Real-time stroke volume measurements for the optimization of cardiac resynchronization therapy parameters

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Aims
We investigated the utility of real-time stroke volume (SV) monitoring via the arterial pulse power technique to optimize cardiac resynchronization therapy (CRT) parameters at implant and prospectively evaluated the clinical and echocardiographic results.

Methods and results
Fifteen patients with ischaemic or non-ischaemic dilated cardiomyopathy, sinus rhythm, Class III congestive heart failure, and QRS >150 ms underwent baseline 2D echocardiogram (echo), 6 min walk distance, and quality of life (QOL) questionnaire within 1 week of implant. Following implant, 0.3 mmol lithium chloride was injected to calibrate SV via dilution curve. Atrioventricular (AV) delay (90, 120, 200 ms, baseline: atrial pacing only) and V-V delay (20 to 80 ms in 20 ms increments) were varied every 60 s. The radial artery pulse power autocorrelation method (PulseCO algorithm, LiDCO, Ltd.) was used to monitor SV on a beat-to-beat basis (LiDCO, Ltd.). Optimal parameters were programmed and echo, 6 min walk, and QOL were repeated at 6–8 weeks post-implant. Nine patients had 5% increase in SV after optimization (Group A). Six patients had 5% improvement in SV (Group B). Compared with Group B, Group A had significant improvements in left ventricular ejection fraction (LVEF) (11.0 ± 8.5 vs. 0.8 ± 2.0%) and decrease in left ventricular end-diastolic dimension (LVEDD) (−0.6 ± 0.4 vs. −0.2 ± 0.2 cm) and 6 min walk (346 ± 226 vs. 32 ± 271 ft, P ≤ 0.05). Group A patients also tended to have greater improvement in the septal-to-posterior wall motion delay on M-mode echo (P = 0.07).

Conclusion
Real-time SV measurements can be used to optimize CRT at the time of implant. Improvement in SV correlates with improvement in LVEF, LVEDD, and 6 min walk, and improvement in echocardiographic dyssynchrony.

Keywords
cardiac resynchronization therapy • stroke volume • congestive heart failure

Introduction
Congestive heart failure (CHF) continues to be among the most serious health problems in the world, with an incidence and prevalence that are resulting in massive health care expenditures. The ultimate therapy, heart transplantation, is limited to a fraction of the heart failure population due to ineligibility and low donor availability. In the effort to develop novel therapies for CHF, cardiac resynchronization therapy (CRT) has proved to be particularly successful. Multiple clinical trials have demonstrated that CRT can improve symptoms, exercise tolerance, and left ventricular (LV) function in patients with depressed systolic function and intraventricular conduction delays.1–6 Furthermore, other studies have demonstrated a mortality benefit from CRT.7

Application of CRT remains a challenge, both from the technical aspect of implantation and from the viewpoint of optimizing pacing parameters for the individual patient. The latter point may partly account for the fact that approximately one-third of patients receiving CRT do not appear to benefit from its application.2,4,8 Meanwhile, CRT devices have become increasingly sophisticated, with the ability to vary timing between the atria and ventricles as well as between the right and left ventricles. Various methods

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have been used to optimize device programming for CRT, including standard and tissue Doppler echocardiogram (echo) techniques, invasive haemodynamic monitoring, and radionuclide imaging. These methods are hampered by being time consuming, cumbersome, invasive, or difficult to apply at the time of implant. A recent report highlighted the inconsistency of echocardiographic based measures of dyssynchrony to predict the clinical response of CRT, suggesting potential problems using the same techniques to optimize device parameters.

Recently, a technique that uses the autocorrelation-derived arterial pulse power to monitor stroke volume (SV) on a beat-to-beat basis has been developed. Such a technique, which only requires a peripheral arterial line, has been used in a variety of clinical settings and has been validated as accurate when compared with established methods. The purpose of this study is to evaluate the ability of this technique to optimize CRT parameters in a series of patients with Class III CHF undergoing CRT.

Methods

This research protocol was approved by the Columbia University Institutional Review Board, and informed consent was obtained from every subject. This is a prospective non-randomized study, with each patient serving as his own control. The study subjects were selected as consecutive, consenting, unequivocal candidates for CRT based on current AHA/ACC guidelines. All patients had Class III heart failure with dilated ischaemic or non-ischaemic cardiomyopathy, left ventricular ejection fraction (LVEF) <30%, and left bundle-branch block or constant right ventricular (RV) apical pacing with QRS complex wider than 150 ms. All patients were on comprehensive medical regimens for CHF, including diuretics, ACE-inhibitor or ARB agents, and beta-blockers. All patients were in sinus rhythm.

Within 1 week before implantation, patients were asked to perform a 6 min walk and complete a quality of life (QOL) questionnaire (Minnesota Living with Heart Failure). In addition, trans thoracar echocardiograms were performed, with particular attention to LVEF, LV end-diastolic dimension (LVEDD), and septal-to-posterior wall motion delay (SPWMD). The CRT devices (or upgrade to CRT for patients with previous implants) were all biventricular defibrillators, and only successful implantations were included in this analysis, which is defined as implantation of the LV lead in a lateral position with adequate pacing and sensing thresholds. As is standard practice in our laboratory for symptomatic or haemodynamically compromised CHF patients, a radial arterial line was placed for blood pressure monitoring throughout the procedure and during defibrillation threshold testing (DFT).

Following DFT testing, the surgical wound was closed and the patient allowed to awake from sedation. While still in the laboratory with stable blood pressure and heart rate, the patient’s arterial line was attached to the monitoring system (LiDCO, UK). A small dose of lithium chloride was injected intravenously (0.3 mmol) to calibrate the device for SV measurements using an indicator dilution curve method. Stroke volume was then measured on a beat-to-beat basis using the pulse power autocorrelation of the arterial pulse pressure method. Stroke volume to optimize CRT parameters

Statistical analysis
Nominal values are compared using Fisher’s exact test. Continuous variables are compared using a paired or unpaired t-tests as appropriate. A P-value of <0.05 is considered significant.

Results

Figure 1 shows a sample plot of SV against programmed AV delay, and Figure 2 is an analogous plot for RV–LV delay. Stroke volumes at baseline ranged from 45.9 to 92.4 mL for the entire group. Nine of the 15 patients displayed a >5% improvement in SV after AV optimization compared with control (‘responders’) and those who did not (‘non-responders’). This SV cutoff was based on previous data obtained during the use of the SV technique to optimize CRT in a previous study at our institution. Echocardiographic and clinical variables were then compared between the responders and non-responders. A value of 130 ms for the SPWMD was used as a cutoff for echocardiographic dyssynchrony based on previous data using this discrimination point.

Statistical analysis
Nominal values are compared using Fisher’s exact test. Continuous variables are compared using a paired or unpaired t-test as appropriate. A P-value of <0.05 is considered significant.
patients in the non-responder group were de novo implants of CRT defibrillators and one patient an upgrade of a previous pacemaker for complete heart block. Seven of the responding patients were de novo implants of CRT defibrillators and two patients were upgrades of a previously implanted pacemaker or defibrillator due to complete heart block. Table 2 lists the post-CRT SV changes and percentage improvement compared with baseline, divided into responders and non-responders. Of the nine responding patients, only two increased SV >5% beyond AV optimization by RV–LV delay optimization. The changes in SV at a paced rate of 70 bpm were also seen at 90 bpm, although the absolute SVs were generally smaller at the higher paced rate. The optimal AV delay was unchanged for seven of the nine responding patients, and the optimal RV–LV delay was unchanged for six of the nine responding patients when comparing optimal parameters at a paced rate of 70 or 90 bpm.

Tables 3 and 4 compare the results of the echocardiographic and clinical variables between the responders and non-responders. There was a significant improvement in LVEF in the responder group, as well as a significant decrease in LVEDD by a paired analysis (P < 0.05). There was no significant improvement in LVEF or LVEDD in the non-responder group by a paired analysis. The mean change in LVEF and LVEDD between the responders and non-responders was also significant by an unpaired analysis (P < 0.05). Of the non-responder group, only one patient had an improvement in dyssynchrony as evidenced by an SPWMD >130 ms pre-CRT that decreased to <130 ms post-CRT. Two patients in the non-responder group had an SPWMD <130 ms before CRT. In contrast, seven of the nine patients in the responder group had an SPWMD >130 ms at baseline that improved to <130 ms after CRT. One patient in the responder group with an SPWMD >130 ms failed to decrease SPWMD post-CRT. One patient in the responder group had an SPWMD <130 ms at baseline. The SPWMD changes approached statistical significance between the two groups. The responder group had a significant improvement in 6 min walk distance by a paired analysis (P < 0.05). The non-responder group failed to have a significant improvement in 6 min walk distance. The mean improvement in 6 min walk distance between the two groups was significantly different as well (P < 0.05). There was no significant difference between the groups in terms of change in QOL scores or improvement in NYHA functional class.

Discussion

Cardiac resynchronization therapy has become a standard part of the armamentarium in the treatment of CHF patients with intraventricular conduction delays. Challenges remain in the application of CRT, the most notable being a non-responder rate approaching one-third of patients. Optimization of CRT parameters is believed to be an important aspect of decreasing the non-responder rate. In this study, we demonstrate the ability of a minimally invasive haemodynamic method to optimize CRT.
Table 2 Stroke volume changes in millilitre or percent increase compared with control (Δ)

<table>
<thead>
<tr>
<th>Optimization parameter</th>
<th>AV delay rate = 70</th>
<th>AV delay rate = 90</th>
<th>V-V delay rate = 70</th>
<th>V-V delay rate = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (n = 9)</td>
<td>4.8 ± 1.2* (6.8 ± 1.7)*</td>
<td>3.3 ± 2.5* (5.1 ± 3.8)*</td>
<td>1.8 ± 1.8* (2.6 ± 2.5)*</td>
<td>2.0 ± 1.5 (3.1 ± 2.3)</td>
</tr>
<tr>
<td>Non-responders (n = 6)</td>
<td>0.8 ± 1.2* (1.2 ± 1.7)*</td>
<td>0.6 ± 0.8* (0.9 ± 1.3)*</td>
<td>0.2 ± 0.6* (0.3 ± 0.8)*</td>
<td>0.7 ± 1.0 (1.0 ± 1.6)</td>
</tr>
</tbody>
</table>

Control is AAI pacing only or atrial RV pacing for pacemaker-dependent patients.

*P < 0.05 responders vs. non-responders for corresponding values.

Table 3 Echocardiographic variables post-cardiac resynchronization therapy

<table>
<thead>
<tr>
<th></th>
<th>LVEF (%) (ΔLVEF)</th>
<th>LVEDD (cm) (ΔLVEDD)</th>
<th>SPWMD improvement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (n = 9)</td>
<td>36.9 ± 8.7* (11.0 ± 8.5)*</td>
<td>5.1 ± 1.0 (−0.6 ± 0.4)*</td>
<td>7**</td>
</tr>
<tr>
<td>Non-responders (n = 6)</td>
<td>25.0 ± 7.9* (0.8 ± 2.0)*</td>
<td>5.9 ± 1.0 (−0.2 ± 0.2)*</td>
<td>1**</td>
</tr>
</tbody>
</table>

ΔLVEF and ΔLVEDD are values relative to baseline pre-CRT.
SPWMD: septal-to-posterior wall motion delay on M-mode echo.
*Defined as SPWMD > 130 ms improving to < 130 ms after optimization.
**P < 0.05 responders vs. non-responders for corresponding values.
***P = 0.07.

Table 4 Clinical variables post-cardiac resynchronization therapy

<table>
<thead>
<tr>
<th></th>
<th>NYHA class improvement</th>
<th>Δ6 min walk distance (ft)</th>
<th>ΔQOL score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (n = 9)</td>
<td>6</td>
<td>346 ± 226*</td>
<td>−14 ± 20</td>
</tr>
<tr>
<td>Non-responders (n = 6)</td>
<td>2</td>
<td>32 ± 271*</td>
<td>−7 ± 8</td>
</tr>
</tbody>
</table>

*P < 0.05.

The current method is able to monitor SV on a beat-to-beat basis, which is ideal for rapidly assessing the effect of small changes in pacing parameters. Such changes may not be noticeable with other techniques that concentrate on global LV function. The changes in SV were qualitatively consistent when pacing at different rates at a given programmed setting. The smaller SV at higher paced rates probably reflects decreased diastolic filling time with more rapid pacing in the absence of a physiological need for higher cardiac output. The results appear to corroborate the results of Naqvi et al. using radial artery tonometry, although in that study CRT was optimized using echocardiography. The current results also appear to extend the utility of this technique that we previously demonstrated in open-chest post-surgical patients.

Since a positive physiological and clinical response is the desired result of optimization, we hoped to demonstrate that optimization by the SV method correlates with improved echocardiographic and clinical measures. Stratifying the patients as responders and non-responders based on a cutoff of 5% SV improvement, we demonstrated a correlation between the acute increase in SV and echocardiographic parameters of LV remodelling such as improved LVEF and decreased LVEDD, and also clinical parameters such as increase in 6 min walk distance, measured 6–8 weeks after implant (Tables 2 and 3). Furthermore, the response by SV seemed to mirror the improvement in (or lack of) dyssynchrony, as measured by the change in SPWMD. This observation supports the contention that CRT is best suited to patients with ventricular dyssynchrony. We also observed a lesser change in SV during RV–LV compared with AV optimization, in agreement with prior published results.

Limitations

This study is limited by the small number of subjects and short follow-up, which may account for why changes in some parameters such as NYHA class and QOL scores did not achieve statistical significance. Time constraints limited our ability to test other pacing configurations or to perform more measurements for reproducibility, although variability was very low. The current technique requires placement of an arterial line, which may not be standard in all laboratories. The method may also be limited by frequent atrial or ventricular ectopy, which was not a factor with our patients during atrial pacing. Finally, the performance of the SV measurements in a laboratory setting after DFT testing can only reflect cardiac physiology at rest, and the results cannot predict the effect of CRT during exercise.

Conclusion

Optimization of CRT parameters by real-time SV measurements derived from the arterial pulse power autocorrelation is feasible and correlates with clinical and echocardiographic measures of improvement in CHF. The results of this study further confirm that acute haemodynamic optimization of CRT parameters can
impact the overall benefit of CRT. This technique is applicable at the time of implant and may be an additional aid in minimizing the non-responder rate with CRT.

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**Conflict of interest:** none declared.

**References**


