Measurement Precision in the Optimization of Cardiac Resynchronization Therapy

Robert G. Turcott, MD, PhD; Ronald M. Witteles, MD, FACC; Paul J. Wang, MD; Randall H. Vagelos, MD, FACC; Michael B. Fowler, MB, FRCP, FACC; Euan A. Ashley, MRCP, DPhil

Background—Cardiac resynchronization therapy improves morbidity and mortality in appropriately selected patients. Whether atrioventricular (AV) and interventricular (VV) pacing interval optimization confers further clinical improvement remains unclear. A variety of techniques are used to estimate optimum AV/VV intervals; however, the precision of their estimates and the ramifications of an imprecise estimate have not been characterized previously.

Methods and Results—An objective methodology for quantifying the precision of estimated optimum AV/VV intervals was developed, allowing physiologic effects to be distinguished from measurement variability. Optimization using multiple conventional techniques was conducted in individual sessions with 20 patients. Measures of stroke volume and dyssynchrony were obtained using impedance cardiography and echocardiographic methods, specifically, aortic velocity-time integral, mitral velocity-time integral, A-wave truncation, and septal-posterior wall motion delay. Echocardiographic methods yielded statistically insignificant data in the majority of patients (62%–82%). In contrast, impedance cardiography yielded statistically significant results in 84% and 75% of patients for AV and VV interval optimization, respectively. Individual cases demonstrated that accepting a plausible but statistically insignificant estimated optimum AV or VV interval can result in worse cardiac function than default values.

Conclusions—Consideration of statistical significance is critical for validating clinical optimization data in individual patients and for comparing competing optimization techniques. Accepting an estimated optimum without knowledge of its precision can result in worse cardiac function than default settings and a misinterpretation of observed changes over time. In this study, only impedance cardiography yielded statistically significant AV and VV interval optimization data in the majority of patients. (Circ Heart Fail. 2010;3:395-404.)

Key Words: cardiac resynchronization therapy ■ pacing optimization ■ AV delay ■ interventricular interval ■ echocardiography ■ impedance cardiography

Cardiac resynchronization therapy (CRT) decreases morbidity and mortality in populations with reduced cardiac function and conduction abnormalities1–3; however, approximately one third of these patients do not experience benefit.4 Atrioventricular (AV) and interventricular (VV) pacing interval optimization improve hemodynamics acutely5–7 and may enhance the response to CRT relative to default interval settings among both the traditional responder and nonresponder groups. To date, however, results of prospective randomized trials have been mixed.8–12

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The clarification of fundamental issues in pacing interval optimization is still at an early stage. For example, the extent to which optimum AV/VV intervals change with body position and exertion remains unclear,13–16 and data assessing the stability of optima over time have been inconsistent.17,18

Even the definitions of pacing intervals vary among manufacturers, with identical programmed intervals corresponding to very different ventricular pace timing.19 Perhaps the most important fundamental weakness is the lack of statistical tools to quantitatively evaluate the significance of the measured data and to characterize the precision of the estimated optimum AV/VV interval.11,20–22

In this study, we examined multiple commonly used AV/VV interval optimization techniques. Central to our approach is the recognition that the underlying dependence of cardiac function on AV/VV interval is obscured to some degree by measurement noise and that the optimum interval identified by a given technique is in fact an estimation of the true physiologic optimum. The degree to which measured optimization data demonstrate a significant dependence on pacing interval and the precision of estimated optima were rigorously evaluated using new statistical tools based on

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From the Division of Cardiovascular Medicine and Center for Biomedical Informatics Research, Stanford University School of Medicine, Stanford, Calif.
Correspondence to Euan A. Ashley, MRCP, DPhil, Cardiomyopathy Center, Stanford University School of Medicine, Division of Cardiovascular Medicine, Falk CVRC, 300 Pasteur Dr, MC5406, Stanford, CA 94305-5406. E-mail euan@stanford.edu
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**Table 1. Patient Demographics**

<table>
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<th>Patient No.</th>
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<td>31</td>
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<td>66</td>
<td>F</td>
<td>52</td>
<td>HCM</td>
</tr>
</tbody>
</table>

*AS indicates aortic stenosis; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation.
†No atrial lead.
‡No LV capture.
§No atrial bigeminy.

bootstrapping, a computational approach that makes knowledge of the underlying statistical properties of the data unnecessary.23

### Methods

#### Patient Selection

Data were obtained from consecutive patients referred for clinical pacing interval optimization with institutional review board approval. Patients with dual-chamber or biventricular pacemakers or implantable cardioverter defibrillators were included without regard to underlying etiology (Table 1).

#### Optimization Techniques

AV/VV interval optimization was conducted using multiple techniques, as follows:

1. Noninvasive, beat-to-beat estimates of stroke volume (SV) were acquired continuously using impedance cardiography (ICG; BioZ, CardioDynamics, San Diego, Calif) (Figure 1A).24–26 With ICG, changes in thoracic impedance are measured using surface electrodes and then processed by a proprietary algorithm to estimate SV and other hemodynamic parameters. Each test interval was delivered for 60 seconds, with all beats recorded during the last 30 seconds included in the analysis.

2. The remaining techniques were derived from echocardiography using a Philips iE33 System (Philips International B.V., Amsterdam, The Netherlands). The aortic velocity-time integral (A-VTI), which is directly proportional to SV, was obtained by numerically integrating the ejection velocity envelope obtained by continuous-wave Doppler directed in line with aortic flow in the apical 5-chamber view (Figure 1B).20,21 For this and the other echocardiographic techniques, a 10- to 20-second equilibration period followed each programming change. Data then were recorded over 1 to 2 respiratory cycles, with premature and postpremature beats excluded.

3. Mitral inflow velocity-time integral (M-VTI), which is directly proportional to inflow volume, was obtained using pulsed-wave Doppler with the sample volume placed just apical to the mitral leaflets in the apical 4-chamber view (Figure 1C).20,21

4. In contrast to the techniques described above, which attempt to characterize cardiac function by estimates of forward flow, septal-posterior wall-motion delay (SPWMD) provides an assessment of left ventricular (LV) mechanical synchrony.20 As shown in Figure 1D, the transducer signal was directed across the septum and the posterior LV wall in the parasternal long-axis view. Color M-mode Doppler was used to highlight the relative motion of the 2 walls, with minimal lag taken to represent optimal ventricular synchrony.

5. A-wave truncation identifies the optimum AV delay as the shortest pacing interval that avoids truncation of the A-wave21 and is based on the same Doppler waveform as M-VTI. Figure 1E shows an A-wave truncated at 150 milliseconds and untruncated at 180 milliseconds.

Optimization techniques were compared in terms of their ability to detect underlying physiologic changes with pacing interval. Specifically, the statistical significance of the data was quantitatively estimated, as described below. Because A-wave truncation yields a binary assessment at each test interval (A wave is or is not truncated), it is not amenable to the analytic paradigm used for the other techniques. Therefore, for A-wave truncation, we report the number of times each of the 3 readers, blinded to other results, was able to estimate an optimum pacing interval.

Summary statistics were obtained based on all patients referred for clinical optimization and, in addition, with hypertrophic cardiomyopathy patients excluded. Because ICG allows a greater number of data points to be obtained compared with echocardiographic methods, the AV interval optimization analysis was repeated for ICG data using the same number of measurements that were obtained in the corresponding A-VTI data set at each test interval.

#### Statistical Methods

A third-degree polynomial was fit to the data, and the location of the maximum was taken as the estimated optimum interval. For SPWMD, the location of the minimum absolute value of the polynomial was taken as the optimum. Use of a continuous function, such as a polynomial, allows interpolation between test intervals and averaging both at and across test intervals provided that the number of free parameters of the function is smaller than the number of unique test intervals.

The test for statistical significance was based on the formulation of the alternative hypothesis that the measured data do not depend on pacing interval. The probability of obtaining the observed data under this null hypothesis was estimated using bootstrapping.22,23 A test statistic s was defined to be equal to the area bounded above by the best-fitting polynomial and below by the minimum value of the polynomial, as illustrated in Figure 2. The test statistic is not unique; other measures also would be acceptable if they possess the property that their value varies depending on how "physiologic" the optimization data are. Specifically, if an underlying physiologic optimum exists, and if the range of test intervals was appropriately selected to span the optimum, then the test statistic should be larger than what would be obtained under the null hypothesis in which there is no dependence on pacing interval. The greater the difference in cardiac function at the optimum pacing interval and the extreme of the test range, the greater the value of s. For each optimization data set, 1000 surrogate bootstrapped data sets were generated by randomly selecting data points from the original data set with replacement and without regard to test interval. This process yields surrogate data sets with the same number of data points at each test interval as the original but replaces the original mapping between

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*Note: This text contains clinical data and should be used for educational purposes only. It is not intended for diagnostic use.*
Figure 1. Raw optimization data. A, Impedance cardiography is measured noninvasively using surface electrodes and provides estimates of multiple hemodynamic parameters, including stroke volume (SV). B, Aortic velocity-time integral is measured with continuous-wave Doppler at the left ventricular outflow tract and is directly proportional to ejected SV. C, Mitral velocity-time integral (M-VTI) is measured with pulsed-wave Doppler echocardiography and is directly proportional to inflow volume. D, Septal-posterior wall-motion delay is obtained using tissue Doppler imaging. The VV interval that minimizes the delay is taken as representing optimum synchrony. E, A-wave truncation uses the same images as M-VTI to identify the pacing interval at which the A-wave becomes truncated by ventricular systole. The image shows the A-wave truncated when a 150-ms AV delay is used and untruncated with a 180-ms AV delay.
Assessment of A-VTI Variability

The variability of the measured A-VTI data was quantified by calculating the average and SD over all measurements made at an AV delay of 120 ms, which by protocol were acquired over at least 1 respiratory cycle at 4 different times during the recording session. To allow comparison with previously published values, a transformation was derived that converts the coefficient of variation (defined as SD divided by mean) to the average difference of successive measurements. Specifically, $\mu_s = 2\text{CV} \sqrt{2/\pi}$, where $\mu_s$ is the average difference in successive measurements, and CV is the coefficient of variation. This result is based on the transformation $y_i = |x_{i1} - x_{i2}|/\mu_s$, where $x_{i1}$ represents successive A-VTI measurements at a given pacing interval in a given patient; $y_i$ the normalized difference in A-VTI measures in a given patient, and the subscript $i$, patient-specific values. The derivation assumes that $x_{i1}$ and $x_{i2}$ are independently drawn from a Gaussian distribution whose mean $\mu_i$ and SD $\sigma_i$ can vary among patients but whose coefficient of variation $CV_i$ remains fixed for all patients, that is, $CV_i = \sigma_i/\mu_i = \text{constant}$. Data acquisition and device programming are summarized in Table 2.
Table 2. Summary of Data Acquisition, Analysis, and Pacemaker Programming

<table>
<thead>
<tr>
<th>Data acquisition</th>
</tr>
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<tr>
<td>AV and VV interval optimization were conducted independently, with simultaneous</td>
</tr>
<tr>
<td>biventricular pacing during AV optimization and an AV delay of 120 ms during VV</td>
</tr>
<tr>
<td>optimization.</td>
</tr>
<tr>
<td>Data were recorded from each patient at a single session in the following order:</td>
</tr>
<tr>
<td>ICG (AV), ICG (VV), A-VTI (AV), M-VTI/A-Wave truncation (AV), A-VTI (VV), SPWMD</td>
</tr>
<tr>
<td>(VV)</td>
</tr>
<tr>
<td>Consecutive beat-to-beat measures of cardiac function were recorded over at least</td>
</tr>
<tr>
<td>1 respiratory cycle.</td>
</tr>
<tr>
<td>Test intervals were delivered in random order with 20–30 ms spacing.</td>
</tr>
<tr>
<td>The 120 ms AV delay and 0 ms VV interval were repeated 4 times over the duration</td>
</tr>
<tr>
<td>of the recording to assess stability.</td>
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</tbody>
</table>

Data Analysis

A 3rd degree polynomial was fit to the data, with the location of the maximum serving as the estimated optimum (for SPWMD, the optimum was the location with the minimum absolute delay)

A P value reflecting the statistical significance of measured data was obtained

The 95% CI of the estimated optimum was obtained

For A-wave truncation, the shortest AV delay that avoided A-wave truncation was selected as optimum, and the fraction of patients for whom an optimum could be determined was noted

Pacemaker Programming

The statistical significance, 95% CI, and physiologic plausibility of the measured data were considered

The pacemaker was left at default settings (AV delay = 120 ms, VV interval = 0 ms) for statistically insignificant data sets, wide 95% CIs that included the default setting, or physiologically implausible data. Otherwise, the estimated optimum pacing interval was programmed.

Results

Patient demographics are presented in Table 1. Of the 20 sequential, unique patients referred for clinical pacing optimization, 18 had biventricular pacemakers or implantable cardioverter defibrillators and 2 had dual-chamber devices. The LV lead in 1 patient failed to capture, and another patient with chronic atrial fibrillation had a biventricular device without an atrial lead. Patients who underwent AV delay optimization were in sinus rhythm with the AV delay initiated by an atrial sensed-event in all cases.

AV delay optimization data from a single patient are presented in Figure 3. As with the ICG data shown here (left panel), when statistically significant data were obtained they typically exhibited an inverted U appearance, indicating that the estimated optimum interval was in the interior of the range of test intervals. Statistically insignificant data typically had a best-fitting polynomial that was flat relative to the intrinsic variability of the data.

The average and SD of the measured A-VTI data were calculated over all beats (10 to 31, median 20) recorded from each patient during AV optimization at the 120-ms test interval. The ranges of the per-patient average and SD of the A-VTI data were 6.7 to 56 cm and 0.73 to 5.1 cm, respectively. The median sample coefficient of variation was 0.075, which corresponds to an average normalized difference in successive measurements of $\mu_y = 0.12$, consistent with previous reports of $\mu_y = 0.1 \pm 0.1$.27

The VV optimization data shown in Figure 4 are from the same patient whose AV optimization results are presented in Figure 3. As with this individual, for most patients, VV optimization yielded insignificant results more frequently than did AV optimization.

The number of statistically significant data sets is summarized in Table 3. For both AV and VV optimization, A-VTI, M-VTI, and SPWMD yielded data that were indistinguishable from the null hypothesis (ie, failed to demonstrate a statistically significant dependence on pacing interval) the majority of the time. As shown in Table 3, this finding remained true whether patients with hypertrophic cardiomyopathy were included or excluded from the analysis. ICG was significantly different from the null hypothesis 84% of the time for AV delay optimization and 75% of the time for VV interval optimization. Excluding patients with hypertrophic cardiomyopathy from the analysis, the null hypothesis could be rejected 81% and 75% of the time, respectively.

![Figure 3](https://via.placeholder.com/150)

Figure 3. AV delay optimization. Data were obtained from an individual patient at a single optimization session. Impedance cardiography (ICG) and aortic velocity-time integral (A-VTI) yielded statistically significant results, although the 95% CI of the estimated optimum was much narrower for ICG than for A-VTI. Mitral velocity-time integral (M-VTI) data were not statistically significant. Solid curve indicates best-fitting third-degree polynomial; X, location of estimated optimum pacing interval; horizontal line, 95% CI of estimated optimum.
Among the statistically significant data sets, the optimum AV delay estimated by ICG differed from the default value (120 ms) by an average magnitude of 57 ms, and 63% of the estimates differed from default by at least 50 ms. Among the statistically significant, ICG-derived VV interval data sets, estimated optima differed from the default value (0 ms) by an average of 52 ms, and 75% of the estimates differed by at least 30 ms. Repeating the ICG AV interval optimization analysis using the same number of measurements at each test interval as the A-VTI recordings continued to yield statistically significant results in the majority of patients, with 81% of the reduced ICG data sets having $P$ values $<0.05$.

An optimum AV delay could be estimated by 3 independent readers using A-wave truncation 69%, 75%, and 94% of the time. The estimates of each reader are compared with ICG results in Table 4. The relationship between optima predicted by ICG and A-wave truncation was variable, with the Pearson correlation coefficient ranging from 0.02 to 0.67 for the 3 readers.

Although the analysis presented above is based on unique patient visits, 1 patient underwent both ICG and echocardiographic optimization on 2 separate occasions separated by 3.5 months. As shown in Figure 5, in both cases ICG yielded similar-appearing, statistically significant results. The estimates of the optimum pacing intervals were precise, with narrow 95% CIs, and had good concordance, with 91 ms at the first optimization and 67 ms 3.5 months later. In contrast, in neither optimization session did A-VTI yield statistically significant results. The wide 95% CI of the initial A-VTI optimum predicted that subsequent optimization attempts would be unlikely to identify a similar optimum interval.

**Discussion**

In this study, multiple clinically accepted AV and VV interval optimization techniques were used in single sessions in a heterogeneous group of 20 patients. For 62% to 86% of patients, A-VTI, M-VTI, and SPWMD yielded data that were statistically indistinguishable from the null hypothesis; that is, the majority of the time these measures yielded data that did not show a significant dependence on AV or VV interval. With A-wave truncation, it was possible for 3 independent readers to estimate an optimum AV delay 69%, 75%, and 94% of the time. ICG performed better than the echocardiography methods, yielding statistically significant data 84% of the time for AV delay optimization and 75% of the time for VV interval optimization. Notably, the echocardiography techniques tested here represent the most commonly used approaches to AV/VV interval optimization.

In previous studies, SPWMD failed to predict a response to CRT, and interval optimization using A-VTI neither improved clinical outcomes nor yielded acute data that were distinguishable from a negative control. The poor precision of these techniques demonstrated in this study may account for the lack of clinical utility seen in the earlier work.

AV/VV interval optimization traditionally has been conducted without consideration of the intrinsic variability of the measured data. Test intervals often are delivered in a nonrandom order, sweeping systematically from one end of the test range to the other, and the AV or VV interval associated with the best average measure of cardiac function typically is taken at face value to represent the underlying physiologic optimum. Although efficient, the traditional approach has important drawbacks. A nonrandom order of test intervals allows systematic error to be introduced into the measured data in a way that cannot be subsequently corrected by averaging (eg, with subtle drift of the Doppler angle over the course of data collection). Furthermore, without considering the intrinsic variability of the measured data, it is not possible to characterize the precision of the estimated optimum AV/VV interval.

In the absence of knowledge about its precision, an estimated optimum AV/VV interval may in fact be spurious and associated with worse cardiac function than the population-derived, default setting (eg, a sensed AV delay of 120 milliseconds) (Figures 2, 3, and 5). In addition, although multiple studies have suggested that optimum pacing inter-
The fact that any optimization technique carries some degree of imprecision requires caution when designing randomized prospective trials. Two electrogram-based optimization techniques sponsored by competing manufacturers are currently undergoing clinical trials. In 1 design,\textsuperscript{32} patients are randomized to the experimental optimization technique or a control arm that may or may not include AV and VV interval optimization. If optimization is performed, it is conducted at the physician’s discretion without a requirement to examine the precision of the measured data, raising the possibility of a programmed AV or VV interval that yields worse cardiac function than population-derived default settings. By design, the trial will not address the question of whether the experimental technique is superior to default settings. In contrast, another clinical trial\textsuperscript{33,34} uses a 3-arm design in which patients are randomized to the experimental technique, a control arm in which population-derived default settings are used, and a conventional optimization arm in which a specific optimization technique is uniformly used. This study design allows direct comparisons between the experimental technique and both default settings and the specific conventional optimization method, and for comparison of the conventional technique to default settings.

Statistical significance testing may provide a useful way to evaluate the quality of competing optimization techniques. It avoids prespecifying a gold standard, and although demonstration of improved clinical outcomes in well-designed trials ultimately is required, the approach presented here offers a way to narrow the very wide field of plausible optimization techniques without the resource requirements of a prospective clinical trial.

Although a rigorous, quantitative analysis is desirable, statistical significance can be evaluated informally by plotting the measured data against pacing interval. With test intervals delivered in a random order, if the data exhibit the expected inverted U shape and are tightly clustered about the overall curve, then one can be confident that the estimation of optimum AV/VV interval is precise; repeating the process...
likely would yield a similar result. On the other hand, if the plot is relatively flat compared with the intrinsic variability of the measured data, then the estimate of the underlying optimum is imprecise and heavily influenced by measurement variability. In this case, repeating the optimization process likely would yield a very different estimated optimum AV/VV interval. The statistical tools used here along with plotting capability have been made available on the Internet.\textsuperscript{35}

In the majority of patients examined in the present study, ICG generated precise estimates and A-wave truncation yielded data from which an optimum could be inferred, although often with significant interreader variability and marginal correlation with the ICG-predicted optima. Notably, neither ICG nor A-wave truncation has been clinically validated in prospective interval optimization studies. In addition, unanswered fundamental questions include whether the physiologic optimum interval evolves over time and whether it changes between rest and exertion or between supine and upright posture. A study that compares estimated optimum intervals obtained at both supine rest and upright exertion in the same patient, perhaps using motion-tolerant ICG, would add important insight into these basic questions. In the absence of such data and given the theoretical potential benefit of pacing optimization, our approach is to accept an estimated optimum interval if quantitative and qualitative analyses suggest that the estimate has good precision. Particular attention should be paid to the effect of outliers and the overall shape of the curve compared with the measurement variability.

That ICG continued to yield statistically significant data in the majority of patients, even when using an identical number of data points as the A-VTI analysis, suggests that it has a superior intrinsic signal-to-noise ratio and that the acquisition time can be substantially shortened from the 60 s per test interval that was used in this study. The superior noise properties of ICG may be partly due to the automatic and objective nature of data acquisition and analysis in contrast to A-VTI, which requires the sonographer to physically hold the probe in a fixed position and the reader to manually demarcate the envelope of the velocity waveform.

A wide variety of optimization techniques have been advocated, including multiple approaches to the assessment of systolic function, diastolic function, and electrical and mechanical synchrony.\textsuperscript{9,19–21,24–26,30,36–40} Although each has a rationale that is mechanistically plausible, consideration of the neurohormonal derangements of heart failure and the therapeutic interventions that have been successful lead us to view SV and its surrogates as parameters that when optimized are most likely to translate into clinical benefit. Specifically, it is now well established that ameliorating the effects of sympathetic tone in these patients leads to improved clinical outcomes.\textsuperscript{41} For a given cardiac output, maximizing SV would minimize sympathetic tone. Indeed, the effects on the neurohormonal system of increased mechanical efficiency may contribute to the salutary effects of CRT, which remains the only contractility-enhancing intervention demonstrated to prolong life.\textsuperscript{42} Theoretical arguments may not account for important effects, however. For example, an increase in SV at the expense of greater oxygen consumption may not benefit

\begin{figure}
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  \includegraphics[width=\textwidth]{figure5.png}
  \caption{Stability of estimated optima over time. Impedance cardiography and aortic velocity-time integral were obtained from the same patient at baseline and 3.5 months later. In this patient, the ICG data were highly significant, the appearance of the data on repeat optimization recapitulated the baseline data, the estimated optima were concordant between the 2 sessions, and the 95\% CIs of the estimates were narrow. In contrast, the A-VTI data did not show a statistically significant dependence on pacing interval, and the estimated optima were highly discordant between the 2 optimization sessions. Accepting the A-VTI-estimated optima without a consideration of their statistical significance or precision would lead to the erroneous conclusion that the optimum AV delay had changed in the intervening 3.5 months.}\end{figure}
the patient with ischemic heart failure. Ultimately, any proposed optimization technique must be validated by randomized prospective trials with hard clinical end points, a goal which to date has not been frequently achieved.8–12

Limitations
The study was based on a small and heterogeneous population comprising successive patients referred for clinical pacing interval optimization. Multiple conventional optimization techniques were examined for their ability to yield statistically significant results. This property is necessary but not sufficient for improved clinical outcomes, which were not examined in this study.

Conclusions
Optimization of AV and interventricular intervals in CRT requires assessment of the variability of the measured data. Accepting an estimated optimum without considering its precision may result in worse cardiac function than default settings in the individual patient and confound results in clinical trials. In the small, heterogeneous pacemaker population examined here, echocardiographic techniques yielded statistically insignificant data in the majority of patients. In contrast, ICG yielded precise estimates of the optimum AV and VV interval in most patients. Further research is necessary to confirm these results, to validate the accuracy of the impedance-predicted optima, and to demonstrate clinical improvement with pacing interval optimization compared to population-derived default settings.

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CLINICAL PERSPECTIVE
Cardiac resynchronization therapy improves morbidity and mortality in appropriately selected patients. Whether further clinical benefit is possible with atrioventricular and interventricular pacing interval optimization remains unclear. Tools to assess the statistical significance of the measured optimization data have not been available previously. In the study reported here, an objective methodology for quantifying the statistical precision of estimated optimum pacing intervals was developed and applied to a number of commonly used optimization techniques. Many of the techniques did not yield statistically significant data in a majority of patients referred for atrioventricular and interventricular interval optimization, a finding that raises questions about the ability of pacing interval optimization to enhance clinical outcomes. The data demonstrate that accepting an estimated optimum interval without consideration of its statistical significance can result in worse cardiac function than default settings and can lead to the erroneous conclusion that the physiological optimum has changed over time. These results highlight the importance of evaluating the precision of measured data when conducting pacing interval optimization for the individual patient and when interpreting the results of clinical trials.
Measurement Precision in the Optimization of Cardiac Resynchronization Therapy
Robert G. Turcott, Ronald M. Witteles, Paul J. Wang, Randall H. Vagelos, Michael B. Fowler
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