Acute electrical and hemodynamic effects of multisite left ventricular pacing for cardiac resynchronization therapy in the dyssynchronous canine heart

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BACKGROUND Multisite left ventricular (multi-LV) epicardial pacing has been proposed as an alternative to conventional single-site LV (single-LV) pacing to increase the efficacy of cardiac resynchronization therapy.

OBJECTIVE To compare the effects of multi-LV versus single-LV pacing in dogs with left bundle branch block (LBBB).

METHODS Studies were performed in 9 anaesthetized dogs with chronic LBBB using 7 LV epicardial electrodes. Each electrode was tested alone and in combination with 1, 2, 3, and 6 other electrodes, the sequence of which was chosen on the basis of practical real-time electrical mapping to determine the site of the latest activation. LV total activation time (LVTAT) and dispersion of repolarization (DRep) were measured by using approximately 100 electrodes around the ventricles. LV contractility was assessed as the maximum derivative of left ventricular pressure ($LVdP/dt_{max}$).

RESULTS Single-LV pacing provided, on average, a $-4.0\% \pm 9.3\%$ change in LVTAT and $0.2\% \pm 13.7\%$ change in DRep. Multi-LV pacing markedly decreased both LVTAT and DRep in a stepwise fashion to reach $-41.3\% \pm 5\%$ ($P < .001$ for overall comparison) and $-14.2\% \pm 19.5\%$ ($P < .02$ for overall comparison) in the septuple-LV pacing configuration, respectively. Single-LV pacing provided a mean increase of $10.7\% \pm 7.7\%$ in $LVdP/dt_{max}$. $LVdP/dt_{max}$ incrementally increased by the addition of pacing electrodes to $16.4\% \pm 8.7\%$ ($P < .001$ for overall comparison). High response to single-LV pacing could not be improved further during multi-LV pacing.

CONCLUSIONS Compared with single-LV pacing, multi-LV pacing can considerably reduce both LVTAT and DRep in dogs with LBBB, but the improvement in contractility is limited to conditions where single-LV pacing provides suboptimal improvement. Further studies are warranted to determine whether these acute effects translate in antiarrhythmic properties and better long-term outcomes.

KEYWORDS Cardiac resynchronization therapy; Multisite left ventricular pacing; Heart failure; Left bundle branch block; Cardiac mapping; Biventricular pacing

ABBREVIATIONS **CRT** = cardiac resynchronization therapy; **DRep** = dispersion of repolarization; **LBBB** = left bundle branch block; **LV** = left ventricular; **$LVdP/dt_{max}$** = maximum derivative of left ventricular pressure; **LVTAT** = left ventricular total activation time; **multi-LV** = multisite left ventricular; **RV** = right ventricular; **single-LV** = single-site left ventricular

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment of patients with symptomatic heart failure, severely impaired left ventricular (LV) function, and conduction disorders, most often in the form of left bundle branch block (LBBB). Large randomized trials have demonstrated that CRT improves quality of life and symptoms as well as reduces heart failure–related hospitalizations and mortality. However, approximately one-third of the patients appear not to respond significantly to CRT.[1] Because CRT is a relatively expensive and invasive technique, requiring virtually irreversible device implantation, there is considerable interest in attempts to improve the response rate. While most attention has been focused on criteria for patient selection, an at least equally important approach is to improve therapy delivery. As the benefits of CRT are particularly thought to result from improved electrical resynchronization of the LV, multi-site LV pacing has arisen as an alternative strategy for improving the success rate of CRT. However, thus far this

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question has not been specifically addressed. Human data are restricted to LV pacing at 2 sites (triventricular pacing), and acute hemodynamic studies evaluating the role of triventricular pacing have shown conflicting results.[2–5]

The hypothesis of the present study was that both electrical resynchronization and hemodynamic function improve with an increasing number of LV pacing sites. In order to investigate this hypothesis, experiments were performed in dogs with chronic LBBB.[6] In this well-established animal model of dyssynchrony, we pursued optimal resynchronization by using near real-time electrical mapping to locate and stimulate the latest activation of 7 predetermined LV pacing electrodes: first 1 and then 2, 3, 4, and all 7 electrodes simultaneously. This design allowed an extensive comparison of many pacing sites and invasive hemodynamic measurements.

Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The protocol was approved by the Animal Experimental Committee of Maastricht University.

Experimental setup

The experiments were performed on 9 adult mongrel dogs of either sex and unknown age, weighing 22.0 ± 0.5 kg. After the induction of Pentothal, anesthesia was maintained by the infusion of midazolam (0.25 mg/(kg · h) intravenously) and sufentanil (3 μg/(kg · h) intravenously). LBBB was created by radiofrequency ablation 16 weeks before the acute experiment, allowing for ventricular remodeling to occur.

Surface electrocardiograms were recorded from the limb lead electrodes. LV pressure and volume were measured by using a combination of 7-F catheter-tip manometer and conductance catheter, and right ventricular (RV) pressure measured by using a 7-F catheter-tip manometer (CD-Leycom, Zoetermeer, The Netherlands). These catheters were introduced into the carotid artery and jugular vein, respectively. After thoracotomy, 2 multielectrode bands for recording and pacing were positioned around the heart, one approximately 1 cm below the base and the other around the mid-level. Each of these customized bands contained 2 rows of electrodes (2 × 30 and 2 × 22, respectively), approximately 1 cm apart. To measure the electrical activation of the septum, an 8-pole multielectrode catheter (Daig Livewire TC, Minnetonka, MN) was placed through the jugular vein in contact with the RV septum.

Temporary myocardial pacing leads (Medtronic, type 6500, Minneapolis, MN) were sutured to the epicardial surface of the roof of the right atrium and to the LV apex. Seven predefined epicardial electrodes were used for the LV pacing protocol: at the anterior, lateral, and posterior walls of both the basal and the mid-level of the LV (from the bands) and at the LV apex (lead).

After instrumentation and hemodynamic stabilization, electrical mapping and hemodynamic measurements were acquired simultaneously. For all 7 epicardial electrodes, the pacing threshold was determined. Each LV electrode was first used for single-LV pacing, the order of which was randomized per dog. Subsequently, a second LV electrode was added, being the 1 of the 6 remaining with the longest activation time (located in the latest activated region) during single-LV pacing, as assessed by epicardial mapping (Figure 1). The same procedure was repeated for the third and the fourth LV electrode (Figure 1). Finally, all 7 LV electrodes were paced together (5 and 6 electrodes together were not tested). The ventricular pacing mode was DOO, 10 beats/min above the sinus rhythm. Baseline atrial pacing measurements were repeated at each pacing site in the AOO mode at the same rate. The paced AV interval was set at 70 ms, and full capture was confirmed by cardiac mapping

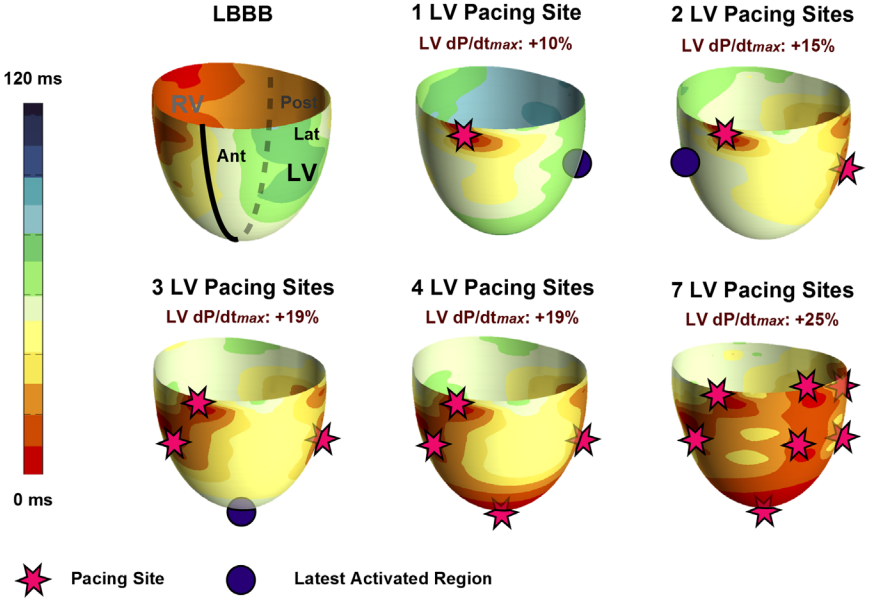

Figure 1 Overview of the pacing protocol. Three-dimensional epicardial activation maps of both ventricles during LBBB activation and single-, dual-, triple-, quadruple-, and septuple-LV pacing configurations in the same dog. In this example, single-LV pacing started with the basal-anterior LV electrode (center panel, top row). During single-LV pacing, the latest remaining electrode was middle-posterior (blue dot) and was thereby used for the dual LV-pacing configuration (right panel, top row). Each time the latest activated electrode was added to achieve triple and quadruple-LV pacing (bottom row, left and middle maps). Finally, the 7 electrodes were paced together. LBBB = left bundle branch block; LV = left ventricular; LVdP/dt_{max} = maximum derivative of left ventricular pressure; single-LV = single-site left ventricular.