Validation of Automated Monitoring of Cardiac Output for Biventricular Pacing Optimization

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Biventricular pacing (BiVP) can increase cardiac output (CO) during acute failure of the left ventricle (LV) after cardiac surgery. This CO benefit is maximized by adjustment of atrioventricular (AVD) and interventricular (VVD) pacing delays. Real-time CO calculation could facilitate this optimization. Accordingly, we compared real-time automated analysis (AA) of CO with manual analysis (MA) in an animal model of pressure overload of the right ventricle (RV). In six anesthetized pigs, pacing leads were placed on the right atrium, RV, and LV. Complete heart block was induced with ethanol injection, and RV systolic pressure was doubled with a pulmonary artery snare. Atrioventricular pacing delay was varied over seven common values and VVD over nine, in random sequence. Two LV pacing sites (LVPS) were also tested. Aortic flow velocity, measured by ultrasonic flow probe, was integrated by AA and MA to calculate CO. Interexaminer Reliability Coefficient (IRC) was determined by Analysis of Variance (ANOVA) for two 10-second runs in each animal. Cardiac output-AVD and CO-VVD relations were similar for AA and MA. Interexaminer Reliability Coefficients were 0.997 and 0.994 for MA vs. AA. Automated analysis was available in real-time. Manual analysis was delayed at 2 hours or more. Automated analysis merits development for real-time optimization of intraoperative BiVP. ASAIO Journal 2010; 56:265–269.

Biventricular pacing (BiVP) is approved for patients with ischemic or dilated cardiomyopathy, New York Heart Association functional classes III or IV heart failure, left ventricular (LV) ejection fraction ≤35%, and QRS duration >120 ms. In these patients, BiVP can improve symptoms, exercise capacity, quality of life, systolic function, LV size, and mitral regurgitation. The mortality of congestive heart failure has also shown to decrease with BiVP.

In responders, BiVP improves the efficiency of contractile function and reverses remodeling of the LV. BiVP overcomes regional conduction delays and systolic and diastolic dysfunction of advancing heart failure while increasing energy efficiency. Judged by effects on cardiac output (CO), our laboratory demonstrated that temporary BiVP is the preferred method when pacing is needed for heart block after cardiac surgery.

Acute effects of BiVP function can be potentiated by optimization of heart rate (HR), atrioventricular pacing delay (AVD), interventricular pacing delay (VVD), and LV pacing site (LVPS). Function can deteriorate if critical parameters are incorrectly adjusted. Furthermore, only 20–40% of patients do not improve objectively with BiVP and are labeled “nonresponders.”

Our laboratory is studying temporary BiVP in patients with LV dysfunction after cardiac surgery. Cardiac output is the primary optimization parameter. BiVP is appealing after heart surgery, because it can increase CO and reduce myocardial oxygen consumption (MVO₂) while standard inotropic agents increase CO but expend MVO₂. Our study investigates optimization within tight temporal constraints. We initially monitored CO using real-time readouts from a digital flowmeter. However, retrospective, protocol-based manual analysis (MA) of intraoperative data revealed that real-time digital readouts were imprecise. Our MA algorithm improves precision but is tedious and impractical for operating room decisions. Accordingly, we are developing real-time automated analysis (AA), based on the MA algorithm. The present communication reports validation of AA in an right ventricle (RV) pressure overload (RVPO) animal model established in our laboratory.

Methods

All animal studies were performed according to the Guide for the Care and Use of Laboratory Animals by the National Institute of Health. The Columbia University Institutional Animal Care and Use Committee approved the experimental protocol.

Animal Preparation

Six female domestic pigs (30–40 kg) were anesthetized intramuscularly with atropine (0.02 mg/kg), ketamine (20 mg/kg), and xylazine (0.5 mg/kg). Pigs underwent endotracheal intubation and were mechanically ventilated with 100% oxygen and 1–2% isofluorane. Arterial blood gasses were monitored and maintained within normal physiologic ranges. Normal saline (0.9%, 10 ml/kg/h) was infused via an 18-gauge angiocatheter inserted into an ear vein. Normal temperature was maintained with a heating pad and monitored with a
rectal thermometer. Continuous electrocardiogram monitoring was implemented through standard leads. Systemic arterial pressure was monitored via a 20-gauge femoral artery angiocatheter, pressure transducer, and recording system.

After median sternotomy and longitudinal pericardiotomy, the pulmonary artery was dissected free and loosely snared with umbilical tape. Left ventricular short-axis epicardial twodimensional echocardiograms, at the papillary muscle level, were recorded and planimetered on a GE Vivid 7 echocardiography system (GE Vingmed Ultrasound AS, Horten, Norway). During steady states, minima in cyclic variation in heart motion identified beats at end-expiration for analysis. End-diastole was identified on the echocardiograms as the frame with the largest end-diastolic area (EDA) in the late phase of ventricular filling. End-diastolic area was defined by planimetry of the ventricular endocardial borders in accordance with American Society of Echocardiography standards and methods previously described. End-diastolic area was used for data normalization.

Temporary bipolar epicardial pacing leads (Medtronic, Inc, Minneapolis, MN) were sewn on the right atrial appendage, RV outflow tract, and two sites on the LV: inferomedia and posterior descending artery. Leads were connected to a custom-housed InSync III pacemaker (Medtronic), and pacing and sensing were confirmed. An lidocaine bolus was infused (3 mg/kg intravenously) and drip started at 50 g/kg/min to supress arrhythmias. Heart block was induced by injection of 0.5 ml aliquots of 100% ethanol into the bundle of His. Atrial tracking dual-chamber mode BiVP, using one of the two LVPS (randomly selected before initiation of the surgery), was initiated at an HR of 90 beats/min or 10 beats/min above the intrinsic rate with an AVD of 150 ms and a VVD of 0 ms.

Anticoagulation was achieved with intravenous heparin (300 IU/kg). Calibrated 5 French micromanometer catheters (Millar Instruments, Inc, Houston, TX) were inserted into the RV and LV. A calibrated, closely fitting ultrasonic flow probe (Transonic Systems Inc, Ithaca, NY) was placed on the ascending aorta and coupled with ultrasonic gel. Right ventricular pressure overload was induced by tightening the snare on the pulmonary artery band until RV systolic pressure doubled. To induce pressure overload was induced by tightening the snare on the pulmonary artery band until RV systolic pressure doubled. To optimize BiVP, CO was monitored while AVD was varied across seven settings (90–270 ms, in 30 ms increments) with VVD held constant at 0 ms, producing the first run of AVD optimization. This was repeated to produce the second run. The AVD producing the highest CO (averaged between the two runs) was then selected and held constant while VVD was varied across nine settings [+80 (RV paced first) to −80 (LV paced first) in 20 ms increments]. Interventricular pacing delay optimization was also accomplished using two runs. Settings were implemented in a random sequence determined individually for each experiment. Testing intervals were 10 sec in duration. The entire optimization protocol was then repeated using the second LVPS. Animals were humanely sacrificed at conclusion of the experiment.

Data Recording and Processing

Analog data for the ECG, arterial pressure, aortic flow velocity, and LV and RV pressures were sampled by the two systems: MA and AA. For MA, sampling was at 200 Hz by a 16-channel analog-to-digital converter (ADIInstruments, Milford, MA), and data were recorded on a personal computer (Apple Computer, Cupertino, CA). For AA, sampling was also at 200 Hz by a 16-channel adapter to an analog-to-digital converter (BNC-2111 National Instruments, Austin, TX). Signals were then sent to a PCI extensions for Instrumentation (PXL) system (National Instruments PXI-1042Q, Austin, TX) and displayed in a custom LabVIEW (National Instruments, Austin, TX) program. Changes in pacemaker setting were marked in both systems. Automated analysis was programmed to compute CO instantaneously using algorithms similar to MA. For MA, resulting data were imported into MatLab (The MathWorks, Inc, Natick, MA). Aortic flow velocity was integrated over an entire beat to compute CO. For AA, the known respiratory rate (RR) and HR were used to compute beats per respiratory cycle (beats = HR/RR); whereas for MA, visual note of variation in mean arterial pressure was used.

Statistical Analysis

Data for each value for AVD and VVD were recorded in duplicate in each animal (two runs). Ectopic beats were eliminated. Ectopy was defined as a ±5 beat per minute change in HR for AA, while visual inspection was used for the MA. Beats before and after an ectopic contraction were also deleted from the calculations. The last beats in a setting were analyzed, with the final beat skipped in case it was part of the subsequent setting. Cardiac output for each beat was expressed as a percentage of the average CO for that run, and these percentages were averaged over a single, complete respiratory cycle to produce the normalized CO for each setting. The normalized CO from corresponding settings in the two runs were averaged to produce the normalized CO for each AVD and VVD. Results for AVD and VVD optimization were then expressed as plots of normalized CO vs. the timing value tested.

For the Interexaminer Reliability Coefficient (IRC), the mean CO for each setting was divided by the EDA for the animal. From these values, an analysis of variance (ANOVA) table was generated to provide the appropriate components of variance necessary to calculate the IRC, as recommended by Fleiss. All data were analyzed using SAS system software (SAS Institute Inc., Cary, NC).

Results

Plots of AVD and VVD optimization from a single, representative animal are illustrated in Figure 1, A and B. The AVD relation in Figure 1A is curvilinear. Cardiac output increases to a maximum of 104% at 120–150 ms and then declines. There are no significant differences between the AA and MA analysis, but the AA relation is available in real-time, whereas the MA curve requires hours to complete.

The CO-VVD relation is more complex and is illustrated in Figure 1B. The peak value for CO, 103%, is achieved at a VVD of +40 msec. Cardiac output is higher for positive VVDs. Positive VVD indicates that pacing of the RV precedes the LV. Interventricular pacing delay testing was performed at the optimum AVD for each animal, generally 120–150 ms. Again, no significant differences between AA and MA are observed.

Figure 2, A and B correlate MA and AA. Each data point represents a unique setting in a single animal, divided by the EDA for that animal. Figure 2A contains 84 data points (7 AVD
settings × 2 LVPS × 6 animals), whereas Figure 2B contains 108 points (9 VVD settings × 2 × 6). Cardiac output-AVD and CO-VVD relations are similar for AA and MA. Interexaminer Reliability Coefficients are 0.997 and 0.994 for MA vs. AA.

Discussion

In the model of RVPO employed, AA was fast and accurate, and results were statistically indistinguishable from MA. The coherence of AA and MA is demonstrated by IRCs of 0.997 and 0.994. Additional studies are needed in patients to confirm that AA is reliable in the operating room environment. At present, we employ electromagnetic flow probes for human studies, awaiting improved ultrasonic flow probe designs. Electromagnetic probes have greater sensitivity to interference from pacing artifacts, and the AA algorithm may need modification to take this into account.

The results reported here for effects of AVD and VVD optimization in RVPO are similar to previous reports from our laboratory. Right ventricular pressure overload involves acute failure of the RV and is distinguished from power failure after cardiac surgery, which usually affects the LV. Our model also diverges from the clinical situation in use of complete heart block to simulate intraventricular conduction delays/left bundle branch block common in BiVP recipients. Finally, the myocardium in our pig model is functionally normal, as opposed to chronic dysfunction in patients with heart failure. Our studies indicate that the mechanism of action of BiVP in acute RVPO is recruitment of LV pressure work through the interventricular septum to support pressure generation by the failing RV. Our studies of acute LV failure in a model of aortic insufficiency indicate that benefits of BiVP in that setting are attributable to recruitment of RV pressure generation to support the failing LV.

Although BiVP can increase CO by 20% or more, optimization steps may involve increments in CO of <5%, approaching the limits of accuracy of present methods. Changes in CO

![Figure 1. A: Effect of AVD delay on normalized CO. A plot from a single representative animal is shown. Each data point is the average of the mean normalized CO for corresponding settings in two runs. The mean normalized CO for a given setting in a given run is the average CO for all beats in one full respiratory cycle in that setting, expressed as a percentage of the average CO for all beats in that run. A curvilinear relation is described, with peak CO at physiologic AV delays of 120–150 ms. The solid line is the manual analysis (MA) result, and the dashed line is automated analysis (AA) result. Error bars indicate ± SEM. B: Format similar to 1A, illustrating effect of interventricular delay on CO. A complex relation is described, with positive values for VVD (RV first pacing) associated with higher values for CO than negative VVDs (LV first pacing). Peak CO occurs at a VVD of 40 ms, with the RV paced 40 ms before the LV.](image1)

![Figure 2. Comparison of CO normalized to LV end-diastolic area (EDA) for automated and manual analysis (MA). Each data point is the mean CO for corresponding settings in two runs, divided by the LV end-diastolic-area for the animal. Cardiac output for each setting represents the average CO for all beats in one full respiratory cycle during testing of that setting. A: AVD; B: VVD. Error bars indicate ± SEM.](image2)
during a respiratory cycle can be on the order of 10% between peak and trough.\textsuperscript{10} There is also concern that testing intervals of 10 seconds may not be valid and that extended periods of time are needed to allow functional equilibration of the RV and LV, as well as volume redistribution between pulmonary and systemic circuits.\textsuperscript{9} Finally, although it is clear that CO is physiologically important and closely related to organ perfusion, it is possible that there may be more important predictors of recovery from surgery. In light of these difficulties, alternative BiVP optimization indices have been studied. These include QRS duration, which can predict response to BiVP\textsuperscript{17} and, in some hands, is a useful monitor of BiVP efficacy.\textsuperscript{18} Other indices that have been studied include intracardiac electrograms, the first derivative of LV and RV pressure, MAP, PulseCO, echocardiography,\textsuperscript{19} and peak endocardial association.\textsuperscript{20} As this is written, however, none of these methods has emerged as superior or reliable, either for BiVP optimization or patient selection.\textsuperscript{21} BiVP optimization is critical to improving clinical results and cost effectiveness and has recently been reviewed.\textsuperscript{22} We are examining these issues in our clinical trial.

Potential benefits of temporary BiVP for LV failure after cardiopulmonary bypass (CPB) have been delayed by incomplete understanding of the appropriate role for this therapy. BiVP with VVD = 0 ms was shown to increase CO 10–15%, in patients with complete heart block after open heart surgery, using a standard temporary universal dual-chamber pacemaker (DDD) with both RV and LV leads connected to the ventricular output terminal.\textsuperscript{23} However, the benefits of BiVP in acute LV failure after CPB are not uniformly predictable. In at least one study, BiVP was not superior to standard DDD pacing in this setting,\textsuperscript{24} although our own data suggest that BiVP is effective after CPB.\textsuperscript{25} Nevertheless, uncertainty in this regard suggests that temporary, postbypass BiVP in the absence of heart block should still be considered investigational and should not be employed without patient consent and appropriate safeguards, including an Investigational Device Exemption from the Food and Drug Administration (FDA) in the United States. Hazards associated with BiVP after CPB include the possibility that mistimed pacing can actually worsen cardiac function, that removal of temporary wires can cause bleeding or injury to bypass grafts, and that undersensing can cause triggering of atrial or ventricular arrhythmias. Importantly, appropriate criteria for implementing this therapy are as yet undefined. Finally, optimum timing criteria appear to be different from those used in permanently implanted BiVP devices. Indeed, the possibility exists that the optimum pacing protocol may continuously change in the early stages after CPB and that an automated, self-optimizing pacemaker will ultimately be needed for maximum benefit. Be that as it may, there presently is no temporary pacemaker with adjustable AVD and VVD timing approved by the FDA. Thus, while temporary BiVP ultimately may be widely applied, it remains an investigational therapy in the near-term.

Conclusion

Real-time, AA of CO appears feasible and accurate. The method is promising for intraoperative optimization of temporary BiVP in patients with acute LV power failure after open-heart surgery.

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References

18. Bertini M, Ziacchi M, Bilii M, et al: Interventricular delay interval optimization in cardiac resynchronization therapy guided by...


