Tailoring cardiac resynchronization therapy using interventricular asynchrony.

Validation of a simple model

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PACING THERAPY for patients with heart failure (HF) and conduction disorders acutely improves left ventricular (LV) pump function (4, 13) and also results in long-term benefit (1, 5, 10). However, optimal application of the therapy is not straightforward. Two issues are dealt with in the present study: the atrioventricular (AV) delay and the use of LV or LV + right ventricular (RV) [i.e., biventricular (BiV)] pacing. Choice of a physiological AV delay is known to be important for optimal filling in conventional pacing in hearts with complete AV block. However, in cardiac resynchronization therapy (CRT), employing either LV or BiV pacing, the choice of AV delay may be more complicated. After all, LV and BiV pacing in hearts with left bundle branch block (LBBB) also influence the degree of resynchronization (4). In LBBB hearts, activation occurs from the endings of the right bundle branch. Resynchronization can occur when the wavefront from intrinsic activation fuses with the wavefront originating from especially the LV pacing site. The contribution of the latter becomes stronger at shorter AV delays (26). Moreover, while multisite pacing was the initial designation of CRT, several studies in dogs with LBBB (26) and in patients indicate that improvement of LV pump function can be equally large during BiV and single-site LV pacing (4, 6, 13).

There are various diagnostic tools to assess optimal resynchronization. Most of these tools relate to measuring asynchrony between RV and LV [interventricular asynchrony (interVA)] or asynchrony within the LV [intraventricular asynchrony (intraVA)]. Several studies indicate that optimal hemodynamic effect of CRT coincides with minimal intraVA (23, 26, 32). Unfortunately, assessment of intraVA is relatively complex [nuclear imaging or echocardiographic wall motion analysis (9), extensive electrical mapping (3), magnetic resonance (MR) tagging (15), strain rate imaging (8), or multisite tissue Doppler imaging (TDI) (23)]. Measurement of interVA, on the other hand, is easier [time differences of aortic and pulmonary artery opening times and simple TDI (22) or RV and LV pressures (27)]. However, during CRT in patients and in dogs with LBBB, optimal pump function coincides with incomplete, rather than complete, restoration of interVA (14, 26). The lack of correlation between minimal intraVA and interVA appears paradoxical, and it questions the use of interVA for optimizing CRT.

Confusion on the hemodynamic effects of LV vs. BiV pacing and on the role of intraVA and interVA may relate to lack of a clear concept of how optimal resynchronization is achieved. The aim of the present study was to test the validity of a simple pathlength model for intraventricular and interventricular resynchronization during pacing in a LBBB heart and to investigate whether this model would help to improve the use of interVA for optimizing resynchronization in the individual patient. To this purpose the pathlength model is first validated using data from intraVA and interVA in dogs with chronic LBBB (28). Subsequently, in patients with both ischemic and dilated cardiomyopathy

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who were candidates for CRT, we investigated whether interVA could be used to tailor resynchronization to the individual patient.

METHODS

Model for Cardiac Resynchronization

The top panel of Figure 1 shows the conceptualized paths of the intrinsic and pacing-induced depolarization waves in the LV wall of LBBB heart, paced at the LV lateral wall. Also presented is the simulated behavior of intraVA and interVA as a function of the timing of LV stimulation (AV delay). Conduction is assumed to occur exclusively through muscle fiber conduction, fibers being primarily oriented in the circumferential direction. Consequently, during LV pacing with short AV delay (complete capture), the activation wavefront spreads from the pacing site around the LV toward the septum and the RV wall (I). This situation is associated with an arbitrary degree of intraVA and interVA as indicated in Fig. 1, B and C.

During LBBB without pacing, the intrinsic depolarization wave starts at the RV surface of the septum and travels around the LV circumference. The same activation pattern occurs when LV stimulation occurs after completion of intrinsic activation (long AV delays) (III). During situation III, intraVA is equal to that in situation I because we assume a circularly symmetric LV geometry. The levels of interVA in situations I and III (X and Y, respectively) are not necessarily equal because the ventricles are not symmetric in right-to-left direction.

During LV stimulation with intermediate AV delays, the intrinsic and pacing-induced depolarization waves merge (fusion), and intraVA and interVA change linearly, as indicated by Fig. 1. Important, the minimum intraVA value is reached at a value of interVA halfway that during LBBB and during LV pacing at short AV delay.

Because our previous study showed that maximal improvement of pump function during pacing is achieved if intraVA is maximally reduced (26), we hypothesized that maximal hemodynamic benefit of CRT occurs when interVA equals (X + Y)/2.

Animal Experiments

Animal handling was performed according to the Dutch Law on Animal Experimentation (WOD) and the European Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of the Maastricht University. Details of the animal experimental procedure are presented elsewhere (27, 28). In short, experimental LBBB was created in six dog hearts by radiofrequency ablation. Measurements were performed under midazolam-sufentanyl anesthesia after 8 wk of LBBB, when the hearts were significantly dilated (~30%) and hypertrophied (~20%) (28). Pacing leads were attached to the right atrium, RV apex, and LV lateral wall. Atrial sensed RV, LV, and BiV pacing (VDD mode) was performed with AV delays ranging from 30 to 120 ms in 10-ms steps. ECG was recorded from the limb leads, and LV pressure was measured using a Sentron catheter-tip manometer. The hemodynamic response to pacing was evaluated by calculating the average maximum rate of rise of LV pressure (LV dP/dtmax) from all beats during one ventilation cycle.

Electrical intraVA was determined using endocardial electrical activation times as obtained from a 64-electrode basket catheter. The maximal difference in endocardial activation time was taken as a measure for intraVA.

Mechanical interVA was determined using measurements of RV and LV pressure with high-fidelity catheter-tip pressure manometers and calculating the timing difference of the upslopes of LV and RV pressures using cross correlation. This measure has been validated by extensive computer simulations and animal experiments (27). Positive timing differences indicate an earlier LV than RV pressure rise.

Patient Study

To investigate to what extent interVA can be used to optimize CRT, we used data from 29 patients enrolled in the Pacing Therapies for Congestive Heart Failure (PATH-CHF). Complete inclusion and exclusion criteria, study design, and end points have been presented earlier (4). The most important inclusion criteria were dilated cardiomyopathy of either idiopathic or ischemic etiology in New York Heart Association (NYHA) class III or IV, a QRS duration ≥ 120 ms and a PR interval ≥ 150 ms.

Detailed information on pacemaker implantation was presented elsewhere (4). In short, patients were under general anesthesia when chronic pacing leads were implanted in the right atrium and the RV...
Fig. 2. Typical example of LV endocardial electrical activation times (top) and normalized LV (PLV) and right ventricular (RV) pressures (PRV) and calculated interVA values (bottom) in a canine left bundle branch block (LBBB) heart during LV pacing with short AV delay (situation I), AV delay that resulted in maximal improvement of maximum rate of rise of LV pressure (LV dP/dt<sub>max</sub>) (situation II), and baseline LBBB without pacing (situation III).

Fig. 3. A: typical example of relation between AV delay and change in LV dP/dt<sub>max</sub> (ΔLV dP/dt<sub>max</sub>), intraVA, and interVA measured during LV pacing in a canine LBBB heart. The solid lines for intraVA and interVA were fitted to the measurements. The high r values indicate an excellent correlation between model and measurements. B: group data for LV dP/dt<sub>max</sub>, intraVA, and interVA during LV pacing with shortest possible AV delay (I), LV pacing with the AV delay that resulted in maximal improvement of pump function (II), and during baseline (unpaced) (III). ΔLV dP/dt<sub>max</sub> values are relative to LBBB (III) values. *P < 0.05 vs. III; †P < 0.05 vs. I.
and attached to the epicardium of the LV via a limited thoracotomy. The LV pacing site varied from the apex to midlateral segments. RV, LV, and aortic pressures were acquired by two 8-F dual-transducer catheters (model SPC-780c, Millar Instruments).

Atrial sensed LV, RV, and BiV pacing was performed (VDD mode) at 5 preset AV delays, equally spaced between 0 ms and the patient’s intrinsic PR interval measured at the RV lead (−30 ms). With the use of an external pacing device (FlexStim, Guidant) (4), 15 beats of normal sinus rhythm were followed by 5 paced beats. The FlexStim device varied pacing site (RV, LV, or BiV) and AV delay in random order so that at the completion of the protocol, each combination had been tested five times. Hemodynamic data (LV, RV, and aortic pressure) were acquired throughout the protocol.

Pressures were digitized at 200 Hz and analyzed offline for calculation of LV dP/dt max, end-diastolic LV pressure (LVEDP), and aortic pulse pressure. In the absence of changes in heart rate and vascular load, pulse pressure directly correlates with cardiac output (29). The hemodynamic response to pacing in each of these parameters was calculated by averaging each parameter from the last four beats of the pacing sequence and is presented as a relative or absolute change compared with baseline (the immediately preceding 6 non-paced beats) (4). In the patients, interVA was determined using the same approach as in the dogs.

Statistics

The statistical significance of the hemodynamic response compared with baseline and/or differences between pacing modes was evaluated using one-way ANOVA for repeated measurements, followed by appropriate post hoc testing. P < 0.05 was considered significant. Data are presented as means ± SD. Linear regression was used to evaluate correlation between simulations and measurements. Comparison between predicted and observed interVA at maximal hemodynamic response was made by means of linear regression and calculation of the standard error of the estimate (SEE).

RESULTS

Animal Study

Figure 2 shows examples of endocardial activation maps and RV and LV pressure recordings during LBBB (situation III) and LV pacing at short AV delay (situation I) and at intermediate AV delay (situation II). It can be seen that the sequence of electrical activation during LBBB is virtually opposite from LV pacing at short AV delay. Accordingly, interVA is negative during LBBB and positive during LV pacing at short AV delay. In situation II interVA was smallest in combination with a value of interVA almost exactly in between that during situations I and III. Similar to the model (Fig. 1), in the experiment interVA changed in a linear manner when varying AV delay during LV pacing (Fig. 3A, bottom). The maximum value of LV dP/dt max was achieved when interVA was virtually at its minimal value and interVA at half the value between that during LBBB and during LV pacing at short AV delay. For the whole group of animals, maximal improvement in LV dP/dt max was ~15% (Fig. 3B, top). This maximal improvement was obtained at values of interVA of ~12 ms, approximately one-half the value during both LBBB and LV pacing (on average 23 and 25 ms, respectively). This is in agreement with the model, predicting that when two activation waves merge exactly halfway, a perfectly circular LV wall, interVA is reduced by 50% (Fig. 1). Similarly, the interVA value at which optimal LV dP/dt max was found was close to the (X + Y/2 value predicted by the model (Fig. 3B, bottom). This (X + Y/2 value was significantly lower than zero because interVA was more negative during LBBB (−32 ± 7 ms) than positive during LV pacing at short AV delay (+3 ± 13 ms).

Figure 4 shows that changes in interVA are smaller during RV and BiV pacing than during LV pacing. More specifically, when shortening AV delay, BiV pacing decreased interVA only to a fixed (negative) value (Fig. 4, bottom). In the seven animals studied, this value was not significantly different from the (X + Y)/2 value (~12 ± 5 ms vs. −10 ± 7 ms, respectively). When plotting the percent change of LV dP/dt max as a function of interVA, the data points from BiV and LV are virtually superimposed (Fig. 4, top). Maximal increase in LV dP/dt max was not significantly different during LV and BiV pacing (15.5 ± 5.4% vs. 15.8 ± 5.7%, respectively). During
optimal BiV pacing, intraVA was $11 \pm 4$ ms, not significantly different from intraVA during LV pacing with an AV delay that resulted in optimal LV $dP/dt_{\text{max}}$ (see above).

**Patient Study**

**Group response during pacing.** In 22 of 29 patients, the mean increase in LV $dP/dt_{\text{max}}$ during all RV, LV, and BiV pacing settings was $15.2 \pm 8.9\%$. These patients were defined as the group of responders. This responder group was characterized by a significant degree of intrinsic interVA ($-50 \pm 17$ ms). In contrast, in 7 of 29 patients, LV $dP/dt_{\text{max}}$ did not increase during ventricular pacing, but actually slightly and significantly decreased ($-5.8 \pm 3.6\%$). In these patients, intrinsic interVA was $-5 \pm 10$ ms (not significantly different from zero). This group was defined as the nonresponder group.

In nonresponders, pacing in all modes created significant interventricular desynchronization accompanied by a reduction in hemodynamic performance (data not shown). For the remainder of the results, only data from the responders will be considered.

Figure 5 depicts that the RV and LV pressure tracings of a responder during LV pacing behave similarly to those in the LBBB dog heart (Fig. 2). In the example of Fig. 5, LV pacing at 105 ms already increased interVA from $-40$ ms (Fig. 5D) to $-23$ ms (Fig. 5C) and increased further to finally positive values when further shortening the AV delay (Fig. 5, A and B).

The effects of RV, LV, and BiV pacing for the whole group of responders are summarized in Table 1. RV pacing could decrease interVA from $-50 \pm 17$ to $-24 \pm 17$ ms, whereas BiV and LV pacing resulted in less negative and even positive interVA values, respectively (Table 1; see also Fig. 8, C and D). Pacing increased LV $dP/dt_{\text{max}}$ (LV $>$ BiV $>$ RV pacing, Table 1). LV pacing was able to increase LV $dP/dt_{\text{max}}$ and pulse pressure slightly but significantly more than BiV pacing, and this difference was associated with a significantly less negative interVA. This difference between LV and BiV pacing is elaborated in more detail below. Maximum LV $dP/dt_{\text{max}}$ occurred at significantly reduced interVA but at unchanged LVEDP (Table 1) and heart rate (data not shown).

**Individual prediction of optimal interVA in responders.** Figure 6 shows for two patients that LV $dP/dt_{\text{max}}$ peaked at an interVA value very close to the $(X + Y)/2$ value. Figure 6, right, indicates that also for the entire group, maximum LV $dP/dt_{\text{max}}$ occurred in situation II at an AV delay not significantly different from the predicted $(X + Y)/2$ value. Interestingly, LV $dP/dt_{\text{max}}$ was also significantly higher than baseline (situation III) during LV preexcitation (situation I). In situation I, LV $dP/dt_{\text{max}}$ was $18 \pm 3\%$ above baseline compared with $26 \pm 13\%$ in situation II, the difference between situations II and I being statistically significant. The reduction in AV delay required to achieve situation I leads to a small but significant reduction in LVEDP (from $19 \pm 8$ mmHg in situation II to $15 \pm 6$ mmHg in situation I). To investigate to what extent this reduction in LVEDP and the desynchronization indicated by the increase beyond $(X + Y)/2$ play a role in the reduction in LV $dP/dt_{\text{max}}$ between situations II and I, we compared LV with BiV pacing. During LV and BiV pacing, LVEDP decreased to exactly the same extent when shortening AV delay. However, the reduction in LV $dP/dt_{\text{max}}$ from situation II to situation I was significantly larger during LV pacing ($9.4 \pm 4.9\%$) than during BiV pacing ($6.2 \pm 2.9\%$).

| Table 1. Maximal change in hemodynamic parameters relative to baseline during LV, BiV, and RV pacing, and interVA and \(\Delta LVEDP\) ventricular at maximum LV \(dP/dt_{\text{max}}\) and PP |
|-----------------|-----------------|-----------------|-----------------|
| Max interVA, ms | 21 $\pm 28^{*+\ddagger\S\}$ | $-7 \pm 19^{\ddagger\S\}$ | $-24 \pm 17^{\S\}$ |
| Max \(\Delta LVEDP\), % | 26.4 $\pm 13.1^{*+\ddagger\S\}$ | 24.4 $\pm 12.3^{+\ddagger\S\}$ | 11.7 $\pm 7.2^{\S\}$ |
| InterVA at max, ms | $-5 \pm 20^{\dagger\S\}$ | $-16 \pm 19^{\S\}$ | $-28 \pm 17^{\S\}$ |
| \(\Delta LVEDP\) at max, mmHg | $-0.6 \pm 2.3$ | $-1.3 \pm 2.5$ | $-0.5 \pm 2.2$ |
| Max \(\Delta PP\), % | 14.6 $\pm 10.1^{*\S\}$ | 13.2 $\pm 9.4^{*\ddagger\S\}$ | 6.2 $\pm 5.3^{\S\}$ |
| InterVA at max, ms | $-15 \pm 28^{*\S\}$ | $-20 \pm 21^{\ddagger\S\}$ | $-35 \pm 18^{\S\}$ |
| \(\Delta LVEDP\) at max, mmHg | $-0.3 \pm 2.4$ | $-1.0 \pm 2.9$ | $-0.3 \pm 2.6$ |

Values are means $\pm$ SD in $n = 22$ responders. InterVA, interventricular asynchrony; LV, BiV, and RV pacing are left ventricular, biventricular, and right ventricular pacing; LV $dP/dt_{\text{max}}$, maximal rate of rise of LV pressure; LVEDP, LV end-diastolic pressure; PP, pulse pressure. Significant differences ($P < 0.05$, Tukey test): *vs. baseline; † vs. BiV pacing; ‡ vs. RV pacing; § vs. zero.
During BiV pacing (5.5 ± 6.3%). This difference coincided with an increase in interVA beyond (X + Y)/2 during LV but not during BiV pacing (see Fig. 8). These data indicate that desynchronization at least partly explains the decrease of LV dP/dt max from situation II to situation I.

Between patients, intrinsic interVA varied considerably (ranging from 83 to 15 ms; Fig. 7A) and so did interVA at peak LV dP/dt max (ranging from -42 to +31 ms; Fig. 7A). Nevertheless, the interVA value at maximal hemodynamic response was accurately predicted by the “halfway value” of the model (SEE 6 ms, Fig. 7B). Also the actual maximal hemodynamic response was very close to that at the predicted interVA (SEE = 2.7%; Fig. 6C). Also the prediction of interVA at which pulse pressure is optimal was accurate (SEE = 12 ms) and so was the predicted maximal response of pulse pressure (SEE = 2.6%). Compared with optimal interventricular resynchronization, complete interventricular resynchronization (interVA = 0) reduced hemodynamic response depending on how much optimal interVA differed from zero (r = 0.75). For individual patients this reduction could be as large as 19.7% and 9.3% for LV dP/dt max and pulse pressure, respectively.

InterVA during BiV pacing. To evaluate if our model can also be applied for BiV pacing, we compared the hemodynamic response during BiV pacing and LV pacing at equal interVA values. Figure 8, A and B, shows that, when plotting the change in LV dP/dt max as a function of interVA, equal values of LV dP/dt max are achieved at equal interVA during LV and BiV pacing. In 11 of 22 patients, BiV pacing was not able to increase interVA to the optimal value (Fig. 8, A and C). These patients were retrospectively classified as type I responders (Table 2). In the remaining 11 patients, peak LV dP/dt max during BiV pacing was equal to that during LV pacing and was obtained at the same optimal interVA, even though this interVA value was reached at different AV delays during LV and BiV pacing (Fig. 8, B and D, type II responders). Other variables (interVA at peak LV dP/dt max and pulse pressure, intrinsic interVA and degree of synchronization achieved by LV pacing) were not significantly different between type I and II responders. However, the degree of synchronization achieved by RV pacing was significantly smaller in type I than in type II patients (Table 2, Fig. 8).

DISCUSSION

The present study indicates that the changes in intraVA and interVA as a function of the timing of LV pacing in LBBB dogs and those in interVA as a function of the timing of LV and BiV pacing in CRT candidates can be accurately simulated using a simple pathlength model. As predicted by the model, the average value of interVA during intrinsic activation and LV pacing at short AV delay accurately predicts optimal hemodynamic effect. This prediction was also accurate in the individual patient, despite the considerable variation in intrinsic interVA between patients and the presence of ischemic cardiomyopathy in half of them. The model underestimates the...
hemodynamic performance during relatively early LV activation, suggesting that additional factors may play a role under these circumstances.

Validity of the Pathlength Model

The good fit of the experimental data (both from dogs and patients) with the model predictions on optimal resynchronization indicates that the simplified impulse conduction properties assumed in the model are accurate enough to predict gross LV impulse conduction and pump function. The most important assumption is that impulse conduction in LBBB and paced hearts occurs predominantly through muscular conduction and without a major role for Purkinje conduction. This assumption was made based on the studies by Myerburg et al. (17), showing that impulses exit the conduction system at only a few points. The robustness of the pathlength model in predicting optimal hemodynamics is further supported by the similar relations between interVA and pump function, found in the patients and animals. In dogs, proximal LBBB has been induced on purpose in otherwise normal hearts, whereas in patients the site of conduction block may vary (21). Also, one-half of the patients had ischemic heart disease, and patients were treated with various drugs (4). Moreover, the degree of hypertrophy was most likely more pronounced in patients (80%; Ref. 19) than in the dogs with chronic LBBB (~25%; Ref. 28). The similar relation between resynchronization and pump function in dogs and patients can be understood when one considers that optimal resynchronization is dependent on optimal fusion of the impulse wavefronts and that those wavefronts are broad, both in transmural and tangential direction. This idea is supported by data from electrical (21, 25, 26) and mechanical mapping (30, 31) in LBBB and paced hearts. These considerations explain why, for the purpose of optimizing total LV pump function, the first-order approximation on impulse conduction in our model is sufficient to predict optimal resynchronization with >90% accuracy. The observation that the model predicts optimal resynchronization equally well in experimental proximal LBBB and in clinical LBBB with presumably variable origin indicates that the model is valid for any kind of abnormal ventricular impulse conduction where myocardial impulse conduction through the rapid conduction system is presumably negligible.

A difference between the model predictions and the data is that, in patients and in five of six dogs, LV pacing at short AV delay resulted in a higher LV dP/dtmax than during baseline (LBBB) despite similar degrees of intraVA. This relatively high LV dP/dtmax occurred even at a slightly decreased LVEDP, presumably related to incomplete filling due to the short AV delay.

The relatively good hemodynamic performance of LV preexcitation has also been shown in a canine model of heart failure and LBBB. There it was found that during LV pacing in failing hearts, in contrast to normal hearts (20), electrical asynchrony within the LV coincides with mechanical asynchrony (15). One possible explanation is that during LV pacing the septum is less prestretched in the failing than in the normal heart (20). This could be due to larger stiffness of the septum or to the high diastolic RV pressure. The early systolic prestretch gives rise to pronounced shortening later during systole. The lack of such prestretch would thus reduce the amount of mechanical asynchrony.

Therefore, the pathway model presented in the present study proves to be very useful in predicting the optimal resynchronization, but for more refined predictions, like early LV activation, it needs to be extended. A clinical implication of the relatively good performance of LV preexcitation is that, in case of uncertainty on the point of optimal resynchronization, for LV pacing one would rather choose an AV delay that is too short than too long.

BiV Pacing vs. LV Pacing

The present study not only supports earlier findings that LV pacing can improve hemodynamics at least as well as BiV pacing (6, 13), but it also provides a possible explanation. First, the benefit of LV pacing primarily originates from fusion of the LV pacing-derived wavefront with that from intrinsic conduction. The smaller response during BiV pacing in ~50% of the responders is related to an insufficient degree of resynchronization (and so of the degree of fusion between 2 wavefronts) achieved with simultaneous BiV pacing. It seems likely that different timing of LV and RV stimulation, nowadays available on most heart failure pacemakers, can make BiV pacing as effective as LV pacing. Data from a small group of patients

Fig. 7. A: interVA values during baseline (BL) and at peak LV dP/dtmax. B: actual interVA at peak LV dP/dtmax vs. the predicted interVA at maximal hemodynamic response (see text and Fig. 1). Linear regression: slope = 1.00 ± 0.07, offset = 10 ± 2 ms, r = 0.96, and standard error of the estimate (SEE) = 6 ms. C: maximum hemodynamic response vs. hemodynamic response at predicted interVA. Linear regression: slope = 1.02 ± 0.05, offset = 1.5 ± 1.3%, r = 0.98, and SEE = 2.7%.

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support this idea and also show that LV preexcitation is preferred over RV preexcitation (18). Also a study on longitudinal shortening, derived from TDI, showed that individual adjustment of the interventricular stimulation delay to the location of the late contracting regions improved ejection fraction (24).

The observation that the interVA-LV dP/dt\textsubscript{max} relation was exactly the same during LV and BiV pacing indicates that the exact pattern of activation from the RV is not of primary importance to resynchronization. After all, during LV pacing resynchronization occurs by fusion of the impulse wavefront originating from the LV lead with that originating from the right bundle branch, whereas during BiV pacing at short AV interval, RV activation originates solely from the RV lead.

Possible Practical Applications

In the present study, interVA has been assessed using pressure measurements. This approach has the advantage that measurements during many different settings can be performed within a short time, but a disadvantage is its invasive nature. In

Table 2. Difference in maximal LV dP/dt\textsubscript{max} and PP increase between LV and BiV pacing in type I and II responders; interVA at maximum LV dP/dt\textsubscript{max} and PP increase, baseline interVA, and maximum interVA achieved by LV, BiV and RV pacing

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<th>Type II (n = 11)</th>
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Values are means ± SD. Significant differences: *vs. zero (paired t-test); †type I vs. type II (unpaired t-test).
case noninvasive diagnosis is warranted, several alternative approaches are possible, such as the timing difference in opening of aortic and pulmonary valves (measured using echocardiography), or heart sounds or timing differences in RV and LV wall motion (measured using tissue Doppler) (12, 22).

Such individual optimization seems especially relevant in the light of the finding that intrinsic interVA varies considerably between individuals, who all were “responders” to CRT. This variation may be due to abnormalities other than LBBB, influencing the synchrony of contraction between LV and RV, such as infarction, valvular abnormalities, and pulmonary and aortic hypertension. With such variation between patients, it is an important advantage that in the proposed approach for individual optimization of CRT, each patient can be used as its own control.

In a recent tissue Doppler study, Bordachar et al. (7) did not find a significant correlation between the change in interVA and cardiac output when optimal LV-RV stimulation delay was compared with simultaneous BiV pacing. The good correlation between optimal hemodynamics and interVA in the present study may indicate that it is important to take into account the interVA during baseline and during pacing at short AV delay.

Limitations

A possible limitation of the present study is that, in the animal experiments, intraVA was assessed using electrical activation measurements whereas interVA was determined using mechanical measures. However, in canine hearts a good correlation between electrical and mechanical activation has been found using a combination of MR tagging and mapping of epicardial electrical activation (31). This good correlation also appears to be supported by the observation that in the animal studies the relation of optimum resynchronization with intraVA and interVA is very close to that predicted by the pathway model.

Besides the timing of pacing, the pacing site is also an important determinant for improvement of pump function (11). According to the pathlength model, pacing at the latest activated site, exactly opposite to the septum, results in maximal reduction of intraVA, a finding that is confirmed by other studies (2). The fact that in the animal experiments, as well as in the patients, the LV leads were implanted using thoracotomy may have resulted in a better position of the LV lead compared with the majority of patients, where the lead is positioned via the coronary sinus. Future studies are required to validate the present model for leads implanted through this currently more common route. In case of a less optimal pacing site, it can be envisioned that the reduction in intraVA is less pronounced and the interVA during LV preexcitation is less positive. However, the intraVA-LV dP/dt max and interVA-LV dP/dt max relations remain unchanged, so that the best hemodynamic effect using that particular pacing site will still be predicted by the \((X + Y)/2\) value.

In the present study only acute hemodynamic changes due to pacing were investigated. A positive acute hemodynamic response is associated with sustained benefit over a period of 2 years (5), but the relation between acute hemodynamic benefit and clinical course is complex and not yet well established.

The concept of individual optimization of CRT has been addressed using extensive and complex pacing protocols while patients were at rest and supine and dogs were anesthetized. Further studies are required on the validity of the model during more active states, but it is known that desynchronization by classical RV pacing reduces cardiac pump function during exercise (16).

In conclusion, a relatively simple pathlength model is useful to predict optimal resynchronization. With this understanding, measurement of interVA at only a few LV pacing conditions can be used to optimize resynchronization therapy. The wide range of optimal interVA between patients indicates the need for individual optimization of CRT.

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DISCLOSURES

Y. Yu, J. Ding, T. Pochet, A. Kramer, and J. Spinelli are employed by Guidant. A. Auricchio has a patent pending with Guidant, has consultancies with Guidant, and has received honoraria from Guidant. F. W. Prinzen has patents pending with Guidant and Medtronic, has consultancies with Guidant and Medtronic, and has received honoraria from Guidant and Medtronic.

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