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Wall Thickness, Pulmonary Hypertension, and Diastolic Filling Abnormalities Predict Response to Postoperative Biventricular Pacing

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Abstract

Objective—Post-cardiopulmonary bypass biventricular pacing improves hemodynamics but without clearly defined predictors of response. Based on preclinical studies and prior observations, it was suspected that diastolic dysfunction or pulmonary hypertension is predictive of hemodynamic benefit.

Design—Randomized controlled study of temporary biventricular pacing after cardiopulmonary bypass.

Setting—Single-center study at university-affiliated tertiary care hospital.

Interventions—Patients who underwent bypass with pre-operative ejection fraction $\geq 40\%$ and QRS duration ≥ 100 ms or double-valve surgery were enrolled. At 3 time points between separation from bypass and postoperative day 1, pacing delays were varied to optimize hemodynamics.

Participants—Data from 43 patients were analyzed.

Measurements and Main Results—Cardiac output and arterial pressure were measured under no pacing, atrial pacing, and biventricular pacing. Preoperative echocardiograms and pulmonary artery catheterizations were reviewed, and measures of both systolic and diastolic function were compared to hemodynamic response. Early after separation, improvement in cardiac output was positively correlated with pulmonary vascular resistance ($R^2 = 0.97$, $p < 0.001$), ventricle wall thickness ($R^2 = 0.72$, $p = 0.002$), and E/e' , a measure of abnormal diastolic ventricular filling velocity ($R^2 = 0.56$, $p = 0.04$). Similar trends were seen with mean arterial pressure. QRS duration and ejection fraction did not correlate significantly with improvements in hemodynamics.

Conclusions—There may be an effect of biventricular pacing related to amelioration of abnormal diastolic filling patterns rather than electrical resynchronization in the postoperative state.

Keywords

biventricular pacing; cardiopulmonary bypass; diastolic function; pulmonary hypertension

Biventricular Pacing (BiVP) is a well-established therapy for patients with chronic systolic heart failure and evidence of electrical dyssynchrony.¹ There are multiple suspected mechanisms, but acutely it is thought to resynchronize left ventricular contraction when myocardial damage and remodeling have impaired the intrinsic conduction system.² The current primary predictors of response to BiVP are symptomatic heart failure, systolic dysfunction, and prolonged QRS.³ However, a number of preclinical studies have shown BiVP improves hemodynamics in acute volume and pressure overload states when atrioventricular (AVD) and ventriculoventricular delays (VVD) are varied to directly optimize hemodynamics despite normal ventricular electrical conduction and contractility.^{4,5} This model of BiVP was adapted to the post-cardiopulmonary bypass state to act as an adjunct to inotropes or vasopressors. In the Biventricular Pacing After Cardiac Surgery Trial, it was shown that this technique can improve hemodynamics in the first hours after bypass^{6,7} and postoperative day 1 in patients who underwent aortic valve replacement.⁸ It also reduced vasopressor and inotrope requirements,⁹ improved urine output,⁸ and reduced intrinsic heart rate.¹⁰

The exact mechanism of these benefits was not clear, however. The study population included many patients with normal QRS duration or ejection fraction, patients who would not be expected to respond to cardiac resynchronization therapy (CRT). Wide QRS or reduced ejection fraction was not observed to be predictive of hemodynamic improvement, and an alternative mechanism, based on optimization of diastolic hemodynamics, was proposed. It was observed that shortly after separation from bypass, hemodynamics worsened with an increase in heart rate, suggesting impaired ventricular filling and diastolic dysfunction.⁶ Aortic stenosis, a predictor of response in the trial, is known to cause concentric hypertrophy and diastolic dysfunction early in the disease course¹¹ and, in turn, could be exacerbated further by myocardial edema and impaired relaxation. Also, the preclinical studies in a right ventricular pressure overload model, essentially mimicking pulmonary hypertension, had the most robust response to BiVP.⁴

In the current study, preoperative transthoracic echocardiograms and pulmonary artery catheter hemodynamics of the patients enrolled in the trial were analyzed with a hypothesis that markers of diastolic dysfunction and pulmonary hypertension, rather than systolic dysfunction, predicted response to BiVP.

METHODS

The study was a randomized controlled trial with crossover features designed to assess the hemodynamic effects of BiVP with optimized AVD and VVD in the post-bypass patient. Inclusion criteria were a clinical indication for cardiac surgery with cardiopulmonary bypass and clinical features predictive of post-bypass hemodynamic instability: preoperative left ventricular ejection fraction < 40% and QRS duration > 100 ms, or combined mitral and aortic valve replacement regardless of QRS or ejection fraction, as dual-valve surgery

patients have been shown in the past to have higher rates of adverse outcomes.¹² Subjects were excluded for presence of intracardiac shunts, congenital heart disease, post-bypass heart rate greater than 120 beats per minute, second-degree or third-degree heart block, or atrial fibrillation. The study protocol was approved by the institutional review board and was conducted with an Investigational Device Exemption from the Food and Drug Administration.

Preoperative transthoracic echocardiogram measurements were performed in accordance with the American Society of Echocardiography guidelines^{13,14} and confirmed by a board-certified echocardiographer. Ejection fraction was calculated by Simpson's biplane or by visual estimation if quality windows could not be obtained. Relative wall thickness was calculated as (septal thickness + posterior wall thickness)/end-diastolic dimension. Left ventricular mass index was calculated as $\{0.8[1.04\{[(\text{end diastolic dimension} + \text{septal thickness} + \text{posterior wall thickness})^3 - \text{end-diastolic dimension}^3]\} + 0.6]\}$ /body surface area. Hypertrophy was defined as a left ventricular mass index greater than 95 g/m² in women and 115 g/m² in men. Concentric hypertrophy was defined as hypertrophy and a relative wall thickness greater than 0.42, and eccentric hypertrophy was defined as hypertrophy and a relative wall thickness less than 0.42. Pulsed-wave Doppler was targeted at the mitral leaflets for measurement of early diastolic filling velocity (*E*). Pulsed-wave tissue Doppler imaging targeted at the septal and lateral mitral annulus was used to measure early diastolic annular velocity (*e'*) and was calculated as an average of the 2 measurements. *E/e'* was used as a measure of left atrial pressure and is a commonly used surrogate for diastolic filling abnormalities.

Pulmonary artery catheterizations were done as a standard preoperative protocol, with measurements of the following pressures: mean right atrial, right ventricular, peak systolic and end-diastolic, mean pulmonary artery, and pulmonary capillary wedge pressures. Oxygen saturations were measured in the pulmonary artery and via pulse oximetry to calculate Fick cardiac output (CO) and index. Pulmonary vascular resistance was calculated as: (mean pulmonary artery pressure – pulmonary capillary wedge pressure)/CO.¹⁵

Figure 1 depicts a flow diagram of the protocol. Prior to separation from bypass, temporary epicardial pacing leads were sewn to the right atrial appendage, anterior right ventricle, and left ventricle. BiVP was performed with an InSync III biventricular pacemaker (Medtronic, Inc, Minneapolis, MN). CO was measured with electromagnetic (Carolina Medical Electronics, East Bend, NC) or ultrasonic (Transonics Systems Inc, Ithaca NY) probes on the aortic root. Radial artery pressures were used for measurement of mean arterial pressure (MAP).

The initial phase of BiVP testing was conducted after separation from bypass and hemodynamic stabilization (phase 1). VVD was set to 0 ms, CO was measured under 7 AVDs (90 to 270 ms with 30-ms increments), and the setting giving the highest CO was designated optimal. VVD then was optimized in a similar fashion by varying intervals ranging from +80 to –80 ms while fixing the AVD at the optimal setting. Finally, 30-second post-optimization measurements were done during a randomized sequence of no pacing, atrial pacing, and optimized BiVP for measurement of CO and MAP. After completion of

phase 1, patients were randomized to the experimental group for whom the optimized BiVP was continued throughout the study, or standard care, without BiVP.

Phase 2 optimization was performed during closure of the sternum. Optimization procedures were similar to phase 1 but were done using MAP, as the flow probe had been removed. At completion, pacing in the experimental group was set to BiVP with the new optimized settings. Phase 3 optimization was done on postoperative day 1 in the intensive care unit. Optimization was again conducted in a similar fashion based on MAP. The primary endpoint of the study was thermodilution cardiac index prior to phase 3. Patients who were unable to complete pacing protocols in prior phases due to technical issues or surgeon preference could be re-enrolled in later phases according to the original randomization.

Response was defined as the change in CO or MAP between BiVP and heart-rate-matched atrial pacing in the end-phase comparisons. Continuous data within each phase of end-optimization measurements were compared using a paired t-test. Univariate analysis of the relationship between preoperative measurements and response was with Pearson correlation, and significance was determined with a 2-sided independent t-test. Multivariate analysis of preoperative measurements and response was with least squares multivariate regression. The analysis was done as intention to treat. Statistical significance was defined as $p < 0.05$. Multiple comparisons were not done due to the low power of the study. Statistical analysis was performed using SPSS (IBM, Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 109 patients were randomized, and 43 completed the pacing protocol in 1 of the 3 phases. Dropout was due to instability, surgeon preference, pacing failure, or poor waveform tracing. Thirty-two patients had available preoperative transthoracic echocardiograms, and 21 had available preoperative pulmonary artery catheterizations.

Transthoracic echocardiograms and catheterizations were done an average of 12.6 ± 2.5 and 10.6 ± 2.4 days prior to surgery, respectively. Patient demographics and preoperative characteristics previously have been described and are shown in Table 1.⁸ The effects of pacing on CO and MAP are shown in Table 2. The results in phases 1 and 2 already have been published.^{6,7}

In 1 patient with rheumatic heart disease, severe concentric hypertrophy, pulmonary hypertension, and aortic and mitral stenosis, there was an 80% increase in CO and 40% increase in MAP with BiVP over atrial pacing in phase 1, despite a baseline QRS of 100 ms, prolongation of the QRS to 150 with BiVP, and a preoperative ejection fraction of 75%. Figure 2 shows a representative tracing of CO and MAP obtained from this patient in the phase 1 end-optimization comparisons.

Univariate correlations of measured parameters are shown in Table 3. There was no significant correlation between preoperative QRS or ejection fraction and response in any phase. Of the echocardiographic parameters, relative wall thickness had consistent and significant positive correlations with response. E/e' correlated positively with response, but

the correlation was only significant with phase-1 MAP. There was no consistent trend with hemodynamic response and left ventricle mass index in any phase. There was no significant trend between hemodynamic response and hypertrophy pattern. Of the patients with pulmonary artery catheter measurements, there were consistent positive correlations with pulmonary vascular resistance and hemodynamic response in phases 1 and 2. Similar positive correlations were observed with mean pulmonary artery pressure, pulmonary capillary wedge pressure, and right ventricular systolic pressure, although the trends with pulmonary capillary wedge pressure were insignificant. There were no significant predictors of hemodynamic response in phase 3. Figure 3 shows scatterplots of hemodynamic response and relative wall thickness, E/e' , pulmonary vascular resistance, ejection fraction, and QRS. Pulmonary vascular resistance also was correlated significantly with relative wall thickness in phase 1 ($R^2 = 0.70$, $p = 0.001$).

Multivariate analyses are summarized in Table 4. Combined models of pulmonary vascular resistance, relative wall thickness, or E/e' were significantly predictive in phases 1 and 2, with relative wall thickness and pulmonary vascular resistance being more predictive of response than E/e' .

DISCUSSION

The strongest predictors of phases 1 and 2 responses were pulmonary vascular resistance, relative wall thickness, and to a lesser extent, E/e' . There also were trends with pulmonary capillary wedge pressure that did not achieve significance. Combined multivariate models of these markers indicated that pulmonary vascular resistance and relative wall thickness were stronger predictors than E/e' . However, it is unclear if relative wall thickness or pulmonary vascular resistance was most predictive. It would appear that the strongest predictors of early hemodynamic response to BiVP were pulmonary hypertension, wall thickness, and, to a lesser extent, elevated left atrial diastolic pressures.

It is possible that the hemodynamic improvements seen in this study were due entirely to BiVP-mediated diastolic filling optimization. In Figure 2, it can be seen that the increased rate in atrial-only pacing impaired ventricular performance unless accompanied by BiVP. This suggested impaired diastolic filling that improves with BiVP. AVD optimization improved CO from optimization of preload¹⁶ and provided the majority of the benefit in Phase 1. However, approximately 40% of the hemodynamic benefit was due to VVD optimization.⁶ BiVP could also affect hemodynamics by allowing for independent timing of right and left ventricular systole onset. Pre-excitation of either the left or right ventricle could be optimal depending on compliance, filling pressures, and shape of the Frank-Starling curve. Relatively delayed activation could allow for the ventricle with impaired filling to have a longer filling time, larger preload, and improved CO and MAP. Furthermore, if this proposed mechanism was true, it would be, in effect, ventricular electrical desynchronization rather than resynchronization and also would explain why BiVP prolonged rather than narrowed QRS in this study (unpublished data).

The post-cardiopulmonary bypass (CPB) state is associated with impaired mechanical function from ischemia-reperfusion injury, inflammation, and edema, which resolve over

several hours.^{17–19} The edema and impaired relaxation would be expected to worsen left ventricular filling, and filling would be even more impaired with pre-existing diastolic dysfunction or pulmonary hypertension. If BiVP is augmenting diastolic function, it would be expected that the beneficial effect on hemodynamics would diminish with time as edema and impaired relaxation resolve, which was observed in phase 3.

Improvement of diastolic function has been noted in prior studies of both chronic²⁰ and acute postoperative²¹ BiVP, but to the best of the authors' knowledge, it has not been used as a predictor of response in the postoperative state. Handoko et al²² showed that dual-chamber pacing in a rat model of pulmonary hypertension improved both systolic and diastolic function despite the lack of electrical dyssynchrony. To the best of the authors' knowledge, these data represent the first report of a BiVP benefit in humans with pulmonary hypertension but without evidence of electrical dyssynchrony. Pulmonary hypertension has not been shown to be predictive of response in cardiac resynchronization.²³ However, pulmonary hypertension reduces left ventricular filling, also observed with left bundle-branch block or right ventricular-first pacing and causes effective pre-excitation of the right ventricle or delayed activation of the left ventricle and longer diastole. This could be expected to improve hemodynamics in pulmonary hypertension. Therefore, it is not surprising that patients with pulmonary hypertension do worse with simultaneous ventricular activation but may do better with right ventricular pre-excitation.

Other potential mechanisms are right ventricular pre-excitation allowing for increased pressure generation across the septum, as noted in preclinical studies⁴ of improvement of mechanical dyssynchrony, paradoxical septal motion, or alternative depolarization sequences. These mechanisms could lead to more optimal intraventricular pressure gradients, as was assumed in patients with hypertrophic cardiomyopathy who responded to BiVP despite normal QRS.²⁴

There was no evidence that electrical resynchronization, the assumed mechanism of cardiac resynchronization, was at play in this study. The average preoperative QRS in these patients was shorter than that of major cardiac resynchronization trials and guideline recommendations,¹ baseline QRS did not correlate with hemodynamic response in any phase, ejection fraction and systolic dysfunction were not predictive of response, and, overall, there was QRS widening rather than narrowing during BiVP in this study (unpublished data).

The overall hemodynamic benefits seen in this trial are unlikely to provide clinically significant benefit. However, the subgroups identified in these and prior studies indicated there may be a unique patient population who could benefit from post-bypass BiVP. Many patients may have benefited from either left-ventricular or right-ventricular-only pacing, and the sequential pacing may have been unnecessary. A trial aimed at patients with these preoperative characteristics, a period of dual-chamber pacing, and intraoperative and postoperative echocardiograms to better delineate the effects of post-bypass BiVP on both systolic and diastolic function currently is underway.

The goal of the trial was to measure the effects of optimized BiVP on hemodynamics, not to elucidate the mechanism. These results must be interpreted as post-hoc and hypothesis-generating, and, especially given the low power, these trends may have arisen from chance alone. At its conclusion, the trial was underpowered to detect the primary endpoint, and the trial included a highly heterogeneous patient population without consistent underlying pathophysiology, further reducing its power. Several of the nonsignificant trends may have become significant had the study met its original enrollment goals or included preoperative transthoracic echocardiograms and pulmonary artery catheters in each patient. The inclusion criteria specified a relatively normal QRS to improve enrollment. It is possible that a more predominant effect of electrical resynchronization would have been seen with a larger proportion of patients with prolonged baseline QRS. E/e' is a validated measure of diastolic dysfunction. However, it is not validated in patients with mitral valve pathology,¹³ which was present in most of the patients included in this study. Despite this, it may still reflect the abnormal filling patterns felt to be key to the mechanism of BiVP in this patient population.

CONCLUSIONS

While optimized post-bypass BiVP improved hemodynamics, preoperative ejection fraction and QRS were not predictive of response. Rather, wall thickness, pulmonary hypertension, and abnormal diastolic filling patterns were strong predictors of response. This raised the question of alternative mechanisms of benefit to post-bypass BiVP, specifically related to optimization of diastolic filling. Future studies may confirm mechanisms and identify patient populations who will benefit most from this therapy.

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Fig 1.

Biventricular pacing after cardiac surgery trial protocol. Pacing was optimized 1 hour after weaning from bypass (phase 1), 1 hour later after chest closure (phase 2), and on the day after (phase 3). Patients were randomized after phase 1 to either continuous BiVP or standard postoperative management. Optimization included 7 atrioventricular delays and 9 ventriculoventricular delays. Each parameter was tested for 10 (phase 1), 20 (phase 2), or 30 seconds (phase 3) in duplicate and random sequence. Optimization parameters were CO in phase 1 and MAP in phases 2 and 3. The primary endpoint was CI prior to phase 3. BiVP biventricular pacing; CI, cardiac index; CO, cardiac output; CPB, cardiopulmonary bypass; ICU, intensive care unit; MAP, mean arterial pressure; SOC, standard of care; TD, thermodilution. Adapted with permission.⁸

Fig 2.

Representative CO, MAP, and ECG tracings. The highest CO and MAP occur during BiVP, which was tested first. Hemodynamics are worst with AAI pacing in the third sequence. The last sequence, no pacing, shows the same MAP and CO observed in the second sequence, also no pacing. Stability of hemodynamics during the 2 NoP sequences indicates that the underlying contractile state is unchanged. The acute improvement with BiVP indicates hemodynamic improvement with resynchronization. The acute, reversible deterioration with AAI indicates an adverse effect of increased heart rate if not accompanied by resynchronization. This observation is most consistent with a rate-related decrease in diastolic filling. AAI, atrial pacing; BiVP, biventricular pacing; CO, cardiac output; ECG, electrocardiogram; MAP, mean arterial pressure; NoP, no pacing.

Fig 3.

Plots of hemodynamic response to BiVP defined as the difference in CO or MAP between BiVP and AAI pacing and major preoperative predictors of response. Trend lines indicate univariate linear regression by least squares with individual standard deviations. Pearson correlation coefficients and 2-sided t-test significance are shown for each comparison. RWT and PVR were correlated positively with hemodynamic response in phases 1 and 2. E/e' , a marker of diastolic dysfunction, positively correlated with response in phase 1. No markers that correlated with response in phase 3. QRSd and EF did not correlate with response in any phase. AAI, atrial pacing; BiVP, biventricular pacing; CO, cardiac output; EF, ejection fraction; PVR, pulmonary vascular resistance; RWT, relative wall thickness.

Table 1

Baseline Characteristics

Total (n = 43)	
Number of Patients:	
Total:	43
Age (years $\pm$ SD)	67 $\pm$ 12
Ejection Fraction (% $\pm$ SD)	32 $\pm$ 15
QRS duration (msec $\pm$ SD)	111 $\pm$ 24
Male gender (%)	72
Type of Surgery:	
TVR	2
CABG	32
AVR	31
MVR	26

NOTE. Surgery type indicates either in isolation or in combination with other procedures. Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass graft; MVR, mitral valve replacement; TVR, tricuspid valve replacement.

Table 2

Hemodynamic Measurements and QRSd During Postoptimization Comparisons

	Phase 1 (n = 24)	Phase 2 (n = 37)	Phase 3 (n = 29)
CO (L/min)			
NoP	4.5 ± 0.3		4.9 ± 0.2
AAI	4.3 ± 0.3		5.4 ± 3[*]
NoP-AAI p value	0.23		0.01
BiVP	4.8 ± 0.3^{†‡}		5.4 ± 2[‡]
BiVP-NoP p value	0.002		0.007
BiVP-AAI p value	0.003		0.059
MAP (mmHg)			
NoP	74 ± 2	73 ± 2	80 ± 3
AAI	75 ± 2	75 ± 2	81 ± 3
NoP-AAI p-value	0.75	0.07	0.09
BiVP	76 ± 2[‡]	76 ± 2[‡]	82 ± 3[‡]
BiVP-NoP p value	0.001	0.004	0.002
BiVP-AAI p value	0.05	0.08	0.07

Abbreviations: AAI, atrial pacing; BiVP, biventricular pacing; CO, cardiac output; MAP, mean arterial pressure; NoP, no pacing.

^{*} indicates significant difference between NoP-AAI (within phase).[†] indicates significant difference between AAI-BiVP (within phase).[‡] indicates significant difference between NoP-BiVP (within phase).

Table 3

Univariate Regression Correlation Coefficients

	Phase 1 CO Response	Phase 1 MAP Response	Phase 2 MAP Response	Phase 3 CO Response	Phase 3 MAP Response
TTE					
QRS	-0.06 (0.8)	-0.12 (0.6)	-0.12 (0.5)	-0.11 (0.6)	0.05 (0.8)
EF	0.16 (0.5)	0.29 (0.2)	0.09 (0.6)	0.21 (0.3)	0.01 (0.9)
RWT	0.72 (0.002)	-0.79 (< 0.001)	0.60 (0.008)	0.17 (0.5)	0.02 (0.9)
LVTMI	-0.13 (0.6)	0.69 (< 0.001)	-0.19 (0.5)	-0.15 (0.5)	0.46 (0.06)
E/e'	0.56 (0.04)	0.49 (0.08)	0.35 (0.2)	-0.2 (0.4)	0.37 (0.2)
Pulmonary Artery Catheter					
RVSP	0.90 (0.002)	0.68 (0.06)	0.53 (0.05)	0.06 (0.8)	0.50 (0.07)
MPAP	0.86 (0.003)	0.75 (0.02)	0.54 (0.04)	-0.26 (0.3)	0.24 (0.4)
PCWP	0.49 (0.2)	0.50 (0.2)	0.28 (0.3)	-0.40 (0.1)	-0.10 (0.7)
PVR	0.97 (< 0.001)	0.84 (0.01)	0.74 (0.002)	0.23 (0.4)	0.46 (0.1)

NOTE. Parentheses indicate p value, bolded text indicates significant result.

Abbreviations: EF, ejection fraction; LVTMI, left ventricular mass index; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSP, right ventricle systolic pressure; RWT, relative wall thickness; TTE, transthoracic echocardiogram.

Table 4

Multivariate Regression Correlation Coefficients

	Phase 1 MAP	Phase 1 CO	Phase 2 MAP
Model			
RWT, E/e'			
N	13	13	16
Overall (F)	31.8 (< 0.001)	37.8 (< 0.001)	4.494 (0.031)
β			
RWT	0.742 (< 0.001)	0.808 (< 0.001)	0.537 (0.025)
E/e'	0.442 (0.003)	0.355 (0.008)	0.216 (0.332)
RWT, PVR			
N	7	7	13
Overall (F)	37.9 (0.002)	14.896 (0.008)	7.16 (0.010)
β			
RWT	0.088 (0.592)	0.584 (0.023)	0.141 (0.619)
PVR	0.905 (0.002)	0.431 (0.113)	0.648 (0.039)
E/e', PVR			
N	7	7	13
Overall (F)	47.35 (0.001)	6.092 (0.046)	6.875 (0.012)
β			
E/e'	0.141 (0.267)	0.123 (0.671)	-0.04 (0.987)
PVR	0.900 (0.001)	0.777 (0.036)	0.747 (0.007)

NOTE. β indicates standardized partial correlation coefficient. Parentheses indicate p values. Bolded text indicates statistical significance.

Abbreviations: CO, cardiac output; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; RWT, relative wall thickness.