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Left ventricular pacing site and timing optimization during biventricular pacing using a multielectrode patch in pigs

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Objectives: Biventricular pacing is important therapy for congestive heart failure, reversing left ventricular dysfunction in dilated cardiomyopathy. Although left ventricular lead location and right ventricular–left ventricular delay are believed to be critical in biventricular pacing, there is no established technique for optimizing pacing site and timing.

Methods: After median sternotomy in 8 anesthetized pigs, an ultrasonic flow probe was placed on the ascending aorta to measure cardiac output, and pressure catheters were inserted into both ventricles. Temporary bipolar epicardial pacing leads were attached to the right atrium and anterior right ventricle. A patch with 5 bipolar electrodes was placed behind the left ventricle. A temporary bipolar lead was also placed on the left ventricular apex. Complete heart block was established by ethanol ablation. Right ventricular pressure overload was induced by snaring the pulmonary artery until right ventricular systolic pressure doubled. Dual-chamber mode biventricular pacing was instituted at 9 right ventricular–left ventricular delays, +80 ms to −80 ms in 20 ms increments, and 6 left ventricular sites. Data from the 54 combinations of these variables were acquired in a randomized fashion. Mixed model technology was used for statistical analysis.

Results: Qualitatively, two unique site/timing pairs were optimal. Statistically, pacing the obtuse margin at a right ventricular–left ventricular delay of +60 ms (mean cardiac output = 1.80 L/min) and the inferolateral wall at a right ventricular–left ventricular delay of −20 ms (mean cardiac output = 1.79 L/min) was superior to all other site/timing combinations (mean cardiac output = 1.71 L/min; $P = .006$).

Conclusions: Left ventricular pacing site and right ventricular–left ventricular delay can be optimized with a multielectrode patch and randomized data collection. This technique can be used further in clinical studies.

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Increasing clinical evidence suggests that biventricular pacing (BiVP) can be beneficial for patients with congestive heart failure (CHF), right and/or left bundle branch block, and long QRS complexes. Three important clinical studies (InSync, MUSTIC, and MIRACLE) have demonstrated a benefit to patients with CHF as evidenced by improved hemodynamics, quality of life, and decreased hospital admission owing to CHF.[1-3] However, many patients did not respond to BiVP in these trials, suggesting that better techniques of patient selection and pacing optimization are needed. Adjustment of atrioventricular delay, right ventricular–left ventricular delay (RLD), and ventricular pacing site may improve ventricular synchrony and increase cardiac output (CO) and ventricular mechanics during BiVP.

Median sternotomy provides access to the ascending aorta and pulmonary artery, allowing measurement of flow velocity by ultrasonic transit-time flow probes. Transit-time ultrasound has been shown to be an accurate, continuous method of

Abbbreviations and Acronyms

A_{pp}	= area of the normalized RV-LV pressure diagram
BiVP	= biventricular pacing
CO	= cardiac output
dP/dt_{max}	= maximum rate of pressure rise
LV	= left ventricle(ular)
RLD	= right ventricular–left ventricular delay
RV	= right ventricle(ular)

measuring flow and has been validated against a right heart bypass preparation.[4] These flow velocities can be integrated to provide a digital readout of CO.

Open-chest animal models have been used to assess effects of pacing strategies on left ventricular (LV) contractility. Prinzen and associates[5] evaluated the effect of pacing strategies on cardiac function in a canine model using rate of pressure rise (dP/dt) and stroke volume as indices of LV synchrony. To date, there has been no systematic study of the effect of LV pacing site and timing during BiVP. We hypothesized that during BiVP, a multielectrode patch placed in the posterior pericardium could allow for rapid testing of multiple LV sites and RLD and could identify effects of LV site and RLD on CO and other measures of function.

Materials and Methods

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" developed by the Institute of Laboratory Animal Resources and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication number 85-23, revised 1985).

Surgical Preparation

Eight domestic pigs (40–45 kg) were anesthetized with ketamine hydrochloride (20 mg/kg intramuscularly), xylazine hydrochloride (0.5 mg/kg intramuscularly), and atropine sulfate (2 mg/kg intramuscularly). Pigs were intubated and mechanically ventilated, with arterial blood gas values being maintained within physiologic norms. Anesthesia was maintained with inhalation isofluorine (1.5%–2%) in oxygen. An 18-gauge angiocatheter was placed in an ear vein for an intravenous infusion of 0.9% saline. Electrocardiogram leads were attached to the limbs, and the left femoral artery was instrumented with a 20-gauge angiocatheter attached to a pressure transducer to measure arterial pressure. After median sternotomy and longitudinal pericardiotomy, a lidocaine bolus (3 mg/kg intravenously) was given and a lidocaine drip started at 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to suppress arrhythmias. A 24-mm real-time ultrasonic flow probe (Transonic Systems Inc, Ithaca, NY) was placed on the ascending aorta. Temporary bipolar epicardial pacing leads (Medtronic, Inc, Minneapolis, Minn) were placed on the right atrium, anterior surface of the right ventricle (RV), and apex of the LV. A multielectrode patch with 5 bipolar electrodes (Figure 1), corresponding to 5 LV sites, was placed in the posterior pericardium around the LV (Figure 2). Pericardial stay sutures were placed and the pericardium was wrapped around the patch to secure it in place. Pacing wires were connected to a custom-housed InSync III pacemaker (Medtronic) to allow temporary pacing with variable RLD.

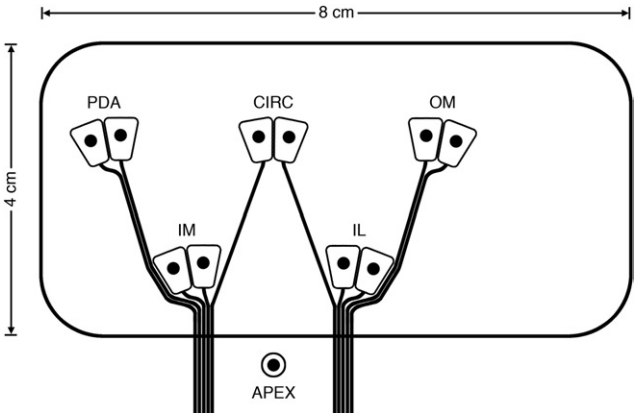

Figure 1. Diagram of the multielectrode patch with 5 bipolar electrodes and corresponding left ventricular sites. Dimensions are indicated in centimeters. Apical leads were sewn in. *APEX,* Apical; *CIRC,* circumflex; *IL,* inferolateral; *IM,* inferomedial; *OM,* obtuse margin; *PDA,* posterior descending.

Once proper function of the pacemaker leads was confirmed, complete heart block was established by injection of 0.5-mL aliquots of 100% ethanol into the region of the bundle of His at the base of the aorta. The cumulative amount of ethanol required to establish complete heart block ranged from 0.5 to 1 mL. Animals were heparinized with 300 IU/kg intravenously, and calibrated 5F micromanometer catheters (Millar Instruments, Inc, Houston, Tex) were placed in both the RV and LV through purse-string sutures. RV pressure overload was induced by snaring the pulmonary artery with umbilical tape until RV systolic pressure doubled.

Atrial tracking dual-chamber mode BiVP was initiated at a heart rate of 90 beats/min with an atrioventricular delay of 150 ms in all animals. Animals were paced at 9 RLDs, +80 ms (RV-first pacing) to −80 ms (LV-first pacing) in 20-ms increments, and 6 LV sites (apex, inferomedial, inferolateral, posterior descending, circumflex, obtuse margin) for 30-second intervals. Data from the 54 possible combinations were acquired in a randomized fashion. Animals were humanely killed at the conclusion of the experiment.

Data Analysis

Analog data for electrocardiogram, arterial pressure, RV pressure, LV pressure, and aortic flow velocity were sampled and transferred through a 16-channel analog-to-digital converter (ADInstruments, Inc, Milford, Mass) to a personal computer (Apple Computer, Cupertino, Calif). CO was determined for each experimental setting by integrating aortic flow velocity over time during a single complete respiratory cycle free of arrhythmia within each 30-second interval. In 7 pigs, ventricular systolic function was assessed from the same cardiac cycles by RV and LV dP/dt_{max}.

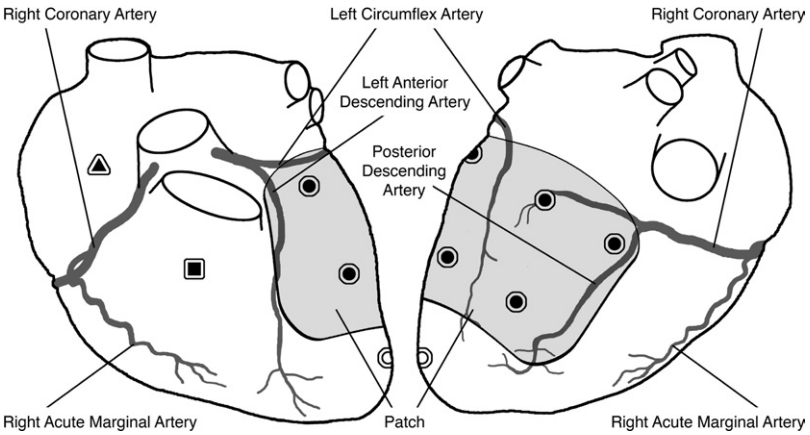

Figure 2. Diagram of the anatomic location of the multielectrode patch and contained electrodes on the left ventricle *(dark circles).* Pacing leads were also placed on the apex *(open circle),* anterior surface of the right ventricle *(square),* and right atrium *(triangle).*

Mechanical interventricular synchrony was quantified by the area of the normalized RV-LV pressure diagram (A_{PP}).[6] A_{PP} expresses synchrony based on the pressure during the complete cardiac cycle, with a loop area of zero indicating complete synchrony and a maximum area of one indicating complete asynchrony. A counterclockwise loop results in positive values, indicating earlier RV than LV pressure generation.

The resulting data were imported into Matlab (The MathWorks, Inc, Natick, Mass). The percentage change in CO from the mean value of all settings was calculated in each pig. The values for each combination of settings were averaged across the group. Results were visualized by use of response surfaces with LV pacing site on the ordinate, RLD on the abscissa, and magnitude represented by a color map linearly interpolated between measured values. Contour lines represent incremental changes. For surfaces of CO and dP/dt_{max}, the highest values are represented by red, and for surfaces of A_{PP}, complete synchrony ($A_{PP} = 0$) is represented by white.

Statistical Methods

LV site/RLD combinations were modeled in SAS via the PROC MIXED procedure for repeated measurements (SAS Institute, Inc., Cary, NC). Owing to the fact that repeated measurements within animals may be correlated, this procedure allows one to model this "correlation structure" commonly referred to as a covariance pattern. This accurate estimate will allow for estimates of the standard errors of measurement and, therefore, more powerful tests. There are a number of various covariance structures to choose from. Three of the more common covariance structures include "compound symmetry," for correlations that are constant for any two points in time, "auto-regressive order one," for correlations that are smaller for time points further apart, and "unstructured," which has no mathematical pattern within the covariance matrix. The compound symmetry structure provided the best fit.

Results

Figure 3 shows a representative plot of beat-to-beat CO measurements over 27 minutes of continuous data collection during 1 experiment. Figure 4 is a response surface plot demonstrating percentage change from the mean CO for all possible LV site/RLD combinations averaged over all 8 experiments. Qualitatively, 2 unique LV site/RLD pairs were optimal. Pacing the obtuse margin at an RLD of +60 ms (mean CO = 1.80 L/min) and the inferolateral wall at an RLD of −20 ms (mean CO = 1.79 L/min) was superior to all other LV site/RLD combinations (mean CO = 1.71 L/min; $P = .006$). Figure 5 shows the average hemodynamic effects of LV pacing site and RLD averaged over 7 experiments using response surface plots. LV dP/dt_{max} increased 14% with negative RLD, reaching a maximum and plateauing around −20 ms. RV dP/dt_{max} increased 30% and A_{PP} decreased to near synchronous with positive RLD, plateauing around +40 ms. LV pacing site only affected LV dP/dt_{max}, with sites near the apex producing the highest values.

Discussion

Recent clinical studies of endocardial BiVP differ in suggesting that cardiac function is maximized by localization of LV pacing leads in the midlateral region of the LV[7,8] or

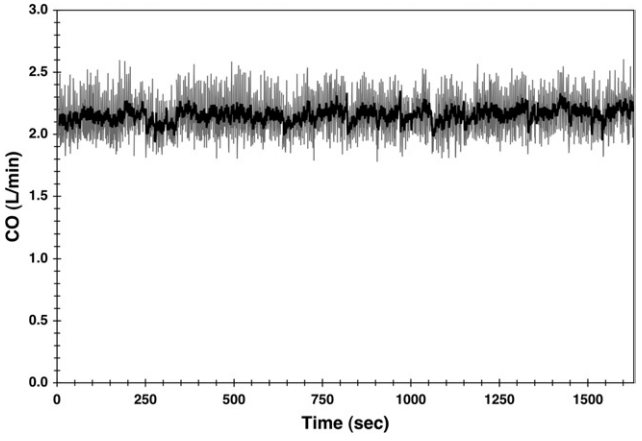

Figure 3. A representative plot of beat-to-beat cardiac output measurements over 27 minutes of continuous data collection during 1 experiment. *CO,* Cardiac output.

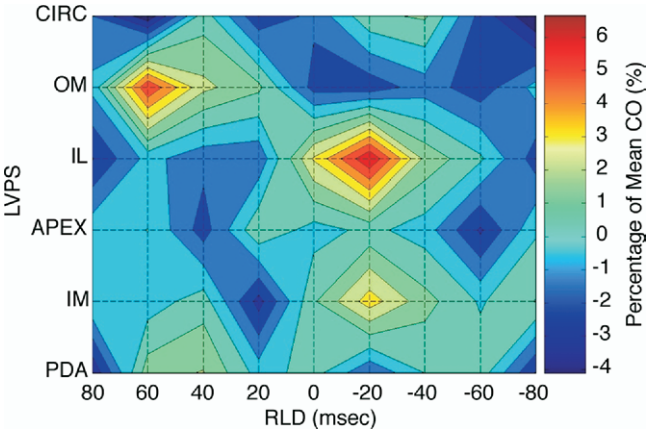

Figure 4. Surface plot demonstrating percentage change from mean cardiac output for all possible left ventricular pacing site/right–left ventricular delay combinations averaged over 8 experiments. Contour lines indicate a 1% change in cardiac output. The highest values are represented by red. *APEX,* Apical; *CIRC,* circumflex; *CO,* cardiac output; *IL,* inferolateral; *IM,* inferomedial; *LVPS,* left ventricular pacing site; *OM,* obtuse margin; *PDA,* posterior descending artery; *RLD,* right ventricular–left ventricular delay.

other locations.[9,10] Endocardial LV lead position is often limited by anatomy of the cardiac veins. Many locations are inaccessible, resulting in implantation failure in 5% to 14% of attempts.[11,12]

Dekker and associates[13] showed that optimal epicardial LV pacing site acutely increased LV stroke volume, dP/dt_{max}, and ejection fraction relative to baseline, whereas suboptimal sites did not change or worsened LV function. The InSync III trial showed that 77% of patients had an optimal RLD other than 0 ms. Optimization acutely increased echocardiographic–Doppler LV stroke volume by 11.3% in these patients, and 17% of these patients experienced 20% or greater improvement in stroke volume.[14]

The present study sought to develop techniques that could be used clinically for optimization of BiVP during epicardial implantation. A multielectrode patch placed in the posterior pericardium allowed for rapid testing of multiple LV sites, avoiding mechanical effects of lead manipulation. Changing both site and RLD simultaneously and in randomized fashion avoids linear effects of one site-timing combination on the next and also eliminates possible bias of the investigators on outcome.

We have used CO as the dependent variable in our BiVP optimization studies, because CO is a fundamental determinant of organ perfusion. However, many other variables have been used clinically for BiVP optimization, including echocardiographic studies of posterior wall motion and ventricular synchrony. Because CO depends on multiple variables and requires time to stabilize, determinants of CO could ultimately prove more valuable for rapid optimization. These determinants could include echocardiographic indices, A_{PP}, or even shortening of QRS duration.

Previous studies from our laboratory have demonstrated that in a similar model of severe pressure overload, CO was maximized with an RLD of +40 ms (RV-first pacing).[15] In that experiment, the LV was paced at only one site, the obtuse margin. In the present study, multiple LV sites were tested and two optimal LV site/RLD combinations were identified: obtuse margin/RLD +60 ms and inferolateral/RLD −20 ms. Our laboratory is in the process of defining mechanisms for the effects of RLD on CO.[16] In a recent study of LV and RV pressure development in our experimental model of RV pressure overload, optimized pacing was associated with statistically significant benefits in RV dP/dt_{max} and interventricular synchrony.[17] In the present study of RV failure, RV function and ven-

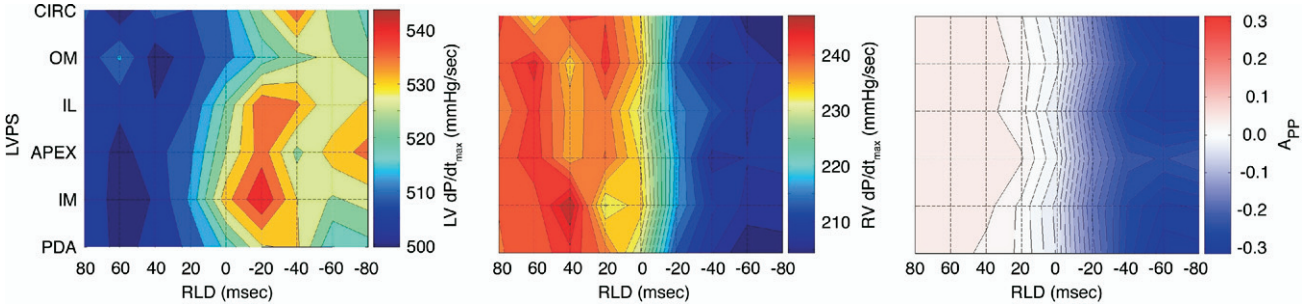

Figure 5. Response surfaces relating left and right ventricular dP/dt_{max} and the area of the normalized right ventricular–left ventricular pressure diagram, A_{PP}, to all possible left ventricular pacing site/right ventricular–left ventricular delay combinations averaged over 7 experiments. *Contour lines* represent 1% changes in measured values. For surfaces of dP/dt_{max}, the highest values are represented by *red,* and for surfaces of A_{PP}, complete synchrony ($A_{PP} = 0$) is represented by *white. APEX,* Apical; A_{PP}, area of the normalized right ventricular–left ventricular pressure diagram; *CIRC,* circumflex; dP/dt_{max}, maximum rate of pressure rise; *IL,* inferolateral; *IM,* inferomedial; *LV,* left ventricle; *OM,* obtuse margin; *PDA,* posterior descending artery; *RV,* right ventricle.

tricular interaction were optimized with an RLD of +40 ms at all LV sites.

This study demonstrates an epicardial BiVP optimization technique applicable to permanent pacing in patients with chronic heart failure and also to temporary pacing in acute heart failure after cardiac surgery. In fact, given the anomaly of publication delays, we[18] have already applied and published the method developed in the present study in a single patient with dilated cardiomyopathy. Results in that clinical study demonstrate effects of site and timing on CO that cover a range of 70%, considerably larger than the 10% variation observed here. This reflects inherent limitations of our models of RV and LV[19] failure and emphasizes the need for a model that manifests advanced LV failure and QRS prolongation resulting from impaired conduction velocity.

However, despite possibly limited clinical relevance, our studies have provided an important opportunity to develop clinically relevant methodology, a team to apply these methods intraoperatively, and improved understanding of the pathophysiology of BiVP.

Optimization of LV pacing site and RLD using a multielectrode patch and randomized data collection provides an innovative, objective, and intuitive tool for solving a critical problem in BiVP. Application of this method in patients can provide unique information that improves clinical results of pacing for heart failure.

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