

# Relation of QRS Shortening to Cardiac Output During Temporary Resynchronization Therapy After Cardiac Surgery

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**Cardiac resynchronization therapy (CRT) can improve cardiac function in heart failure without increasing myocardial oxygen consumption. However, CRT optimization based on hemodynamics or echocardiography is difficult. QRS duration (QRSd) is a possible alternative optimization parameter. Accordingly, we assessed QRSd optimization of CRT during cardiac surgery. We hypothesized that QRSd shortening during changes in interventricular pacing delay (VVD) would increase cardiac output (CO). Seven patients undergoing coronary artery bypass, aortic or mitral valve surgery with left ventricular (LV) ejection fraction  $\leq 40\%$ , and QRSd  $\geq 100$  msec were studied. CRT was implemented at epicardial pacing sites in the left and right ventricle and right atrium during VVD variation after cardiopulmonary bypass. QRSd was correlated with CO from an electromagnetic aortic flow probe. Both positive and negative correlations were observed. Correlation coefficients ranged from 0.70 to  $-0.74$  during VVD testing. Clear minima in QRSd were observed in four patients and were within 40 msec of maximum CO in two. We conclude that QRSd is not useful for routine optimization of VVD after cardiac surgery but may be useful in selected patients. Decreasing QRSd is associated with decreasing CO in some patients, suggesting that CRT can affect determinants of QRSd and ventricular function independently. *ASAIO Journal* 2010; 56:434–440.**

Cardiac resynchronization therapy (CRT) improves cardiac function and symptoms in patients with congestive heart failure. In patients with left ventricular ejection fraction (LVEF)  $\leq 35\%$ , QRS duration (QRSd)  $>120$  msec, and New York Heart Association Class III or IV heart failure, CRT increases LVEF

and exercise tolerance while reducing QRSd, mitral regurgitation, systolic and diastolic ventricular dimensions, morbidity, and mortality.<sup>1,2</sup> CRT also increases myocardial efficiency and can reduce myocardial oxygen consumption.<sup>3</sup> These characteristics make CRT attractive for support of patients with left ventricular (LV) power failure after open-heart surgery (OHS). If effective, temporary CRT might reduce the morbidity, mortality, and cost of OHS.<sup>4–7</sup> Preliminary data from our laboratory,<sup>8–10</sup> as well as others,<sup>11–19</sup> suggest that CRT can increase cardiac output (CO) after OHS, and we are conducting a clinical trial directed at this hypothesis.

The efficacy of CRT is dependent on optimization of atrioventricular delay (AVD), interventricular delay (VVD), and LV lead location.<sup>8–10,20–26</sup> CO is a critical determinant of organ perfusion, but CO optimization is time consuming and may require “washout” periods for equilibration.<sup>27</sup> A more expeditious index would reduce the time required and possibly promote automated optimization. Our laboratory has demonstrated potential utility of QRSd for intraoperative CRT optimization in animals,<sup>28</sup> and the utility of QRSd for VVD optimization in patients during CRT was recently endorsed.<sup>26</sup> Accordingly, we correlated QRSd with CO during VVD optimization for temporary CRT after OHS.

## Patients and Methods

### Patient Population

Seven male patients (mean age:  $68 \pm 11$  years) were enrolled in the ongoing National Institutes of Health-funded Biventricular Pacing After Cardiac Surgery (BiPACS) trial at Columbia-Presbyterian Medical Center, with permission of the attending surgeon. Patients undergoing OHS on cardiopulmonary bypass (CPB) with LVEF  $\leq 40\%$  and a QRSd  $\geq 100$  msec or having simultaneous mitral and aortic valve replacement were eligible. Patients were excluded for intracardiac shunts, congenital heart disease, post-CPB heart rate  $>120$  bpm, 2° or 3° heart block, or atrial fibrillation. Patients could be removed from the study for hemodynamic instability or surgical bleeding, as determined by the attending surgeon. The BiPACS trial is approved by the Columbia University Institutional Review Board (renewed April 2010) and is conducted under an Investigational Device Exemption from the Food and Drug Administration.

### Instrumentation

During CPB, before the aortic cross-clamp was removed, paired temporary unipolar epicardial pacing leads (Medtronic,

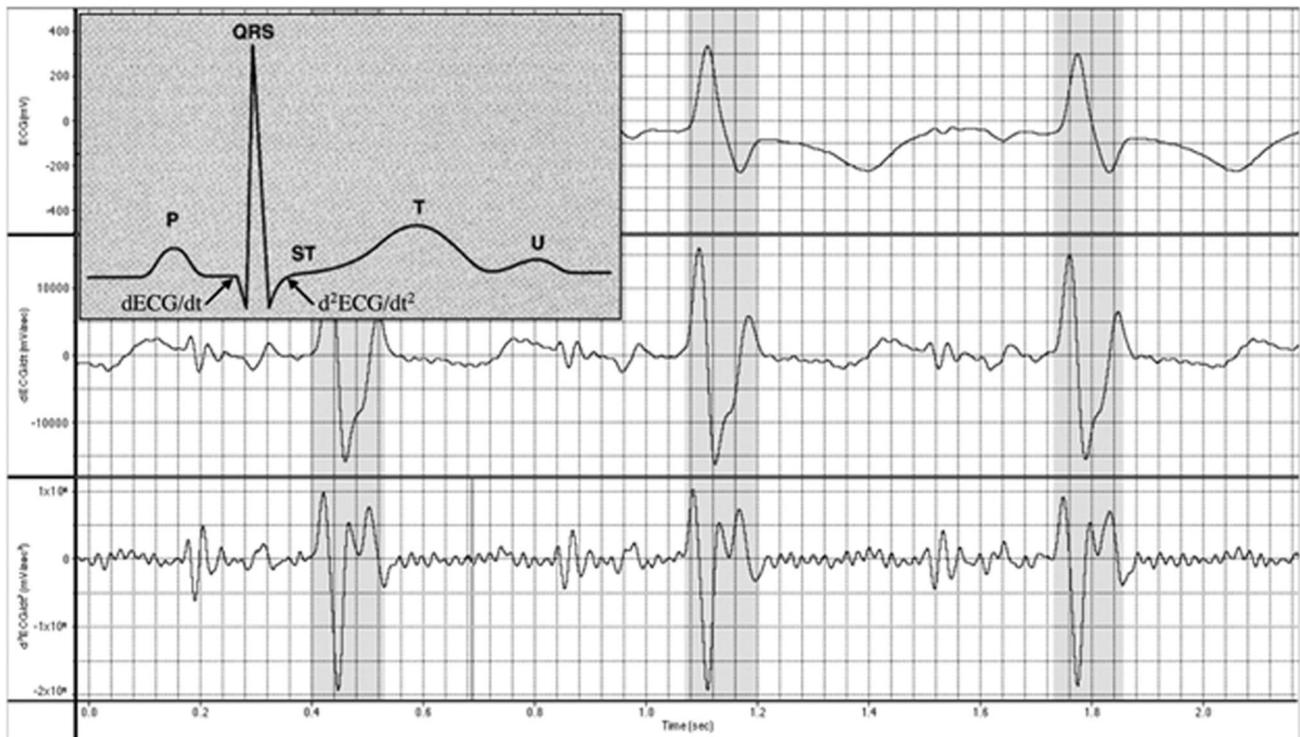
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**Figure 1.** Representative lead II of the electrocardiogram (ECG) (top) during biventricular pacing (BiVP), and the resulting first ( $dECG/dt$ ; middle) and second ( $d^2ECG/dt^2$ ; bottom) derivatives of the ECG. The inset illustrates the onset and end of the QRS complex (indicated by arrows) in an idealized case. First and second derivatives of the ECG are useful for measuring intraoperative QRS duration during changes in BiVP settings from a single lead (see text).

Houston, TX) were sewn to two LV locations (LV1 and LV2) randomly selected from six possible sites, as described previously.<sup>29</sup> After cross-clamp removal, pacing leads were also sewn to the right atrial appendage and the right ventricular (RV) outflow tract. A closely fitting scissor-type electromagnetic flow probe (Carolina Medical Electronics, King, NC) was placed around the ascending aorta to measure instantaneous flow velocity. Lead II of the surface electrocardiogram, radial artery pressure, and aortic flow were sampled by an analog-to-digital converter (AD Instruments, Milford, MA) and recorded on a personal computer (Apple Computer, Cupertino, CA).

#### BiVP Optimization

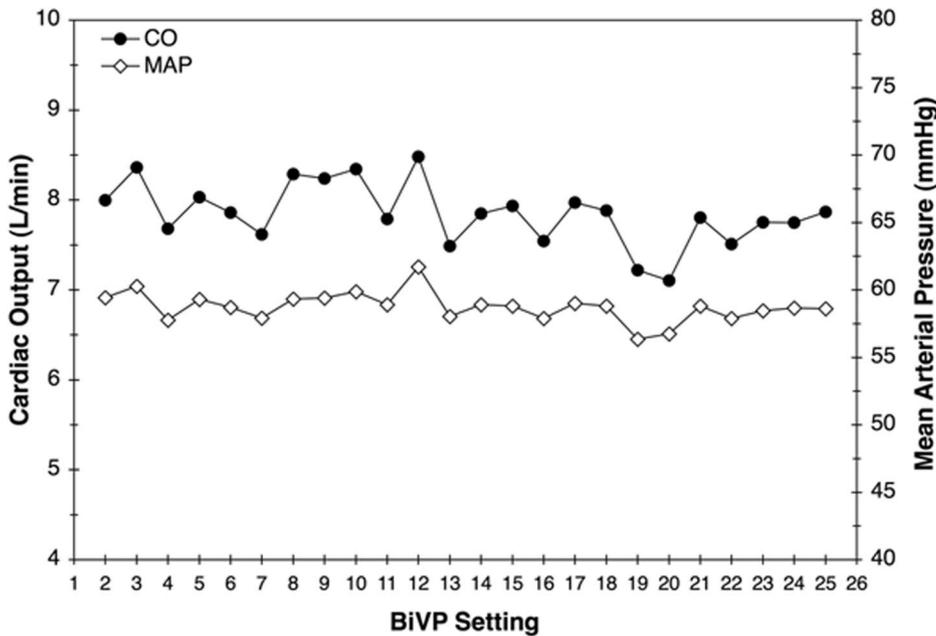
Temporary biventricular pacing (BiVP) was achieved with a customized temporary, external BiVP unit incorporating a shock-mounted permanent generator (InSync III 8042, Medtronic). After testing to confirm lead function, all patients were weaned from CPB using standard clinical protocols.

Patients were stabilized as required by the BiPACS protocol before investigation of CRT dependence. With HR = 90 bpm, LV pacing site = LV1, and VVD = 0 msec, AVD was varied from 90 to 270 msec in 30 msec increments (seven settings) in a random sequence individually determined for each patient. The testing sequence was then repeated, providing each measurement in duplicate. Using the AVD that produced the maximum CO, three pacing modes were tested: DDD using the RV site, DDD with RV + LV1, and DDD with RV + LV2. Each combination was tested twice. Using the LV pacing mode and AVD associated with highest output, VVD was finally varied over nine values from

+80 (RV-first) to -80 msec in 20 msec increments. Parameters were tested in random order, and the sequence was run twice. Each testing period was limited to 10 seconds because of surgical time constraints. Atrial pacing was added if the sinus rate was <90. The total time to complete the protocol was approximately 8 minutes. Default values were used if effects on CO were equivocal. Changes in vasoactive drug administration and infusion of fluid boluses were avoided during testing. After data acquisition, patients were randomized to continuous CRT or no pacing overnight, pending additional testing, and completion of the BiPACS protocol on the first postoperative day.

#### Data Analysis

Data were analyzed offline using Chart v.5.5.4 (ADInstruments). QRSD was determined manually as the time between the onset and end of the QRS complex, measured from the ECG as shown in **Figure 1**. First, the PR interval, ST interval, and pacing artifacts were identified by visual inspection. The onset of the QRS complex was then determined by a change of slope in the PR interval, discounting pacing artifacts, indicated by a local minimum, local maximum, zero crossing, or inflection point in the first derivative of the ECG. The end of the QRS complex was within an interval of diminishing curvature before the ST segment, indicated by a local minimum, local maximum, or inflection point in the second derivative of the ECG, depending on the specific QRS morphology. The accuracy of this procedure was verified by comparison with QRS onset and end-points chosen by a trained cardiologist (M.E.R.).



**Figure 2.** Cardiac output (CO) and mean arterial pressure (MAP) from patient 1, Table 1 during data acquisition. Data reflect hemodynamic stability during the 8 minutes of cardiac resynchronization therapy (CRT) optimization.

The observer measuring QRSd (M.E.S.) was blinded to the corresponding CO.

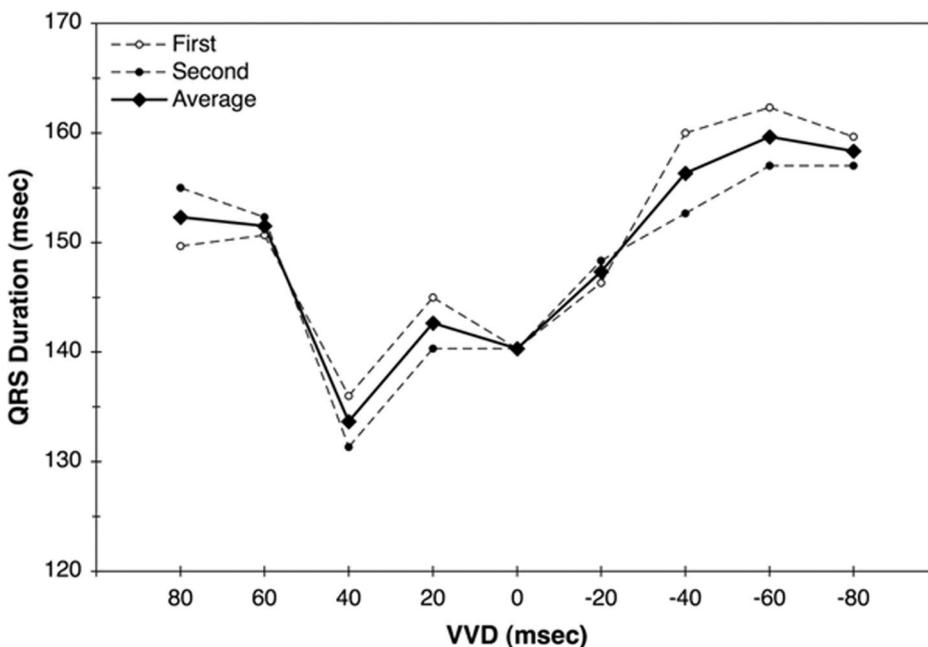
For each VVD setting, QRSd was averaged over three cardiac cycles. Mean arterial pressure was averaged, and CO was measured by integrating aortic flow velocity over one full respiratory cycle, as described previously.<sup>10</sup>

*Statistical Analysis*

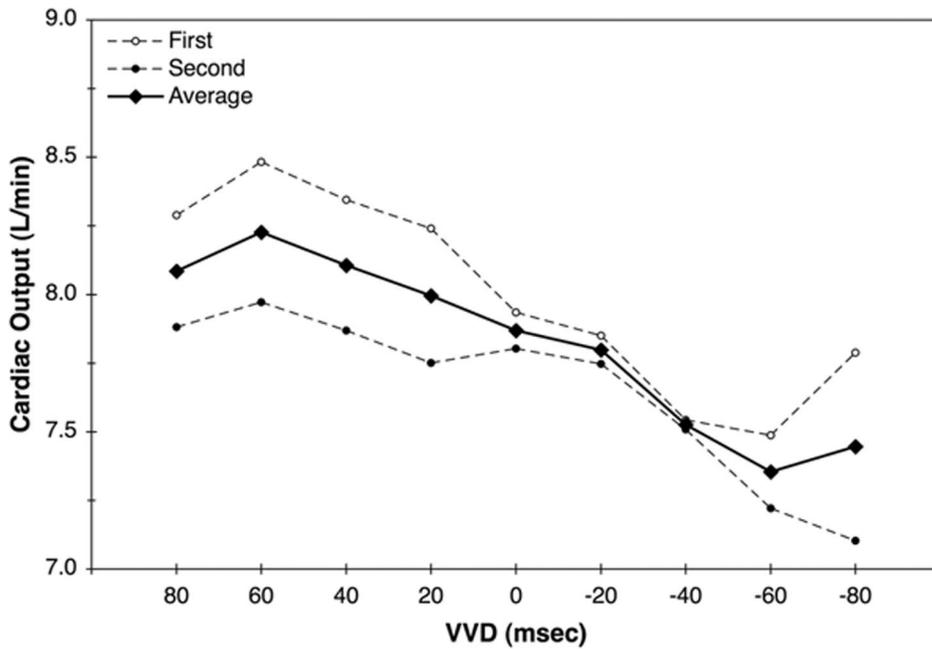
Measurements from duplicate determinations were averaged. QRSd and CO were correlated by linear regression using SAS System software (SAS Institute Inc., Cary, NC).

**Results**

Representative data during aortic valve replacement in patient 1 are illustrated in **Figures 2–5**. **Figure 2** demonstrates overall stability of CO and mean arterial pressure during 8 minutes of CRT optimization. **Figure 3** illustrates the average VVD-QRSd relation and the raw data in two successive sequences of data acquisition. A sharply defined minimum for QRSd occurred at a VVD of +40 msec. A positive VVD in this study indicates the RV is paced before the LV. LV-first pacing is indicated by a negative VVD. The data in **Figure 3** were reproducible, with differences of <5% between successive runs. **Figure 4** illustrates VVD-CO relations in successive data



**Figure 3.** Effect of changes in inter-ventricular pacing delay (VVD) on QRS duration (QRSd) in patient 1. The first and second data acquisition sequences and average result are shown. The shortest QRSd occurs when the right ventricle is paced 40 msec before the left. Variation of QRSd in successive acquisition sequences is <5%.



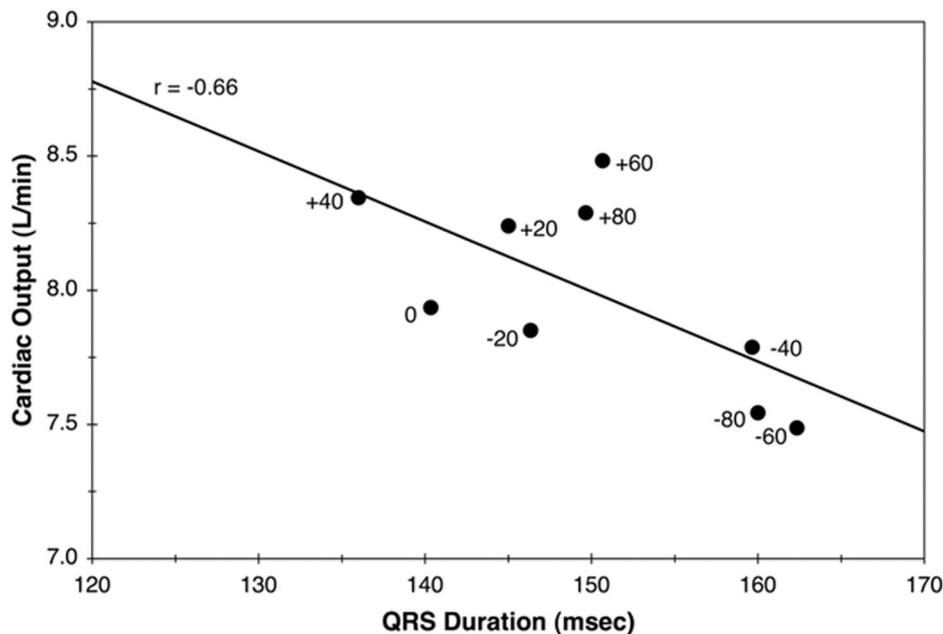
**Figure 4.** Effect of changes in interventricular pacing delay (VVD) on cardiac output (CO) in patient 1. The first and second data acquisition sequences and average result are shown. CO is maximized when the right ventricle (RV) is paced 60 msec before the left, and slope of the relation favors higher CO with RV first pacing. Variation of QRS duration (QRSd) in successive acquisition sequences is 7%–8%.

acquisition sequences and the average result. CO was maximal at a VVD of +60 msec, 20 msec longer than the VVD associated with the shortest QRSd (**Figure 3**). The VVD-CO relation was roughly linear, trending toward higher CO at long VVD, favoring RV-first pacing. Data were reproducible, varying 7%–8% in successive runs. **Figure 5** illustrates the CO-QRSd relation obtained in patient 1 during the first testing sequence. The slope was negative—CO increased as QRSd decreased. The correlation coefficient was  $-0.66$ .

**Table 1** presents surgical procedure, QRS morphology, optimum settings, and correlation coefficients for CO-QRSd relations for each patient. QRSd was shortest with RV-first pacing in five patients and with LV-first pacing in two. CO was

highest with RV-first pacing in five patients and with LV-first pacing in two. As in patient 1, VVD optimization was different in two patients when QRSd was considered then when CO was used. Correlation coefficients for the QRSd-CO relation during VVD testing were generally negative, indicating that CO increased as QRSd decreased. However, the correlation coefficients were generally positive in patients 2 and 7, indicating increases in both QRSd and CO.

Overall, there were clear minima in QRSd in three of seven patients, two of which were within 20 msec of the optimum VVD based on CO criteria. The fourth patient had two minima of QRSd at +60 and  $-20$  msec, but the optimum VVD based on CO was +20 msec.



**Figure 5.** Cardiac output (CO) vs. QRS duration (QRSd) during the first sequence of interventricular pacing delay (VVD) data acquisition for patient 1. The VVD for each point is labeled. Negative slope indicates that shorter QRSd is associated with increasing CO.

**Table 1. Clinical Data and Correlation Coefficients for Cardiac Output—QRSd Relation**

Patient	Patient Characteristics		Optimum BiVP		VVD (n = 9)	
	Surgical Procedure	Conduction Abnormalities	QRSd	CO	SEQ1	SEQ2
1	AVR	LVH, 1° A-V block	RV-first	RV-first	-0.66	-0.54
2	CABG (2), AVR	IVCD	RV-first	LV-first	0.7	-0.01
3	AVR, MvR	RBBB, 1° A-V block	LV-first	LV-first	-0.09	0.24
4	CABG (4), MvR	LBBB	RV-first	RV-first	-0.2	-0.39
5	CABG (4), MvR	iRBBB, 1° A-V block	RV-first	RV-first	-0.08	-0.74
6	CABG (3)	IVCD	RV-first	RV-first	-0.44	-0.18
7	AVR, MvR	LVH	LV-first	RV-first	0.55	0.27

Numerical values are correlation coefficients for CO-QRSd relation.

A-V block, atrioventricular block; AVR, aortic valve replacement; CABG (n), coronary artery bypass (number of grafts); iRBBB, incomplete right bundle branch block; IVCD, intraventricular conduction delay; LVH, left ventricular hypertrophy; MvR, mitral valve repair; MVR, mitral valve replacement; QRSd, duration of QRS complex; CO, cardiac output; SEQ, testing sequence; VVD, interventricular delay.

### Discussion

The operating room is uniquely suited to correlate QRSd and CO, because flowmeters are more accurate and faster than indicator or thermal dilution or other minimally invasive CO measurements. However, despite recent support for QRSd-based optimization,<sup>26</sup> our results are consistent with studies,<sup>30–32</sup> indicating QRSd is not generally useful for this purpose. Our data do indicate that QRSd shortening is useful in some patients (Figure 5), but techniques for identifying these patients are lacking. Concerns about patient selection are also reflected in a reported 30%–40% incidence of clinical failure to respond to CRT.<sup>26,32</sup> Echo-based selection and optimization indices have proven disappointing in clinical trials.<sup>26,33</sup>

Our clinical trial hypothesizes that temporary CRT will increase CO 15% over 12–24 hours in patients at risk of LV power failure after OHS. Preliminary data from this trial demonstrate a 10%–15% increase in CO with CRT and independent effects of AVD and VVD optimization.<sup>34</sup>

Table 1 indicates that only one of our seven patients had left bundle branch block (LBBB) preoperatively, whereas LBBB predominates in dilated cardiomyopathy candidates for CRT. Furthermore, RV-first pacing was best for QRSd shortening in five of seven patients (Table 1), whereas LV-first timing proved best in 80%–85% of patients with chronic heart failure.<sup>26,35</sup> Byrne *et al.*<sup>36</sup> found CRT less effective in dogs with right bundle branch block than in LBBB.

QRSd is inversely related to LV function in cardiomyopathy,<sup>37,38</sup> and QRSd >120 msec is used to select patients for CRT.<sup>39</sup> However, the value of QRSd as a predictor of response to CRT has been questioned.<sup>32</sup> In functional studies, QRSd proved a poor predictor of changes in peak VO<sub>2</sub> during CRT<sup>38</sup> and correlated weakly and inversely with changes in LV  $dp/dt_{max}$ .<sup>41</sup> On the other hand, Alonso *et al.*<sup>42</sup> demonstrated decreased QRSd and functional class and increased peak VO<sub>2</sub> in CRT responders but no change in these variables in nonresponders.

Our animal studies demonstrate that RV-first pacing optimizes hemodynamics in acute RV pressure overload.<sup>21–23</sup> Benefits include increased CO and RV  $dp/dt_{max}$ , improved transeptal synchrony, and transmission of LV pressure work across the interventricular septum. QRSd was also examined in this model.<sup>28</sup> In an aortic insufficiency model, we find LV-first pacing promotes transeptal synchrony and maximizes LV  $dp/dt$ .<sup>23</sup> These studies support the view that VVD optimization is affected by the

pathophysiology and ventricular dependence of the underlying heart failure.

Figure 4 demonstrates increasing CO as VVD increases in favor of RV activation. The opposite relation, favoring LV-first pacing, was observed in two patients. LV-first pacing is believed most effective in shortening QRSd if LV conduction is impaired and should be most effective in supporting cardiac function if the LV is failing. Similarly, RV-first pacing is believed preferable for QRSd shortening when RV conduction is impaired and should benefit cardiac function in primary RV failure. These contrasting and independent effects provide a plausible explanation for why increasing QRSd is associated with increasing CO in two of our patients. VVD optimization is less effective than AVD optimization in clinical studies of CRT.<sup>26</sup>

Regarding potential sources of error and methodologic concerns, patients in BiPACS have concurrent OHS, general anesthesia, and vasoactive infusions and are paced from epicardial LV sites. The method used here for measurement of QRSd was improvised to deal with limitations of ECG recording from a single lead. More sophisticated manual and automated methods have been described.<sup>43</sup> Positive inotropes, vasoconstrictors, and vasodilators were administered during this study, although changes in such agents and volume status were avoided during data collection.

CRT is presently a multibillion dollar market with many unresolved issues related to engineering, instrumentation, and pathophysiology. A positive outcome of the BiPACS trial would provide impetus new areas of investigation, including patient selection and computerized, self-optimizing pacing systems that might both reduce the incidence of nonresponders and also improve the efficacy of temporary CRT for LV power failure after CRT.

The BiPACS protocol is controversial in that patient selection is less restrictive than for “permanent” CRT.<sup>44</sup> Specifically, QRSd of 100–120 msec and LVEF of 36%–40%, allowed by BiPACS, are not approved for clinical implants. This liberalization is justified in part to make BiPACS relevant to the real world of cardiac surgery. Surgical patients in sinus rhythm with an LVEF ≤35% and QRSd ≥100 msec are so rare that a valid clinical trial would require a very expensive protocol involving many centers. Furthermore, data emerging from the BiPACS trial suggest that the benefit of temporary CRT after CPB in-

cludes reversal of temporary depression of ventricular function that follows CPB. Thus, although CRT is superior to AAI pacing at matched heart rates for the data period reported in this study, this benefit does not persist 12–18 hours later<sup>34</sup> and Wang *et al.*, preliminary data, with permission). Furthermore, the benefit of temporary CRT within an hour of CPB increases with increasing preoperative LVEF, which is opposite trends for permanent implants (Spotnitz *et al.*, preliminary data, with permission). Although there is much to be learned as this trial progresses, it is also apparent that the precision of intraoperative data recording has much to offer to current understanding of the pathophysiology of CRT.

### Conclusion

Preliminary data from an ongoing study of CRT after cardiac surgery demonstrate limited utility of QRSd for optimization of VVD. Our data indicate that narrowing of the QRS complex can correlate either positively or negatively with CO during CRT. Additional studies are needed to validate these data and define relevance to the general understanding of CRT.

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