Hemodynamic Superiority of Dual-Site Left Ventricular Stimulation over Conventional Biventricular Stimulation in Heart Failure Patients

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ABSTRACT. The left ventricle (LV) is excited from a single site with conventional biventricular pacing. We theorized that exciting the LV from two sites would improve intraventricular synchrony. Seven heart failure patients (NYHA Class III, QRS >150 ms, left bundle branch block) enrolled in the Milwaukee Multisite Acute CRT Study (MMACS) were analyzed. Two LV leads were placed in widely separated coronary sinus branches with one closer to the apical region (LVA) and the other near the basal region (LVB). Two right ventricular (RV) leads were positioned in the apex (RVA) and in the high septum (RVB). Short sequences of VDD stimulation were delivered in dual-site LV (LVA + LVB) and two biventricular (RVA + LVB, RVB + LVA) configurations with three atrioventricular (AV) delays (16%, 41%, 66% of intrinsic AV interval). For each patient, changes in LV +dP/dt from baseline were calculated for all AV delays and pacing configurations. The mean percentage increase of dP/dt with LVA +LVB was 16.2% ± 8% (p<0.05), which was significantly greater than that of RVA +LVB (10.4% ± 4%) and RVB +LVA (6% ± 5%). Cardiac resynchronization therapy (CRT) with simultaneous dual LV free-wall sites produced a significantly greater increase in dP/dt compared to biventricular CRT with a single LV site.

KEYWORDS. atrioventricular optimization, dP/dt, cardiac resynchronization therapy, heart failure, multisite left ventricular pacing.

Introduction

Cardiac resynchronization therapy (CRT) is widely accepted for treatment of patients with systolic heart failure, impaired left ventricular (LV) ejection fraction and electrical asynchrony. It improves systolic LV function, peak oxygen uptake, exercise tolerance and New York Heart Association (NYHA) Class I–V and, over time, reverses the remodeling and neurohormonal changes accompanying heart failure.6–8 Large randomized trials also showed improved survival with CRT.9 Even so, a third of patients do not respond to CRT.1 There are several possible causes for this. CRT exerts its beneficial effects by more than one mechanism, but perhaps the most important contributing factor is restoration of intra-LV synchrony.2,10–13
is likely a major cause of patients failing to respond to CRT. Central to restoring intra-LV synchrony is the need for rapid and uniform electrical activation of the left ventricle. This is best accomplished by appropriate atrioventricular (AV) timing, such that there is activation of the left ventricle from multiple widely separate sites (via intrinsic conduction, transseptal conduction from the right ventricular (RV) pacing site and activation from the LV pacing site). It also is important that the LV stimulation site be in an optimal location to ensure rapid and uniform spread of electrical current throughout the left ventricle.

Some acute hemodynamic studies suggest that the mid-lateral wall of the left ventricle is the optimal pacing site, but other studies indicate that the optimal site may vary and be patient specific. Various methodologies to determine the optimal pacing site have been used, such as invasive measurement of dP/dt (rate and rise of LV pressure), mechanical asynchrony assessment by tissue Doppler or cardiac magnetic resonance imaging. All remain unproven or too cumbersome for routine clinical use.

We hypothesized that simultaneously pacing two sites in the left ventricle would increase the chances of at least one site being “optimal.” Further, simultaneously stimulating two widely separated LV sites would simultaneously depolarize a larger portion of the left ventricle than stimulation of a single site; thus, dual-site LV pacing would be more akin to rapid depolarization of the entire left ventricle via the His–Purkinje system in the absence of conduction system disease. To test this hypothesis, we conducted a pilot study to determine whether it is clinically feasible to implant two LV leads, and to assess if dual-site LV stimulation would improve hemodynamic response compared with conventional BIV pacing.

Methods

This prospective, single-center study was approved by the Institutional Review Board at Aurora St. Luke’s Medical Center, Milwaukee, WI. An investigational device exemption was obtained from the US Food and Drug Administration to allow use of a custom pacing and recording computer program (Flexstim II, Guidant Corp., St. Paul, MN).

Study population

After informed consent was obtained, 14 patients who met accepted criteria for a CRT-defibrillator (CRT-D) implant enrolled in this study. Study population demographics are detailed in Table 1.

Leads and catheters implantation

Standard operating procedures were used to implant a CRT-D; permanent leads were placed in the right atrial appendage, the right ventricular apex (RVA) and in a coronary sinus branch such that the lateral wall of the left ventricle was paced in a location closer to the apex (LVA) than the base. A temporary 5-French quadripolar pacing catheter was used to pace the high right ventricular septum (RVB), and an Easytrak (Boston Scientific Corp., Natick, MA) permanent LV lead was placed in either an anterolateral coronary sinus branch or the middle cardiac vein. This location was closer to the base (LVB) rather than the apex. Our intent was to pace two widely separated areas of the left ventricle. Figure 1a depicts the pacing sites.

Using a femoral approach, a 6-French pigtail catheter with a high-fidelity pressure sensor (Millar Instruments Inc., Houston, TX) was placed in the LV chamber. All leads and the pressure sensor were connected to the FlexStim II computer program, which controlled the pacing protocol and recorded the LV pressure, surface electrocardiogram and intracardiac electrograms on a beat-to-beat basis, during sinus rhythm as well as pacing.

The acute pacing protocol consisted of 30 beats of atrial-synchronous ventricular stimulation (VDD) in dual-site LV (LVA + LVB) and two standard BIV configurations, each employing both a single RV and a single LV lead. These configurations were RVA + LVB (RV apex + LV base) and RVB + LVA (RV base, i.e. septum + LV apex) (Figure 1b–d). Each configuration was tested at three AV delays, which were proportional (16%, 41%, and 66%) to each patient’s intrinsic AV interval. The order of stimulation site–AV delay combination was random for each patient.

Data analysis

Data analysis was performed by observers blinded to pacing configuration and patient identity. Comparisons were made using paired Student’s t-test. A value of p<0.05 was considered significant. Correlation was performed using Pearson’s chi-square test.

Results

Coronary venous anatomy allowed dual-site LV lead placement in 12 patients. Figure 2 shows a representative patient. Adequate hemodynamic data could not be obtained in two patients because of frequent premature ventricular contractions, and in one patient because of displacement of the pigtail catheter out of the LV. In two additional patients, one of the RV or LV leads

Table 1: Patient demographics (n = 14).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Measurement</th>
<th>Result</th>
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<tbody>
<tr>
<td>Age</td>
<td>Mean ± SD</td>
<td>68.9 ± 8.4</td>
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<tr>
<td>Gender</td>
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<tr>
<td>NYHA Class</td>
<td>III/IV</td>
<td>13/1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>Mean ± SD</td>
<td>25.6 ± 5.3</td>
</tr>
<tr>
<td>Etiology</td>
<td>Ischemic/Non-ischemic</td>
<td>10/4</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>Mean ± SD</td>
<td>162 ± 15</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>Mean ± SD</td>
<td>180 ± 28</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association; SD: standard deviation.
intermittently lost capture. Thus, complete data sets were obtained in seven patients.

Electrical delay within the LV chamber

During sinus rhythm, analysis of intracardiac electrograms from each pacing site was used to assess the activation sequence of various regions of the two ventricles. LV activation was invariably later than RV activation (mean delay 78 ± 31 ms). The mid-lateral apical (LVA) region was later than the basal posterior (LVB) region by 15 ms in four patients. The reverse was true in one patient. In the remaining two patients, LVA and LVB were activated within 10 ms of each other.

The LVA–LVB and LVB–LVA intervals (during LVA and LVB pacing) were 25 ms in four patients (Table 2).

Hemodynamic responses

The baseline dP/dt ranged from 427–952 mmHg/s. During VDD delivery at different AV delays and during different pacing configurations, the dP/dt change compared with intrinsic rhythm varied from −10% to 28%. The optimal AV interval was approximately 66% of the intrinsic AV interval in all patients and in all pacing configurations. No significant variations in intrinsic rhythm were observed during pacing in this patient population (typically intrinsic rhythm varied by no more than 5 bpm during the pacing procedure).
Impact of AV delay and pacing configuration

In the dual-site LV configuration, at the optimal AV interval, there was an average increase in dP/dt of 16.2% ± 8% (p < 0.05), range 8–28%. This increase was significantly greater than that with the RVB + LVA configuration (Figure 3). RVB + LVA tended to produce a greater increase in dP/dt over baseline than RVA + LVB (10.4% ± 4% versus 6% ± 5%, p = NS). Note that during intrinsic rhythm, LVA was activated later than LVB in most patients (Table 2). The differences in hemodynamic response to pacing between RVB + LVA and RVA + LVB configurations seemed to correlate with the LVA–LVB delay during intrinsic rhythm, i.e. when LVA was depolarized significantly later than LVB, the LVA + RVB configuration tended to show greater hemodynamic response than RVA + RVA (Figure 4). Further, the differences in hemodynamic response between LVA + LVB and RVB + LVA tended to be greater when the LVA–LVB interval was longer (Figure 5).

Acute response rates with different pacing configurations

An acute (>5%) increase in dP/dt_max is considered a criterion for identifying an acute responder.² By this criterion, all seven patients were acute responders with the dual-site LV configuration. One patient was classified a non-responder with the RVB + LVA configuration, and there was one non-responder and two borderline responders (dP/dt_max increase of 5%) with an RVA + LVB configuration.

Procedure time and complications

One patient with a previous history of diffuse atherosclerotic vascular disease suffered an ischemic stroke after the procedure. There were no other significant complications.

The mean procedure time was 182 ± 37 min. This included approximately 100 min for hemodynamic measurements and study-related procedures. Mean fluoroscopy time was 28 ± 13 min.
The Flexstim II (Guidant Corp.), which has been validated (pressure sensor catheter (Millar Instruments Inc.) and assess LV performance; we used a high-fidelity system pacing. Padeletti et al. used a conductance catheter to was used, whereas this study employed atrial-sensed cathodes. In Padeletti’s study, atrial-overdrive pacing subsequent study that has been reported in preliminary acute hemodynamic response than the two single LV– single RV site configurations; concordant results were obtained in a previous study that employed triple-site (RV + 2LV) pacing but assessed hemodynamics using echocardiography, and have been confirmed by a subsequent study that has been reported in preliminary fashion. Another study conducted by Padeletti et al. showed discordant results. Padeletti’s study differed from this study in several important respects. It compared triple-site pacing (two LV leads plus RV apical lead) to standard CRT, whereas this study compared dual-site LV-only pacing to standard CRT. Further, one of the two LV leads paced as the anode in Padeletti’s study, whereas both LV leads in this study were cathodes. In Padeletti’s study, atrial-overdrive pacing was used, whereas this study employed atrial-sensed pacing. Padeletti et al. used a conductance catheter to assess LV performance; we used a high-fidelity system (pressure sensor catheter (Millar Instruments Inc.) and the Flexstim II (Guidant Corp.)), which has been validated in several prior trials by other investigators. These differences may account for the differing results obtained by Padeletti et al.

The acute responder rate of 100% with dual-site LV stimulation was greater than has been reported with conventional CRT employing a single RV and a single LV site; indeed, one non-responder and two borderline responders with BIV pacing configurations using a single LV site became acute responders with dual-site LV pacing. Kocovic et al. showed similar clinical results in patients who received a second LV lead after failing to respond to conventional CRT.

Support for the clinical superiority of multisite LV stimulation is also obtained from the mid-term results of an ongoing study of triple-site pacing, which demonstrated a 96% clinical response rate and improved LV reverse remodeling compared with conventional BIV pacing.

These results can be explained by the lack of uniform electrical conduction in diseased myocardium. Zones of slow conduction and anatomic block impede rapid transmyocardial transmission of electrical impulses. Areas of functional block can develop depending upon the pacing site. The variation in LVA–LVB conduction times during intrinsic and paced rhythms supports this concept (Table 2).

Our results also suggest that conduction delay or functional block played an important role in determining the optimal LV pacing site; the LVA site was activated significantly later than the LVB in most patients. Pacing the electrically latest site provides the best response to CRT; our study confirmed this finding since the pacing configuration using LVA (i.e. RVB + LVA) provided a superior hemodynamic response (Figure 4). Cases with greater LVA–LVB delay showed greater hemodynamic improvement with dual-site LV pacing compared with RVB + LVA (Figure 5). An increased LVA–LVB conduction time suggested that either one of the LV leads paced in a zone of conduction or there was anatomic or functional block between the two LV pacing sites. In either case, rapid and uniform depolarization of the LV was impeded. By pacing two separate LV sites, we ensured that (a) stimulation was accomplished on either side of the conduction block and/or (b) at least one of the LV pacing sites did not lie in a zone of slow conduction.

**Clinical implications**

Our study showed that it is clinically feasible to place two separate LV leads via the coronary venous system during a CRT-D implant safely and within a clinically reasonable time in the majority of patients. Dual-site LV stimulation provided greater acute hemodynamic benefit than conventional CRT, and patients who failed to respond with conventional CRT pacing configurations did respond to dual-site LV pacing. If the acute results we obtained are confirmed by randomized long-term studies, we speculate that multisite LV stimulation may become accepted therapy, possibly using a single multipolar lead positioned appropriately in the coronary venous system. Triple Resynchronization In Paced Heart Failure Patients (TRIP HF), a small randomized study, explored the clinical impact of triple-site pacing in patients with atrial fibrillation. Although the primary end point was not met, there was a significant increase in LV ejection fraction with triple-site pacing compared with conventional CRT.
Limitations

Due to time constraints, not all combinations of BIV stimulations were fully investigated (e.g. RVA + LVA, RVB + LVB). Because of the complexity of the study, complete data sets were obtained only in a limited number of patients. Finally, this study focused on acute hemodynamic response; it remains to be seen if this CRT modality will improve clinical outcome.

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References