Hemodynamic Stability During Biventricular Pacing After Cardiopulmonary Bypass

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Objective: To assess the stability of cardiac output, mean arterial pressure, and systemic vascular resistance during biventricular pacing (BiVP) optimization.

Design: Substudy analysis of data collected as part of a randomized controlled study examining the effects of optimized temporary BiVP after cardiopulmonary bypass (CPB).

Setting: A single-center study at a university-affiliated tertiary care hospital.

Participants: Cardiac surgery patients at risk of left ventricular failure after CPB.

Interventions: BiVP was optimized immediately after CPB. Atrialventricular delay (7 unique settings) was optimized first, followed by the left ventricular pacing site (3 unique settings) and then the interventricular delay (9 unique settings). Each setting was tested twice for 10 seconds each time. Vasoactive medication and fluid infusion rates were held constant.

Measurements and Main Results: Aortic flow velocity and radial artery pressure were digitized, recorded, and averaged over single respiratory cycles. Least squares and linear regression/Wilcoxon analyses were applied to the first 7 patients studied. Subsequently, curvilinear analysis was applied to 15 patients. Changes in mean arterial pressure and systemic vascular resistance were statistically insignificant or too small to be meaningful by least squares analysis. During interventricular synchrony optimization, cardiac output and mean arterial pressure decreased (mean changes −5.7% and −2.5%, respectively; with standard errors 2.3% and 1.5%, respectively), whereas SVR increased (mean change 3.1% with standard error 3.4%). Only the change in cardiac output was statistically significant (p = 0.043). Curvilinear fits to data for 15 patients demonstrated progressive hemodynamic stability over the total testing period.

Conclusion: BiVP optimization may be done safely in patients after CPB. With continuous monitoring of mean arterial pressure and cardiac output, the procedure results in no harmful hemodynamic perturbation.

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Congestive Heart Failure is a major health problem in the United States, with an incidence of more than 500,000 patients per year.1 Biventricular pacing (BiVP) improves objective and subjective measures of heart failure in 70% of patients.2-5 Benefits of permanently implanted biventricular pacemakers are increased by optimization of atrioventricular delay (AVD), ventricular pacing site (VPS), interventricular pacing delay (VVD), and heart rate (HR).

The effects of temporary BiVP after cardiac surgery and the benefits in low-output states are not well defined.6-13 The benefits of BiVP optimization in this setting are unknown.14-23 Given that 700,000 cardiac procedures are performed in the US alone, the potential impact of temporary BiVP is substantial. Accordingly, the Biventricular Pacing After Cardiac Surgery (BiPACS) trial examined the effects of temporary optimized perioperative BiVP in cardiac surgery patients with risk factors for developing acute postoperative left ventricular (LV) dysfunction. Patients in the trial underwent BiVP optimization at 3 time points. Phase 1 occurred shortly after separation from cardiopulmonary bypass (CPB) once vasoactive medication and fluid/blood product infusion rates were stabilized. Phase 2 occurred after sternal closure (usually 30-60 minutes after the conclusion of phase 1), and phase 3 occurred on the first postoperative day (12-24 hours after conclusion of phase 2). During BiVP optimization, in all 3 phases, changes in the rates of administration of intravascular volume, anesthetics, and vasoactive medications were restricted. This, in concert with BiVP, may in theory lead to extreme hemodynamic lability, especially in the immediate post-CPB period (phase 1). Although studies of ventricular function have been conducted during this time,24-34 little information is available about intrinsic hemodynamic stability in the absence of external interventions. In this substudy of the BiPACS trial, to assess the safety and reliability of BiVP optimization during phase 1, the authors evaluated the stability of cardiac output (CO), mean arterial pressure (MAP), and systemic vascular resistance (SVR) during this period.

METHODS

The authors analyzed data for 7 patients (7 men, mean age 68 ± 11 years) studied as part of the ongoing NIH-funded BiPACS trial. Patients were included in the BiPACS trial if they underwent cardiac surgery on CPB and had a preoperative LV ejection fraction <40% and QRS duration >100 milliseconds. Patients who underwent concomitant mitral and aortic valve repair or replacement were included irrespective of their ejection fraction and QRS duration. Exclusion criteria were intracardiac shunts, reoperation, congenital heart disease, 2° or 3°
heart block, post-CPB heart rate >120 beats/min, or atrial fibrillation. Patients also were removed from the BiPACS trial if the attending surgeon and/or anesthesiologist deemed that pausing the surgery to facilitate BiVP optimization would be unsafe because of severe hemodynamic instability, severe bleeding, or other causes. None of the patients analyzed as part of this substudy were removed from the BiPACS trial at the conclusion of phase 1. Permission to study each patient was obtained from their attending surgeon before enrollment. All patients gave informed consent to participate in the trial, which was approved by the institutional review board and was conducted under an Investigational Device Exemption from the United States Food and Drug Administration.

During CPB, before the aortic cross-clamp was removed, paired temporary unipolar epicardial pacing leads (Medtronic, Houston, TX) were sewn to 2 locations on the LV surface, LV1 and LV2. LV1 was randomly assigned to a posterior-basal or lateral-basal site. LV2 was randomly assigned to a medial-basal, midlateral, midmedial, or apical site. After cross-clamp removal, pacing leads also were sewn to the right atrial appendage and the anterior right ventricle (RV). A scissor-type electromagnetic flow probe (Carolina Medical Electronics, King, NC) was applied circumferentially around the ascending aorta to measure instantaneous volume flow. Lead II of the surface electrocardiogram, radial artery pressure, and aortic flow velocity were sampled by an analog-to-digital converter (ADInstruments, Milford, MA) and recorded on a personal computer (IMac; Apple Computer, Cupertino, CA) during phase 1 optimization.

Temporary BiVP was initiated with a custom temporary, external BiVP unit containing a shock-mounted permanent BiVP generator (InSync III 8042, Medtronic). Pacing parameters were adjusted with a commercial programmer (Model 2090, Medtronic, Inc, Minneapolis, MN). After testing to confirm lead function, patients were weaned from CPB during BiVP using standard clinical protocols. Default values for initial pacing were atrioventricular pacing (DDD mode) with an HR of 90 beats/min or 10 beats/min above the intrinsic HR but not exceeding 130 beats/min, AVD of 150 milliseconds, VVD of 0 milliseconds, and VPS of LV1. All patients were weaned easily from CPB, generally with the assistance of inotropes and vasoactive pharmacologic agents.

After the final adjustment of anesthesia, volume status, and inotropes, with the patients still cannulated and before the administration of protamine sulfate, phase 1 optimization was conducted in 3 segments. With HR, the LV pacing site, and VVD held constant at default values, AVD was varied randomly across 7 settings (90-270 milliseconds) in 30-millisecond increments. The peak CO for each setting was estimated from the digital readout of the aortic flowmeter. The same 7 settings then were repeated, again in random order, resulting in 2 peak CO values for each AVD, which then were averaged together to produce 1 value for each AVD. The AVD resulting in the highest average CO was chosen as the optimal AVD. The optimum LV pacing site similarly was chosen from among 6 settings (3 unique: RV only, RV + LV1, and RV + LV2) with the HR and VVD held constant at default values and the AVD held constant at the optimum AVD. Finally, with the AVD and LV pacing site held constant at their optimum values and the HR held constant at the default value, the optimum VVD was chosen based on 18 settings (9 unique: +80 [RV first] to −80 [LV first] in 20-millisecond increments) using the methods described for AVD optimization. A total of 38 settings (14 AVD + 6 LV pacing site + 18 VVD) were tested for 10 seconds each. The total time to complete optimization was approximately 8 minutes. No pacing (ODO mode), AAI pacing (AAI mode at the default HR), and optimized BiVP (determined by optimal AVD, LV pacing site, and VVD) were then compared in three 30-second intervals. Default values were used when effects on CO were equivocal. Changes in vasoactive drug infusion rates and incremental volume infusion from the heart-lung machine and other sources were avoided during testing but were allowed in intervals between optimization segments. All of these described procedures and interventions were undertaken as part of the BiPACS trial. This article focuses on data analysis for a subset of patients studied as part of that trial.

Aortic flow and arterial pressure data were imported into Matlab (The MathWorks Inc, Natick, MA) and processed with custom routines. CO and MAP for each testing segment were averaged over 1 respiratory cycle. The beginning and end of a respiratory cycle were defined from minima in MAP. Data near the end of each segment were used, allowing time for stabilization of pacing-induced hemodynamic changes. SVR was calculated as SVR = MAP/C0. The slopes of CO, MAP, and SVR versus time and the validity of the regression were determined for each patient by least squares mean regression analysis. Results indicated a need for additional focus on VVD testing (described later).

The slopes were used to calculate absolute changes over the VVD testing period. The absolute changes were compared with the random variability expected between patients, which were expressed by the standard deviation of variance. Wilcoxon analysis tested for parameter changes more than 5% versus the mean during VVD optimization.

Subsequent to the initial data analysis, data were reviewed for the first 15 consecutive studies. CO and MAP were averaged for all 38 settings during the 3 optimizing segments. Data were analyzed graphically with linear or curvilinear fits as indicated by additive mixed effects models.

RESULTS

The representative variation of cardiac output during VVD testing in patient 1 is shown in Figure 1. At +60 milliseconds (setting numbers 25 and 30), CO was 5.0% higher than the average for the interval and 4.3% higher than the average CO at VVD = 0 milliseconds, which is the default setting. Phasic
A mean regression line superimposed on the data indicates that CO decreased 8.3% overall during VVD testing in this patient.

Least squares analyses of CO, MAP, and SVR over the AVD, VVD, and VPS segments of phase 1 are presented in Tables 1 through 3. Changes in CO in the AVD and VPS segments are not statistically significant. The decrease during the VVD segment is statistically significant, but the absolute change is less than the standard deviation of the interpatient variability. MAP declines significantly during the AVD segment, but the absolute change is less than the standard deviation of interpatient variability. MAP changes during the VPS and VVD segments are not statistically significant. SVR changes during all 3 segments of phase 1 are not statistically significant.

Because CO, the ultimate endpoint of the BiPACS trial, changed significantly during VVD testing, stability during this segment was analyzed further. Table 4 presents linear regression analysis of changes in CO, MAP, and SVR. MAP changed by less than 1% in 4 of 7 patients and less than 10% in all patients. CO changed less than 10% in 6 of 7 patients but more than 15% in 1 patient. SVR changed less than 10% in 5 of 7 patients and less than 15% in 6 of 7 patients. For patient 2, SVR and CO changed more than 15%. On average, CO decreased 5.7% ± 2.3%, MAP decreased 2.5% ± 1.5%, and SVR increased 3.1% ± 3.4%. Only the change in CO was statistically significant (p = 0.043).

Figures 2 and 3 show CO and MAP data, respectively, in 15 patients, including all 38 10-second data segments. Figure 2 superimposes a linear regression and error limits, as defined by a linear mixed effects model. An overall downward trend in CO is demonstrated, but the change is too small to be clinically important. Figure 3 includes a curvilinear fit required by the additive mixed effects model. Again, there is a statistically significant downward trend that is too small to be considered clinically important.

**DISCUSSION**

The potential lability of hemodynamics immediately after weaning from CPB is affected by the interplay of inotropes, anesthetics, vasoconstrictors, and vasodilators. Changes in contractility are critical. For some patients, contractility returns to normal after CPB, whereas others require a combination of pharmacologic support, electrical pacing, mechanical support, and surgical intervention to maintain contractility. Changes in core and blood temperature, the delayed onset of action of vasoactive drugs, and the depth of anesthesia are also potentially confounding variables.

Hemodynamic instability after CPB might interfere with BiVP optimization and could make it difficult to assess independent effects of BiVP. However, the linear regression in Figure 1 and the regressions in Figures 2 and 3 are consistent with the clinical impression that changes in CO and MAP occur relatively slowly in the absence of specific interventions. Thus, the authors attribute rapid phasic changes in the figures to the effect of randomized changes in pacemaker settings. Indeed, when such data are rearranged in a linear sequence of the independent variable, changes in CO and MAP are also found to occur gradually in recognizable patterns.
Potential benefits of temporary BiVP are likely to be most important in phase 1, emphasizing the potential importance of optimization at this time. Furthermore, because 30% of patients do not respond to permanent biventricular pacing, it is imperative to understand the physiology and details of optimization. It is unlikely that complex protocols will be required for the general application of temporary postoperative BiVP, but the present study was designed to define the value and risks from optimization. This interim substudy was intended to objectively assess variation in hemodynamics during phase 1 in order to confirm that continued phase 1 testing is justified. Least squares analysis of individual testing segments in phase 1 compared standard deviation of hemodynamic parameters with variance between patients. Although some of the hemodynamic changes were statistically significant, the absolute values of the observed variations were too small to jeopardize patient welfare.

Small but statistically significant changes in CO were revealed by least squares analysis during VVD optimization and led to more detailed analysis. Wilcoxon analysis revealed a 2.5% decrease in MAP, a 5.7% decrease in CO, and a 3.1% increase in SVR. Although these small changes seem acceptable overall, the change in CO exceeds the 5% change that was arbitrarily defined as an upper limit. Furthermore, patient 2, for whom MAP did not change, exhibited a 15% decrease in CO during VVD testing. No clinical deterioration was observed in this patient, and the possibility of artifacts in the data cannot be excluded completely. Nevertheless, the present authors have developed and deployed new technology to accurately assess changes in CO in real time.

Figure 2 shows a diminishing decrease in CO totaling less than 5% during the entire testing period. Figure 3 shows an initial decrease in MAP that reverses as SVR increases. Based on these data, the authors have established decreases in MAP of 10% and in CO of 15% as the safe upper limit in studies of patients after CPB.

In summary, the present results support the view that hemodynamic stability over 10 minutes after the conclusion of CPB is sufficient for studies of cardiac function in most patients. Such studies should be conducted with careful hemodynamic monitoring, however, with established limits to protect patient welfare.

REFERENCES