Published in final edited form as:

ASAIO J. 2012 ; 58(3): 191–196. doi:10.1097/MAT.0b013e31824aefce.

Clinical Validation of a Real-Time Data Processing System for Cardiac Output and Arterial Pressure Measurement During Intraoperative Biventricular Pacing Optimization

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Abstract

Biventricular pacing (BiVP) improves cardiac output (CO) and mean arterial pressure (MAP) after cardiopulmonary bypass (CPB) in selected patients at risk for acute left heart failure after cardiac surgery. Optimization of atrioventricular delay (AVD) and interventricular delay (VVD) to maximize the hemodynamic effect of pacing requires rapid and accurate data processing. Conventional *post hoc* data processing (PP) is accurate but time-consuming, and infeasible in the intraoperative setting. We created a customized, real-time data processing (RTP) system to improve data processing efficiency, while maintaining accuracy. Biventricular pacing optimization was performed within 1 hour of the conclusion of CPB in 10 patients enrolled in the Biventricular Pacing After Cardiac Surgery trial. Cardiac output, measured by an electromagnetic flow meter, and arterial pressure were recorded as AVD was randomly varied across seven settings and VVD across nine settings. *Post hoc* data processing values calculated by two observers were compared to RTP-generated outputs for CO and MAP. Interexaminer reliability coefficients were generated to assess the dependability of RTP. Interexaminer reliability coefficient values ranged from 0.997 to 0.999, indicating RTP is as reliable as PP for optimization. Real-time data processing is instantaneous and therefore is more practical in a clinical setting than the PP method. Real-time data processing is useful for guiding intraoperative BiVP optimization and merits further development.

Biventricular pacing (BiVP) is an important adjunctive therapy for chronic congestive heart failure and is indicated in patients with New York Heart Association functional class III/IV heart failure, left ventricular ejection fraction (LVEF) < 35%, and QRS duration (QRSd) > 120 msec.¹ Biventricular pacing improves contractile efficiency² and reverses remodeling of the left ventricle (LV),³ as shown by improvements in LVEF, end-diastolic volume, myocardial

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Disclosure: The authors have no conflicts of interest to report.

perfusion imaging, 6 minute walk distance, and quality of life (QoL) score.^{4–7} However, 30–40% of patients do not improve with BiVP and are labeled as nonresponders.⁸

Adjustment of atrioventricular delay (AVD), interventricular delay (VVD), heart rate (HR), or left ventricular pacing site (LVPS) leads to acute changes in hemodynamic, echocardiographic, and electrocardiographic parameters.^{9,10} This observation has sparked interest in optimization of these parameters with the goal of maximizing the benefits of BiVP and reducing nonresponder rates.

We have previously demonstrated the benefits of optimized BiVP in patients with atrioventricular block after open heart surgery.¹¹ Our ongoing Biventricular Pacing After Cardiac Surgery (BiPACS) clinical trial seeks to determine the hemodynamic effects of optimized temporary perioperative BiVP in patients who are at risk of developing acute decompensated heart failure after surgery on cardiopulmonary bypass (CPB). Preliminary data from the BiPACS trial demonstrate 10–13% improvements in cardiac output (CO) with optimized BiVP as compared to atrial pacing or to sinus rhythm.¹² Cardiac output is measured directly using an electromagnetic or ultrasonic flow probe placed on the ascending aorta. Both AVD and VVD contributed to the overall hemodynamic benefit of pacing.¹²

Integration of flow velocity must consider variation resulting from positive pressure ventilation. This can be accounted for by integrating flow velocity in consecutive beats over a time period equivalent to one or more respiratory cycles. Data acquisition can then begin at any point in the respiratory cycle. Adjustments must also be made for atrial or ventricular ectopic beats. Our initial analysis indicated that CO by *post hoc* data processing (PP) was superior to intraoperative spreadsheet calculations based on digital readouts. Problems with digital readouts included flow meter processing delays, respiratory variation, and ectopic beats. However, PP is tedious and may require a trained investigator hours to complete. This is impractical for optimization within the temporal constraints of the operating room environment.¹³ Real-time data processing (RTP) might overcome this limitation. Accordingly, we are developing a custom RTP system for CO and mean arterial pressure (MAP). We previously compared RTP and PP in an animal model and found RTP to be accurate, rapid, and reliable.¹⁴ The current study reports the validation of RTP in a clinical setting.

Methods

Data were collected during the BiPACS randomized clinical trial at Columbia University Medical Center. This study, previously described,¹² was approved by the Institutional Review Board of Columbia University Medical Center and was conducted under an Investigational Device Exemption from the United States Food and Drug Administration (IDE#: G050189). All enrolled patients gave informed consent. Two groups of patients undergoing cardiac surgery on CPB were eligible: 1) patients in sinus rhythm, with LVEF 40%, and QRSd 100 msec, and 2) patients undergoing combined mitral and aortic repair or replacement, regardless of LVEF and QRSd.

Data Acquisition

As CPB is concluding, temporary bipolar epicardial pacing wires (Medtronic, Inc, Minneapolis, MN) are sewn to the right atrium (RA), right ventricle (RV), and two randomly assigned sites on the LV. The RA and RV wires are part of the clinical standard of care. A custom-housed Medtronic InSync III 8042 pacemaker (Medtronic, Inc) under programmer control (CareLink 2090; Medtronic, Inc.) is connected to the pacing wires, and pacing and sensing functions are confirmed.

For PP analysis, lead II from a surface electrocardiogram, aortic flow from an electromagnetic aortic flow probe (Cliniflow II Model FM701D; Carolina Medical Electronics, East Bend, NC) and arterial pressure from a radial artery line were recorded. Data were sampled at 200 Hz by a 16 channel analog-to-digital converter (PowerLab; ADInstruments, Inc, Milford, MA) and recorded in Chart 5.0 (ADInstruments, Inc) on a personal computer (iMac; Apple Computer, Cupertino, CA). For RTP, data were sampled at 200 Hz by a 16 channel adapter (BNC-2111; National Instruments, Austin, TX) connected to an analog-to-digital acquisition device (PXI-6220; National Instruments) and interfaced with an embedded computer controller (PXI-8196; National Instruments) running custom programs in LabVIEW 8.20 (National Instruments). Changes in pacemaker settings were indicated by timing marks in both systems. The response frequency of the flow probe was 10–25 Hz. Mean arterial pressure was obtained from a fluid-filled radial artery clinical monitoring line. The interposed fluid column introduces time delays and the transducer decreases the frequency response to an estimated 0–30 Hz.

Optimization Protocol

Phase 1 BiVP optimization was conducted after separation from CPB, protamine administration, decannulation, and hemodynamic stabilization. Ventilator settings, intravenous and inhalational medication, blood product, and fluid infusion rates were held constant during optimization sequences and adjusted if necessary among the following sequences: 1) BiVP was initiated at 90 bpm (or 10 bpm above intrinsic HR if necessary). Seven values for AVD ranging from 90 to 270 msec were tested in duplicate in random sequence. The optimal AVD was selected based on the highest CO determined by spreadsheet averaging of digital readouts (Microsoft Excel). 2) LVPS was tested similarly. 3) VVD was optimized last, testing nine VVD values between –80 msec (LV first pacing) and +80 msec (RV first pacing) in duplicate and random sequence. Testing intervals for each setting were 10 seconds in duration. Patients were subsequently randomized to BiVP or standard of care groups for 12–24 hours. Default values were used for BiVP if results of testing were indeterminate or if hemodynamic instability was indicated by a 10% change in MAP during testing.

Biventricular pacing optimization was repeated during skin closure (phase 2) using MAP as the optimization parameter. Testing periods were increased to 20 seconds. Other aspects of phase 2 optimization were identical to phase 1.

Data Analysis

For PP, digitized data were exported from the Powerlab System in text format and processed using custom routines in Matrix Laboratory (MATLAB) (The MathWorks, Inc., Natick, MA). For each testing interval, data over one full respiratory cycle free of ectopic beats were used to calculate CO (phase 1) and MAP (phases 1 and 2) for each parameter combination tested. Respiratory cycles were defined by minima in MAP by visual inspection of the arterial pressure tracing in MATLAB. Data near the end of each tested setting were preferred to maximize hemodynamic stability. Average CO and MAP were calculated for each combination of pacing parameters.

For RTP, CO (phase 1) and MAP (phases 1 and 2) were computed, averaged, and displayed in real time at the conclusion of each testing parameter. Real-time data processing calculated average CO and MAP for all beats in the respiratory cycle selected. Heart rate and respiratory rate defined the number of beats per respiratory cycle. Cycles containing ectopic beats were avoided wherever possible. Ectopy was defined as a ± 5 bpm change in beat-to-beat HR. When ectopy was present, ectopic beats and the beat immediately preceding and following the ectopic beat were eliminated from calculations.

Statistical Analysis

For all data in phases 1 and 2, each value for CO or MAP generated by RTP was compared to values produced by PP. Two observers, PP 1 and PP 2, performed PP independently. These data were used to create an analysis of variance table, from which interexaminer reliability coefficient (IRC) values were calculated using the JL Fleiss method.¹⁵ An IRC cutoff of 0.75 was considered to indicate excellent agreement, as laid out by Fleiss.¹⁵ Data were analyzed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Data are reported for 10 patients in whom data were adequate for automated calculations. Figure 1A shows AVD optimization plots based on real-time (RTP) and *post hoc* (PP 1 and PP 2) data processing from a patient 077 during phase 1. Cardiac output increases as AVD increases, maximum CO being achieved at an AVD of 240 msec. Figure 1B illustrates pairwise correlations among RTP, PP 1, and PP 2 in the same patient, indicating close agreement between the two measures. Figure 1C shows VVD optimization plots from patient 077 during phase 2, using MAP as the optimization measure. Right ventricle-first pacing tended to be more favorable than LV-first pacing, with maximum MAP achieved with VVD of +60 and +80 msec. Pairwise correlations in MAP among RTP, PP 1, and PP 2 are shown in Figure 1D.

Interexaminer reliability coefficient values comparing RTP to both PP observers and comparing PP 1 to PP 2 are presented in Table 1. All comparisons based on CO or MAP calculations yield IRC values very close to 1.00. There is no statistically significant difference between RTP and PP for any of the measures. Using Fleiss's guidelines, RTP is extremely reliable.

Discussion

We are developing RTP to improve the accuracy of hemodynamic data for intraoperative pacing optimization. The present results demonstrate that RTP and PP are equivalent in accuracy, and PP is the current gold standard for accuracy. *Post hoc* data processing is not useful in our trial, because a delay of an hour or more is required to analyze an optimization run, even with high-quality data in the hands of an experienced analyst. *Post hoc* data processing is thus costly in personnel time and impractical for clinical decision making. In contrast, RTP is available in real time at low personnel cost. Potential weaknesses are discussed below.

Real-time data processing is not inferior in accuracy to PP and is available in real time for clinical decision making. Furthermore, availability of RTP allowed us to eliminate digital readouts for CO and MAP calculation. These digital readouts were quickly discarded for optimization based on obvious errors related to artifacts. Real-time data processing analysis was a laboratory-validated alternative¹⁴ at the time and was obviously superior qualitatively when compared to available alternatives. The present results support this decision, but effects of high-grade ectopy remain an important problem not well accounted for in our laboratory study.¹⁴

In considering differences between our clinical and laboratory studies, the laboratory setting potentially allowed respiratory variation to be eliminated by intermittent pauses in ventilation. Fortunately, this expedient was avoided in our laboratory validation, positive pressure ventilation being maintained throughout. Second, flow tracings are potentially cleaner in the laboratory through control of grounding, sizing, fit, positioning, and selection of flow probes. In fact, an important factor is our use of ultrasonic, noise-resistant probes in the laboratory, while electromagnetic flow probes that produce comparatively noisier signals were used in the BiPACS trial during the current study. These electromagnetic probes now serve as a backup during studies and have been otherwise replaced in favor of the ultrasonic probes. Aortic flow is often well described by the first 10 harmonics of the signal (Transonics Systems, Inc., Ithaca, NY); the 10 Hz default filter setting was used when necessary on the electromagnetic flow signal. A third difference affecting clinical data is greater prevalence of ectopy, discussed below.

Post hoc data processing and RTP can compensate for respiratory variation if an appropriate sequence of beats is selected. The effect of respiratory variation is important in the intraoperative setting and is altered by myocardial edema and closure of the thoracic cavity with restoration of negative intrapleural pressure. Consideration of respiratory variation is, thus, a vital component of our RTP protocol.

Published data from the BiPACS trial indicate that optimized BiVP significantly improves CO in surgical patients during phase 1.¹² Optimization of AVD and VVD individually contributes to the overall benefit. In some patients, use of nominal pacing protocols can produce inferior hemodynamics. The need for optimization must, however, be balanced with the temporal constraints of the operating room, where optimization can extend operative and

anesthesia times. Fully automated pacing optimization currently seems a distant goal, but RTP is an important first step in that direction.

Alternative end points for BiVP optimization include NYHA class, QoL score, 6 minute walk distance,⁶ QRS duration,¹⁶ first derivative of LV and RV pressure,^{17,18} peak endocardial association,¹⁸ LVEF,¹⁹ thermal dilution cardiac index, MAP/stroke volume ratio,²⁰ radial artery waveform analysis by tonometry (e.g., Sphygmocor; Medical Inc, Lisle, IL),^{21,22} or PulseCO (LIDCO, Sawston, Cambridge, UK),²³ pressure-volume loops,^{24,25} and electrical velocimetry using thoracic impedance changes to assess mean aortic blood flow acceleration²⁶ have also been used. More recently, real-time 3D echo technology, using pulsed Doppler, and intracardiac echocardiography have been used.^{27,28} As understanding of BiVP improves, the search for the best index continues²⁹; therefore, it is important for optimization systems to remain flexible.

The most important limitation of RTP analysis is in processing ectopic beats. Ectopic beats are identified in the present protocol by changes in HR. The ectopic beats are then discarded, together with beats immediately preceding and following. Figure 2 shows the electrocardiogram and AP traces from a patient during a 20 second test of a single VVD setting in phase 2. In this data recording (respiratory cycle = 8 beats), there were two ectopic beats in the last respiratory cycle. *Post hoc* data processing analysis of a full respiratory cycle yielded a MAP of 70.1 mm Hg. The RTP method removed five of eight beats (the two ectopic beats and the preceding and following beats), yielding a MAP of only 65.0 mm Hg, based on its analysis of the remaining three beats. While this erroneous value did not affect the result of our optimization, it is nonetheless a limitation with the potential to incorrectly skew data. This limitation is being addressed in software revisions to the RTP method. Furthermore, an experienced user can extend, time permitting, the length of a setting enough to complete a respiratory cycle once ectopy is observed.

Unpublished data from the BiPACS trial indicate that both CO and MAP may be useful for BiVP optimization, although MAP may be less useful in phase 1. The current study extends previous flow probe validation studies from our laboratory.^{30,31} Alternative techniques used for hemodynamic calculations include spreadsheet calculations based on manually selected beats from digitized data. Validated RTP would ultimately improve the accuracy of hemodynamic calculations for determination of the optimum pacing protocol. Frequent or sustained arrhythmias would require cessation of the pacing optimization protocol. Default values for BiVP could then be used, if indicated.

In addition to the benefits shown in the context of the BiPACS trial, the unique features of RTP may be applicable to other areas of patient management requiring rapid assessment of acute hemodynamic changes. The system was developed with a wide clinical application strategy. It is compatible with all pacemakers in the market and may use indices that are available in most EP and surgery procedure rooms and newer methods.^{31,32} The use of the system does not present any additional risk to patient. It provides the clinician with a quantitative assessment that will facilitate the treatment course to take.

Conclusion

The present clinical validation confirms the accuracy and reliability of RTP for BiVP optimization in surgical patients. The system, previously validated in an animal model, performs as well as PP, but results are available in real-time. This allows rapid, real-time optimization of BiVP at the time of surgery and may be useful for other treatment optimization, to improve postsurgical outcomes.

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Figure 1.

Atrioventricular delay (AVD) and interventricular delay (VVD) testing in patient 077. Effect of AVD on cardiac output (CO) in phase 1 (A). Cardiac output is normalized as % change vs. average for each run. Each point is the average of two calculations. Standard errors are indicated. Calculations by RTP, PP 1, and PP 2 are similar. Prolongation of AVD is associated with increasing CO to a peak at AVD of 240 msec. Atrioventricular delay of 270 msec was not tested because it exceeded the intrinsic paced AVD and would thus result in lack of ventricular capture. Linear regressions comparing CO data from AVD testing (B). Each regression is based on six data points. Calculations correlate closely. Effect of VVD on mean arterial pressure (MAP) in phase 2 (C). Format is similar to top left. Calculations by RTP, PP 1, and PP 2 are similar. MAP is greatest at a VVD of +40 msec and declines on either side of that value. Linear regression comparing MAP data from VVD testing (D). Format is similar to top right. There is a strong correlation between the RTP and both PP calculations. BiPACS, Biventricular Pacing After Cardiac Surgery.

Figure 2.

Effect of ectopy on RTP. Twenty seconds of electrocardiogram (ECG) and arterial pressure (AP) data are shown from patient 049 during phase 2 interventricular delay optimization. Eight heart beats correspond to one respiratory cycle. Segments used for real-time data processing (RTP) and *post hoc* data processing observer analysis are marked. Ectopic beats (arrows) caused RTP to omit five beats, and MAP was calculated to be 65.0 mm Hg. *Post hoc* data processing observer analysis in ectopy-free segment calculated MAP to be 70.1 mm Hg. BiPACS, Biventricular Pacing After Cardiac Surgery.

Table 1.**BiPACS Interexaminer Reliability Coefficient**

	Phase 1		Phase 2
	CO	MAP	MAP
RTP vs. PP 1	0.9987	0.9987	0.9967
RTP vs. PP 2	0.9987	0.9984	0.9966
PP 1 vs. PP 2	0.9996	0.9996	0.9989

Values calculated from measurements in 10 patients.

BiPACS, Biventricular Pacing After Cardiac Surgery; CO, cardiac output; MAP, mean arterial pressure; PP 1, *post hoc* data processing observer 1; PP 2, *post hoc* data processing observer 2; RTP, real-time data processing.