyocardial conduction so the rate of LV activation may not be changed appreciably with pacing, but the contraction will be advanced to synchronize with the intrinsic RV and septal contraction. On the other hand, while RV pacing may advance LV contraction, it also will replace any preserved intrafascicular activation of the apex and septum with slower intramyocardial activation, which could reduce LV contractile function (30).

**Comparison of LV and biventricular pacing.** For similar reasons, we might expect the combination of RV and LV pacing to be less effective than LV pacing for improving contractile function. In fact, it has been reported consistently that LV pacing results in a slightly larger improvement in systolic function than biventricular pacing in atrial-synchronous modes (6, 10, 13). We also observed a small but statistically larger LV dP/dt\textsubscript{max} increase with LV pacing in group 1 patients, along with evidence that atrial-synchronized LV pacing can provide better biventricular resynchronization than biventricular pacing. LV pacing consistently could advance the LV contraction to start before the RV contraction, whereas biventricular pacing typically could not. The peak increase in LV dP/dt\textsubscript{max} with LV pacing occurs at an average AV delay of 90 ms, which is 26 ms longer than the AV delay at which the NPP loop area passes through a minimum and LV contraction begins to precede RV contraction. Therefore, the optimal resynchronization to increase LV contractile function with LV pacing occurs with a fusion of intrinsic RV activation and paced LV activation. The peak LV dP/dt\textsubscript{max} increase with biventricular pacing occurs at shorter AV delays (75 ms), perhaps because the minimum NPP loop area occurs at shorter delays (20 ms). Thus atrial-synchronized biventricular pacing may have two disadvantages in patients with intact AV conduction: 1) biventricular asynchrony is minimized at shorter AV delays that are associated with reduced preload, and 2) the simultaneous RV pacing may substitute slower intramyocardial conduction for preserved intrafascicular conduction in regions contributing to LV contractile function. Clinically, these disadvantages are likely minor because the hemodynamic differences with biventricular pacing are small. Biventricular pacing may have advantages over LV pacing for biventricular resynchronization of patients with heart block or atrial tachyarrhythmia, when intrinsic activation is absent or irregular so fusion is not an option.

**Contractile function decreases.** When biventricular pacing patients with large baseline asynchrony (group 1) at short AV delays, the LV dP/dt\textsubscript{max} declined from the peak improvement at a middle AV delay, likely because preload is reduced at the shorter AV delays, which has been demonstrated in a similar patient cohort (5). On the other hand, the NPP-loop area con-
continued to decrease from its value at a middle AV delay with biventricular pacing at the shorter AV delays, indicating a further improvement in biventricular synchrony at the shorter AV delays that would be expected to further improve LV dP/dt_{max}. Because the opposite was observed, preload effects may dominate the change in LV dP/dt_{max} at the short AV delays, perhaps because once the left ventricle is fully recruited by pacing, further changing biventricular synchrony may not have an appreciable effect on LV contractile function. The LV dP/dt_{max} almost always decreased from baseline with any pacing in patients with small baseline asynchrony (group 2), even with biventricular pacing, which only slightly increased the NPP loop area. On the other hand, LV pacing dramatically increased the NPP loop area from baseline while LV dP/dt_{max} decreased no more than with biventricular pacing. These results suggest that NPP-loop area changes are not sufficient to explain worsened contractile function. Nor is preload a likely explanation, since decreases in contractile function occurred even at the middle to long AV delays when preload is actually increased (5). We propose that in heart failure patients without baseline biventricular asynchrony, all pacing may reduce contractile function by replacing intrafascicular conduction with slow intramyocardial conduction, similar to the effects of pacing in normal hearts (24, 28, 29).

Limitations. An important limitation of the NPP loop area method is that it only measures the global effect of contraction, which prevents it from providing any information about the regional wall motion effects that may have created the phase differences between the RV and LV pressures. For example, by itself, this measure cannot separate a delayed septal contraction from a delayed RV contraction because septal contraction is responsible for a large percentage of the total RVP increase. Furthermore, by assessing the phase difference between RVP and LVP throughout the whole cardiac cycle, the NPP loop area does not provide any information about the relative importance of systolic versus diastolic phase differences. Tissue Doppler imaging and other techniques that measure intraventricular mechanical asynchrony are able to examine the local phenomena that may be responsible for the phase differences detected by the NPP loop area. For instance, they have shown that LBBB is associated with significant left intraventricular regional contraction delays, such as lateral wall contraction after aortic valve closure (26). Such intraventricular asynchrony undoubtedly contributes to a phase shift between RV and LV pressure changes, which would appear as an increase in the NPP loop area, and which when corrected by pacing, would appear as a decrease in NPP loop area. Thus, with this metric, we cannot exclude the possibility that biventricular resynchronization occurs simultaneously with intraventricular (regional) resynchronization nor determine which might be the root mechanism for contractile function improvement with pacing. Another limitation to note is that the chronic clinical impact of biventricular asynchrony and resynchronization may differ from the acute hemodynamic effects reported here, although short-term clinical benefit with cardiac resynchronization therapy is associated with improved intraventricular mechanical synchrony (26, 32) and is more evident among patients exhibiting larger baseline electrical asynchrony (7) and more evident for group 1 than group 2 patients after 1 mo of pacing.

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