Mechanistic insights into the benefits of multisite pacing in cardiac resynchronization therapy: The importance of electrical substrate and rate of left ventricular activation

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BACKGROUND Multisite pacing (MSP) of the left ventricle is proposed as an alternative to conventional single-site LV pacing in cardiac resynchronization therapy (CRT). Reports on the benefits of MSP have been conflicting. A paradigm whereby not all patients derive benefit from MSP is emerging.

OBJECTIVE We sought to compare the hemodynamic and electrical effects of MSP with the aim of identifying a subgroup of patients more likely to derive benefit from MSP.

METHODS Sixteen patients with implanted CRT systems incorporating a quadripolar LV pacing lead were studied. Invasive hemodynamic and electroanatomic assessment was performed during the following rhythms: baseline (non-CRT); biventricular (BIV) pacing delivered via the implanted CRT system ($BIV_{implanted}$); BIV pacing delivered via an alternative temporary LV lead ($BIV_{alternative}$); dual-vein MSP delivered via 2 LV leads; MultiPoint Pacing delivered via 2 vectors of the quadripolar LV lead.

RESULTS Seven patients had an acute hemodynamic response (AHR) of $<10\%$ over baseline rhythm with $BIV_{implanted}$ and were deemed nonresponders. AHR in responders vs nonresponders was $21.4\% \pm 10.4\%$ vs $2.0\% \pm 5.2\%$ ($P < .001$). In responders, neither form of MSP provided incremental hemodynamic benefit over $BIV_{implanted}$. Dual-vein MSP ($8.8\% \pm 5.7\%$; $P = .036$ vs $BIV_{implanted}$) and MultiPoint Pacing ($10.0\% \pm 12.2\%$; $P = .064$ vs $BIV_{implanted}$) both improved AHR in nonresponders. Seven of 9 responders to $BIV_{implanted}$ had LV endocardial activation characterized by a functional line of block during intrinsic rhythm that was abolished with BIV pacing. All these patients met strict criteria for left bundle branch block (LBBB). No nonresponders exhibited this line of block or met strict criteria for LBBB.

CONCLUSION Patients not meeting strict criteria for LBBB appear most likely to derive benefit from MSP.

KEY WORDS Cardiac resynchronization therapy; Multisite pacing; Noncontact mapping; Left bundle branch block; Acute hemodynamic response

ABBREVIATIONS **AHR** = acute hemodynamic response; **AV** = atrioventricular; **BIV** = biventricular; **$BIV_{alternative}$** = biventricular pacing delivered via the temporary left ventricular lead; **$BIV_{implanted}$** = biventricular pacing delivered via the implanted cardiac resynchronization therapy system; **CRT** = cardiac resynchronization therapy; **DSM** = dynamic substrate mapping; **LBBB** = left bundle branch block; **LV** = left ventricle/ventricular; **$LVendoAT_{10-90}$** = time delay between the 10th and 90th centiles of activation; **$LVendoAT_{total}$** = total LV endocardial activation time; **MPP** = MultiPoint Pacing; **MSP** = multisite pacing; **RV** = right ventricular

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Introduction

Cardiac resynchronization therapy (CRT) for patients with systolic heart failure and electrical dyssynchrony is one of the major advances in cardiovascular medicine in the past 20 years.[1,2] Despite extensive efforts, the rate of response to CRT has remained static, and current guidelines reflect the fact that the strongest evidence is in patients with left bundle

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branch block (LBBB), QRS duration >150 ms, and little or no scar.[3]

CRT is generally accepted to achieve its therapeutic benefit by electrical resynchronization of the left ventricle (LV). It has been hypothesized that LV stimulation from >1 site, multisite pacing (MSP), may allow more complete synchronization and improve response.[4] Several studies have evaluated the acute hemodynamic effects of delivering CRT with MSP, either via 2 anatomically separated LV leads (dual-vein MSP) or via 2 vectors of a single multipolar LV lead (MultiPoint Pacing [MPP], St. Jude Medical, St. Paul, MN), with conflicting results.[5–10] Some authors have shown an improvement in hemodynamics with MSP, whereas others have shown little incremental benefit if the single LV pacing site is optimized.[7,11]

We have previously shown a small but nonsignificant improvement in acute hemodynamics with MSP (either multivein or multipolar) compared to standard CRT.[12] Data from canine studies have shown that MSP (from up to 7 sites) produces little incremental acute hemodynamic benefit when response to single-site LV pacing is favorable.[13] In this study, we sought to assess whether either form of MSP resulted in the correction of suboptimal hemodynamic response to CRT or whether biventricular (BIV) pacing from an alternative site was sufficient. We also sought to evaluate the electrical rationale for any hemodynamic improvement with the use of noncontact electroanatomic mapping in intrinsic rhythm and during pacing.

Methods

The study was approved by the local ethics committee, and each patient provided written informed consent. The study population consisted of 16 patients with a chronically implanted CRT system (with a quadripolar LV lead) in situ for at least 3 months (St. Jude Medical). Data comparing the effect of endocardial pacing and MSP in part of this cohort have been previously reported.[12] Inclusion and exclusion criteria and CRT system implant details can be found in the online supplemental material.

Hemodynamic and electroanatomic study

A second temporary coronary sinus pacing lead was implanted along with a noncontact mapping array (EnSite 3000, St. Jude Medical) and high-fidelity pressure wire capable of recording $LVdP/dt_{max}$ (both into the LV cavity; see the online supplemental material).

Measurement of acute hemodynamic response

$LVdP/dt_{max}$ was recorded for at least 20 seconds to ensure steady-state conditions during any pacing configuration. $LVdP/dt_{max}$ during atrial pacing (AAI) or right ventricular (RV) pacing (if the patient was in atrial fibrillation) at 5–10 beats above the intrinsic rate was used as baseline. A waiting period of at least 20 seconds was observed after any change in pacing settings to achieve hemodynamic stabilization. These methods have previously been shown to reliably measure $LVdP/dt_{max}$.[14–16] Results for each pacing protocol were expressed as a percentage change from baseline. To minimize baseline drift in acute hemodynamic response (AHR), baseline was reassessed immediately before and after every change in pacing configuration. The mean of these 2 readings (immediately before and after each pacing intervention) served as the reference to which particular pacing intervention was compared. Data from premature ventricular complexes were discarded.

Pacing protocol

A pacing protocol was performed with an atrioventricular (AV) delay of 100 ms (when in sinus rhythm) and with simultaneous RV and LV stimulation (VV interval = 0 ms). Where multisite stimulation was performed via 2 electrodes of the quadripolar LV lead, the delay between the 2 electrodes was set at the lowest possible interval (5 ms).

In the present analysis, the AHR to the following pacing configurations was compared (Figure 1):

1. BIV pacing delivered via the implanted CRT system ($BIV_{implanted}$; Figure 1A) was compared to baseline. Patients were deemed acute responders if the AHR to BIV pacing was ≥10% over baseline.[16]
2. In those patients who did not exhibit a favorable acute response to CRT delivered via the implanted system, $BIV_{implanted}$ (Figure 1B) was compared to BIV pacing delivered via the temporary LV lead ($BIV_{alternative}$) and then either MPP (Figure 1C) or dual-vein MSP (Figure 1D).
3. The same comparison was also made in patients with a favorable acute response to $BIV_{implanted}$.

Assessment of electrical data

LV endocardial activation in intrinsic rhythm was assessed in all patients. Isopotential maps derived from the EnSite array were analyzed to determine whether patients exhibited a line of functional conduction block, as first described by Auricchio et al.[17]

The following electrical parameters were recorded for each pacing configuration (see the online supplemental material):

1. Paced QRS duration.
2. LV transmural conduction time (TMCT).
3. Total LV endocardial activation time ($LVendoAT_{total}$). Endocardial maps were obtained at baseline and in each pacing configuration.
4. Time delay between the 10th and 90th centiles of activation ($LVendoAT_{10-90}$).

The last 3 variables were derived from the custom-developed MATLAB code (MathWorks, Natick, MA).