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Measurement of QRS Duration for Biventricular Pacing Optimization

Catherine M. Albright^{*}, T. Alexander Quinn[†], George Berberian^{*}, Santos E. Cabreriza^{*}, Cara A. Garofalo[‡], Alan D. Weinberg[§], Jose M. Dizon[¶], and Henry M. Spotnitz^{*}

^{*}Department of Surgery, Columbia University, New York, NY, USA

[†]Department of Biomedical Engineering, Columbia University, New York, NY, USA

[‡]Department of Pediatrics, Columbia University, New York, NY, USA

[§]Department of Biostatistics, Columbia University, New York, NY, USA

[¶]Departments of Cardiology, Columbia University, New York, NY, USA.

Abstract

Optimization of left ventricular pacing site (LVPS) or interventricular pacing delay (VVD) improves the efficacy of biventricular pacing (BiVP). Cardiac output (CO) based optimization, however, is invasive and slow. QRS duration (QRSd) is non-invasive and responds rapidly. Accordingly, we investigated the utility of QRSd for BiVP optimization in a model of acute right ventricular (RV) pressure overload. In 7 anesthetized open-chest pigs, BiVP was implemented with right atrial and RV pacing wires. A 6-electrode array was placed behind the LV. Heart block was established by alcohol ablation. The pulmonary artery was snared to double peak RV pressure. Fifty-four combinations of LVPS and VVD were tested in random order over 30 sec intervals. QRSd was assessed from ECG lead II, CO from aortic flow probe, and ventricular function from micromanometers. Comparisons were made with the Pearson's correlation coefficient (r). QRSd narrowing was associated with improved RV function and transseptal synchrony, but correlation with CO was poor. Additionally, QRSd averaged over the last 20 cardiac cycles in each interval was compared to values averaged over successive cardiac cycles following each reprogramming. Seven cardiac cycles after reprogramming, the average r -value went above 0.90 and plateaued. QRSd-based optimization merits further study during BiVP in patients with congestive heart failure.

Keywords

Heart Failure; Cardiac Surgery; Cardiac Function; Electrophysiology; Hemodynamics

Introduction

Biventricular pacing (BiVP) is an important evolving therapy for heart failure. Its efficacy has been attributed to resynchronization of left ventricular (LV) activation.^{1, 2} However, approximately 30% of patients do not respond to BiVP.³ The effectiveness of BiVP can be increased by optimization of atrioventricular delay,⁴ interventricular pacing delay (VVD),⁵ and transvenous⁶ or epicardial⁷ LV pacing site (LVPS). Improved optimization methods are needed to reduce the number and health care costs of non-responders.

Corresponding Author: Henry M. Spotnitz, MD, George H. Humphreys, II, Professor of Surgery, Columbia University College of Physicians & Surgeons, 622 West 168th Street, PH 14-103, New York, NY 10032, Phone: (212) 305-6191, Fax: (212) 305-9724, email: hms2@columbia.edu.

Physiologically, benefits of BiVP optimization are related to increased cardiac output (CO) and organ perfusion.⁸ However, invasive techniques are required to measure CO with a high degree of accuracy, and CO equilibrates slowly after changes in BiVP parameters, limiting its utility for BiVP optimization.

QRS duration (QRSd) is a potential alternative for BiVP optimization. QRSd may be prolonged in heart failure due to hypertrophy, ventricular dilatation, and reduced conduction velocity and/or electrical blocks in the conduction system and myocardium. QRSd has been proposed as a prognostic indicator of patient outcome^{9–11} and mechanical resynchronization in BiVP.¹² QRSd is non-invasive, easily attainable, and equilibrates quickly. However, the number of observations required to accurately measure QRSd during BiVP has not been defined, and the relation of QRSd to changes in ventricular function and hemodynamics during BiVP is not well understood.¹¹ There are many determinants of QRSd, some of which are not directly related to synchrony of contraction.^{9–11, 13–15} Accordingly, we reanalyzed data from a previous laboratory study of critical pulmonary stenosis as a preliminary investigation of the value of QRSd for BiVP optimization during simultaneous changes in VVD and LVPS.

Methods and Materials

All animal studies were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by the Columbia University Institutional Animal Care and Use Committee. The data is from a previous study, described briefly below.¹⁶

Animal Preparation

Seven male pigs (40–50 kg) were anesthetized and instrumented, including standard limb leads for ECG monitoring, micromanometers (Millar Instruments, Houston, TX) to measure LV and right ventricular (RV) pressure, and an ultrasonic flow probe (Transonic Systems, Ithaca, NY) to measure aortic volume flow. Bipolar temporary epicardial pacing leads (Medtronic Inc., Houston, TX) were clipped to the right atrial appendage and sewn into the myocardium of the RV outflow tract. A custom epicardial pacing-array with bipolar-electrodes on a Gore-Tex patch was placed in the posterior pericardium to allow rapid testing of 6 LVPS: apex, infero-medial, infero-lateral, posterior descending artery, circumflex artery, and obtuse margin.

Experimental Protocol

The pacing leads were connected to a custom temporary pacing unit, containing an InSync III pacemaker (Medtronic Inc.). Complete heart block was established by AV node ablation with injection of 0.2 ml aliquots of 100% ethanol into the region of the bundle of His to allow for complete control of the sequence of activation.¹⁷ Critical pulmonary stenosis was induced by snaring the pulmonary artery until peak RV pressure doubled. Dual chamber mode (DDD) BiVP was tested with 54 combinations of VVD and LVPS in random order for 30 sec intervals. VVD was varied between +80 and –80 msec in 20 msec increments (positive VVD indicates RV-first pacing). The heart rate was set at 90 bpm and atrioventricular delay at 150 msec. Animals were humanely put to death at the conclusion of the experiment.

Data Analysis

Hemodynamic signals were recorded on a personal computer (Apple Computer, Cupertino, CA), with ECG sampled at 1000 Hz and pressure and flow at 200 Hz. Offline analysis was performed using custom routines implemented in Matlab (The MathWorks, Natick, MA), as previously reported.¹⁸

The present analysis of QRSd was based on digitized data for ECG lead II. We initially identified QRS morphology changes with changes in BiVP settings. Custom routines were developed to determine QRSd from a wide variety of QRS complex morphologies. The ECG signal was smoothed using an 11-point moving average, and the derivative was taken using a seven point second-order data fit approximation.¹⁹ Then, the characteristic steep slope of the QRS complex was used for its detection.^{20–22} For each beat, the peaks of the derivative were used to determine the QRS upslope and downslope. Onset of the QRS complex was defined as the zero-crossing or inflection point in the ECG derivative immediately before the peak representing the QRS upslope. The end of the QRS complex was defined as the zero-crossing or inflection point immediately after the peak representing the QRS downslope. Whether the zero-crossing point or inflection point was used depended on the particular QRS complex morphology. When the upslope was positive, the zero-crossing point was used, indicating a change in the direction of the ECG. When the upslope was negative, the inflection point was used, indicating a rapid change in the slope of the ECG. The accuracy of this procedure was verified by comparison with QRS onset and end-points chosen by a trained cardiologist for each combination of settings (and thus, QRS morphologies). QRSd was defined as the time between the onset and end of the QRS complex. Global LV and RV electromechanical delay (EMD) were defined as the time from electrical stimulation to the beginning of ventricular contraction, estimated as the interval between the onset of the QRS complex and the onset of ventricular pressure, represented by LV and RV end-diastole.

Hemodynamic indices were averaged over all cardiac cycles in each of the 54 testing intervals. They were visualized using response surfaces, with LVPS on the ordinate, VVD on the abscissa, and magnitude represented by a color map linearly interpolated between measured values. The 54 QRSd measurements were compared to the other variables by calculating the Pearson's correlation coefficient (r). Positive values indicate both variables changed in the same direction and negative values indicate they changed in the opposite direction. As well, to determine the number of measurements after a change in BiVP settings required for average QRSd to stabilize, QRSd averaged over only the last 20 cardiac cycles in each testing interval was correlated with QRSd measured from the first cardiac cycle in each testing interval, as well as QRSd averaged over the first two, three, and greater cardiac cycles. Values are reported as mean $\pm$ SEM.

Results

Similar analysis of CO, LV and RV maximum rate of pressure increase ($dP/dt_{\max}$), and mechanical interventricular synchrony (A_{pp}), using data from this experiment, has been previously reported.¹⁶ However, analysis of QRSd and EMD were not performed. Figure 1 shows a surface plot of QRSd averaged across the seven animals. A decrease in QRSd implies improved electrical synchrony, which is considered important for cardiac function. QRSd decreased $54\pm3\%$ with positive VVD over the worst settings, plateauing between +20 and +40 msec, and was largely unaffected by LVPS.

Figure 2 shows representative correlations of CO, A_{pp} , LV $dP/dt_{\max}$, and RV $dP/dt_{\max}$ with QRSd. QRSd correlated well with A_{pp} (average $r = -0.78\pm0.03$, range = $-0.63 - -0.88$), RV EMD (0.85 ± 0.02 , $0.76 - 0.94$), and LV EMD (0.67 ± 0.06 , $0.37 - 0.82$), in all animals. Correlation with RV $dP/dt_{\max}$ was negative in five animals (-0.72 ± 0.05 , $-0.54 - -0.85$), but positive in two (0.51 and 0.82). Correlation with LV $dP/dt_{\max}$ was good in six animals (0.58 ± 0.02 , $0.50 - 0.65$), but very poor in one (0.00). Correlation with CO was poor in all animals (-0.16 ± 0.05 , $-0.35 - 0.02$).

Figure 3 shows the correlation between QRSd averaged over the last 20 cardiac cycles in each testing interval and QRSd measured from the first cardiac cycle in each interval, as well as

averaged over the first two, three, and greater cardiac cycles. After seven cardiac cycles, the average r -value went above 0.90 and plateaued.

Similar analysis was performed on data from a 71-year-old male patient with NYHA Class IV congestive heart failure who underwent a similar optimization scheme after cardiac surgery for extraction of infected endocardial pacemaker leads, as previously reported.²³ In this case, the patient was not instrumented with pressure transducers and testing intervals were only 15 sec. There was a large effect of both VVD and LVPS, with QRSd decreasing 28% with VVD set at +20 msec and LVPS at the obtuse margin. There was much better correlation between QRSd and CO than seen in the pigs ($r = -0.64$), with decreased QRS duration being associated with increased CO, as shown in Figure 4. QRS stabilization was almost identical to that seen in the experimental animals, as shown in Figure 3.

Discussion

The present study demonstrates that while QRSd is not a good surrogate for CO during BiVP optimization in this model of acute RV failure, it may be a reliable marker of changes in other important hemodynamic indices. Additionally, QRSd can be reliably measured in seven cardiac cycles, less than five seconds at a heart rate of 90 bpm, after a change in VVD and LVPS. This contrasts with 10 seconds for stable CO with invasive measurements^{16, 18} and 30 seconds or more for non-invasive methods.²⁴ Thus, BiVP optimization with QRSd would be possible in less than half the time required by CO based methods.

QRSd, reflecting LV and RV electrical depolarization, is related to conduction velocity through the heart's specialized conduction system and myocardium. The hypothesized relation of QRSd to ventricular function is based on mechanical effects of heterogeneous LV and RV depolarization. According to this concept, delayed activation of some LV segments impairs global contractile force and synchrony, decreasing pump function and ejection fraction. LV function would thus be inversely related to QRSd.^{9–11} In theory, BiVP involves stimulation of late contracting segments, which prevents energy loss associated with stretch and dyskinesis. By pacing bulging or late contracting areas of the ventricle, contractile synchrony is improved. This concept is supported by studies of clinical BiVP, in which shortened QRSd is associated with improvements in function.²⁵ However this theory is contradicted when function of the bulging segment is improved by single site LV pacing, and QRSd increases.²⁶ Similarly, while some studies support a correlation between QRS narrowing and clinical efficacy of BiVP,^{12, 27, 28} contradictory findings have also been reported.^{29–31}

In our model of BiVP in acute RV failure, QRSd correlated favorably with mechanical measures of interventricular synchrony, ventricular contractility, and global electromechanical delay, but not with CO. The shortest QRSd was obtained by RV-first pacing, with little effect of LVPS. In O'Chlainn's clinical study, the shortest QRSd was usually obtained with LV-first pacing, which is explained by predominance of left bundle branch block. Furthermore, in that study the extent of QRSd shortening was dependent on location of the LV lead.³² The contrasting results obtained in the current study may be related to the model used, acute RV failure with heart block, where RV-first pacing has been shown previously to be optimal,¹⁸ and changes in LVPS could be reasonably expected to have a reduced effect.

The poor correlation of QRSd with CO in this study may reflect smaller changes in CO with BiVP than observed clinically, as in the patient presented, where there was good correlation. CO is determined not only by ventricular contractility, but also by preload and afterload. Reduced efficacy of BiVP increases the importance of reflex changes and redistribution of volume between systemic and pulmonary circuits. Measurement and control of changes in peripheral vascular resistance is important for future studies. Limitations of BiVP studies in

animals with normal myocardium and conduction velocity must also be acknowledged, and future studies would optimally employ chronic cardiomyopathy models with bundle branch block.

The fact that QRSd did correlate well with some indices of cardiac function in this study implies that electrical synchrony reflected some aspects of mechanical function. Similar results in patients with congestive heart failure suggest that QRSd reflects electrical and mechanical synchrony of the heart in some clinical settings.¹¹ The results described here imply that improved electrical synchrony with RV-first pacing (shorter QRSd) was associated with improved mechanical interventricular synchrony, RV contractility (both indicated by negative correlations), and global ventricular EMD (indicated by positive correlations), but impaired LV contractility (indicated by a positive correlation). This supports earlier findings,¹⁸ where RV-first pacing improved CO in a similar model by improving RV contractility, mediated by changes in interventricular synchrony. Impairment of LV function in this setting may reflect reduced electrical synchrony of the LV, but changes are minor compared to improvements seen in the RV, which thus presumably dominates overall cardiac performance. QRSd and ventricular EMD were not measured in that study. The decrease in LV and RV EMD with RV-first pacing in the present study is consistent with improved intraventricular synchrony in both ventricles.

Global EMD has been defined as the time between the QRS onset and opening of the aortic valve.^{33, 34} In clinical studies, LV EMD correlated well with QRSd³⁴ and was shorter with BiVP than with RV pacing.³³ Regional LV EMD has been defined as the interval between the QRS onset and the upstroke of the LV apexcardiogram³⁵ or the onset of the septal or LV lateral wall S wave from tissue Doppler^{34, 36–38} (both corresponding to the onset of local systolic motion). Regional LV EMD also correlated well clinically with QRSd³⁴ and decreased with BiVP vs. RV pacing^{36, 38} or no pacing.^{35, 37, 38}

Limitations of the present study include the specific methodology used to analyze QRSd, which involves digitized data for standard ECG lead II. Many techniques have been employed for clinical studies, including automated or manual (caliper based) analysis of multiple leads, with “clinical judgment” imposed where indicated. As no standardized methodology has been suggested, we developed an automated technique based on a single lead that was best suited to our laboratory capabilities. It should also be appreciated that this study was performed in a model of acute RV failure and the results could be significantly different in acute LV failure. This is a critical direction for future work. An important advantage of the present study vs. previous clinical research is the ability to measure changes in both function and QRSd over time during changes in the BiVP protocol. This has been possible in only a few clinical studies to date but is an important feature of our ongoing perioperative BIPACS (Biventricular Pacing After Cardiac Surgery) study.

While this discussion has focused on factors that influence the relation of QRSd and synchrony of contraction, the list of factors influencing QRSd is quite long and includes many considerations that frequently exclude patients from clinical studies. This list includes bundle branch blocks and hemiblocks, heart block, ventricular pacing, ventricular tachycardia, aberrant conduction, myocardial infarction, LV hypertrophy, increased ventricular volume, myocardial edema, hypertension, diabetes, hyper/hypothyroidism, Wolff-Parkinson-White syndrome, congenital heart disease, and a variety of drug effects influencing conduction velocity.^{9–11, 13–15}

We conclude that analysis of seven cardiac cycles after changes in critical BiVP settings is sufficient for measurement of QRSd and that QRSd may be a reliable marker of important changes in cardiac function. However, the utility of QRSd as a surrogate for CO remains

unclear. Thus, QRSd-based optimization merits further study during BiVP in patients with congestive heart failure.

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Figure 1.

Surface plot showing the response of QRS duration to simultaneous changes in LV pacing site (LVPS) and interventricular pacing delay (VVD), averaged across the seven pigs. The shortest QRS duration, which implies improved electrical synchrony, is represented by red, with isolines representing 10 msec changes. All plots have similar ranges. The six LVPS are: APEX, infero-medial (IM), infero-lateral (IL), posterior descending artery (PDA), circumflex artery (CIRC), and obtuse margin (OM).

Figure 2. Representative examples of cardiac output, A_{pp} , left ventricular (LV) dP/dt_{max} , and right ventricular (RV) dP/dt_{max} vs. QRS duration in one pig, showing the correlation coefficient (r) in each.

Figure 3.

Plot of the correlation coefficient (r) between QRS duration (QRSd) averaged over the last 20 cardiac cycles in each testing interval and QRSd measured from the first cardiac cycle in each interval, as well as averaged over the first two, three, and greater cardiac cycles. Values are presented as mean $\pm$ SEM, averaged over the seven pigs. QRSd for the patient is averaged over only the last 5 cardiac cycles due to shorter testing intervals and comparison with the first cardiac cycle is absent due to difficulty in measuring QRSd.

Figure 4.
Plot of cardiac output vs. QRS duration in one patient, showing the correlation coefficient (r).