Optimized temporary biventricular pacing acutely improves intraoperative cardiac output after weaning from cardiopulmonary bypass: A substudy of a randomized clinical trial

Daniel Y. Wang, MD,[a] Marc E. Richmond, MD,[b] T. Alexander Quinn, PhD,[c] Ajay J. Mirani, MD,[b] Alexander Rusanov, MD,[d] Vinay Yalamanchi, BA,[d] Alan D. Weinberg, MS,[e] Santos E. Cabreriza, MBA,[d] and Henry M. Spotnitz, MD[d]

Objective: Permanent biventricular pacing benefits patients with heart failure and interventricular conduction delay, but the importance of pacing with and without optimization in patients at risk of low cardiac output after cardiac surgery is unknown. We hypothesized that pacing parameters independently affect cardiac output. Accordingly, we analyzed aortic flow measured with an electromagnetic flowmeter in patients at risk of low cardiac output during an ongoing randomized clinical trial of biventricular pacing (n = 11) versus standard of care (n = 9).

Methods: A substudy was conducted in all 20 patients in both groups with stable pacing after coronary artery bypass grafting, valve surgery, or both. Ejection fraction averaged 33% ± 15%, and QRS duration was 116 ± 19 ms. Effects were measured within 1 hour of the conclusion of cardiopulmonary bypass. Atrioventricular delay (7 settings) and interventricular delay (9 settings) were optimized in random sequence.

Results: Optimization of atrioventricular delay (171 ± 8 ms) at an interventricular delay of 0 ms increased flow by 14% versus the worst setting (111 ± 11 ms, $P < .001$) and 7% versus nominal atrioventricular delay (120 ms, $P < .001$). Interventricular delay optimization increased flow 10% versus the worst setting ($P < .001$) and 5% versus nominal interventricular delay (0 ms, $P < .001$). Optimized pacing increased cardiac output 13% versus atrial pacing at matched heart rate (5.5 ± 0.5 vs 4.9 ± 0.6 L/min, $P = .003$) and 10% versus sinus rhythm (5.0 ± 0.6 L/min, $P = .019$).

Conclusions: Temporary biventricular pacing increases intraoperative cardiac output in patients with left ventricular dysfunction undergoing cardiac surgery. Atrioventricular and interventricular delay optimization maximizes this benefit. (J Thorac Cardiovasc Surg 2011;141:1002-8)

Supplemental material is available online.

Biventricular pacing (BiVP) is an established therapy for congestive heart failure (CHF), and it is currently the standard of care for select patients with advanced CHF associated with left ventricular (LV) dysfunction and intraventricular conduction delay (IVCD).[1] Permanent BiVP improves LV dimension and function and decreases morbidity and mortality, although it is associated with a nonresponse rate of up to 30%.[2-5] Although the long-term benefits of BiVP are typically not appreciated until several months after implantation, hemodynamic effects of changes to pacing parameters are reflected acutely by metrics such as stroke volume, ventricular dyssynchrony, and the maximal first derivative of pressure (dP/dt_{max}).[6,7] These properties have facilitated the study of the optimization of programmable BiVP parameters, such as atrioventricular delay (AVD) and interventricular delay (VVD), to maximize the hemodynamic benefit of BiVP and to reduce its nonresponse rate.[8-10]

The acute hemodynamic effects of BiVP also enable the study of temporary BiVP as a treatment for low output states after cardiac surgery. Low left ventricular ejection fraction (LVEF) is an independent risk factor for poor outcomes after cardiac surgery.[11] BiVP improves hemodynamics without increasing myocardial oxygen consumption,[7] and therefore it is particularly appealing as a potential therapy in patients undergoing cardiac surgery. Prior studies have assessed temporary perioperative BiVP in heterogeneous groups of patients with varying results.[12-24] Moreover, the

From the Departments of Medicine,[a] Pediatrics,[b] and Surgery,[d] Columbia University, New York, NY; the Department of Physiology, Anatomy and Genetics,[c] University of Oxford, Oxford, United Kingdom; and the Department of Health Evidence and Policy,[e] Mount Sinai School of Medicine, New York, NY.

This study was funded by a grant from the National Institutes of Health (RO1 HL080152 to Dr Spotnitz). Dr Spotnitz is the George H. Humphreys, II, Professor of Surgery. Dr Wang is supported by National Institutes of Health Training Grant T32 HL007854.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Read at the 2009 American Heart Association Scientific Sessions, Orlando, Fla, November 14–18, 2009. Published as an abstract: Wang DY, Richmond ME, Quinn TA, Mirani AJ, Rusanov A, Yalamanchi Y, et al. Optimized temporary biventricular pacing acutely improves intraoperative cardiac output after weaning from cardiopulmonary bypass [abstract]. *Circulation*. 2009;120:S800.

Received for publication April 14, 2010; revisions received June 24, 2010; accepted for publication July 6, 2010; available ahead of print Aug 30, 2010.

Address for reprints: Henry M. Spotnitz, MD, Department of Surgery, Columbia University Medical Center, 622 West 168th St, 10th floor, Vanderbilt Clinic, Rm 1010, New York, NY, 10032 (E-mail: hms2@columbia.edu).

0022-5223/$36.00

doi:10.1016/j.jtcvs.2010.07.004

Abbreviations and Acronyms

AAI = atrial pacing
AVD = atrioventricular delay
BiPACS = BiVP After Cardiac Surgery
BiVP = biventricular pacing
CABG = coronary artery bypass grafting
CHF = congestive heart failure
CO = cardiac output
CPB = cardiopulmonary bypass
dP/dt_{max} = maximal first derivative of pressure
IVCD = intraventricular conduction delay
LV = left ventricle
LVEF = left ventricular ejection fraction
NSR = sinus rhythm with no pacing
RA = right atrium
RV = right ventricle
VVD = interventricular delay

role of optimization of temporary BiVP parameters in the perioperative setting is unclear.[25,26]

The BiVP After Cardiac Surgery (BiPACS) trial is a randomized clinical trial to study the effect of optimized temporary BiVP on cardiac output (CO) in postoperative cardiac surgery patients with preoperative LV systolic dysfunction and an IVCD. Patients undergo BiVP optimization at multiple time points in the intraoperative and postoperative periods and are randomized to continuous optimized BiVP versus standard of care. The hypothesis underlying the BiPACS trial is that CO will increase 15% in patients undergoing temporary BiVP. In this substudy of the BiPACS trial, we hypothesized that optimization of pacing parameters would increase CO. Accordingly, we assessed the contribution of AVD and VVD optimization to the effect of BiVP optimization in the intraoperative period after separation from cardiopulmonary bypass (CPB) and evaluated the effect of optimized BiVP on CO compared with atrial pacing (AAI) and with sinus rhythm with no pacing (NSR).

MATERIALS AND METHODS

BiPACS Trial Study Population

The study protocol was approved by the Columbia University Medical Center Institutional Review Board. Adult patients undergoing elective cardiac surgery on CPB were screened for eligibility to enroll in the BiPACS trial. All patients provided written informed consent. Recruitment was done before the day of the operation by qualified and trained study coordinators and investigators on the study team with permission of the attending surgeon. Inclusion criteria included the following: preoperative CHF, LVEF of 40% or less, and a QRS duration of 100 ms or greater or patients undergoing combined mitral and aortic valve surgery. LVEF and QRS criteria were liberalized from values of 35% and 120 ms, respectively, in the original protocol. Exclusion criteria included the following: atrial fibrillation, second- or third-degree atrioventricular block, congenital heart disease, intracardiac shunts, or heart rate of greater than 120 beats/min after separation from CPB. Preoperative data obtained by means of chart review included the following: LVEF, as measured by means of echocardiographic or left ventriculogram analysis; heart rhythm, QRS duration, and intraventricular blocks from electrocardiographic tracings; the type of operation performed; and demographic characteristics. The BiPACS trial is ongoing, and end points will not be examined until 212 patients have been randomized.

Study Design and Optimization Protocol

Patients in the BiPACS trial are randomized to the 2 treatment groups at the end of phase 1 (within 1 hour of the conclusion of cardiopulmonary bypass) by using randomly permuted blocks of 4, 6, and 8 to avoid imbalances that can occur with simple randomization. A treatment allocation ratio of 1:1 was used; each group will be of equal size. The phase 1 testing described here occurs in all patients before randomization. Optimization of AVD, ventricular pacing site, and VVD are tested in random sequences. Randomization and testing sequences are determined based on forms in sealed envelopes that are not opened until needed. These forms were prepared before enrollment of the first patient. Before separation from CPB, temporary epicardial pacing leads were sewn to the right atrial (RA) appendage, anterior right ventricle (RV), and 2 randomized sites of 6 possible sites on the LV. One of the LV leads (LV1) was placed at the basal LV at either the obtuse margin, circumflex, or posterior regions; the second LV lead (LV2) was placed at either the midinferomedial, midinferolateral, or apical LV. Data from BiVP using LV1 were analyzed in this study. The leads were attached to a Medtronic InSync III permanent biventricular pacemaker (Medtronic, Inc, Minneapolis, Minn) mounted in an external housing unit, and their sensing and pacing functions were tested and confirmed. An appropriately sized electromagnetic flow probe (Carolina Medical Electronics, East Bend, NC) was placed on the ascending aorta. After separation from CPB and establishment of stable inotrope and vasopressor dosing, the BiVP optimization protocol was initiated. The pacing rate was set at 90 beats/min or at 10 beats/min greater than the patient's intrinsic heart rate if greater than 90 beats/min to ensure atrial capture up to a maximum of 120 beats/min. These heart rates were selected empirically. A wider range of heart rates is studied in phase 3 of the BiPACS trial, including cardiac resynchronization therapy at the intrinsic heart rate.

Real-time aortic volume flow, echocardiograms, and arterial pressure signals were collected with an analog-to-digital converter (PowerLab; ADInstruments, Inc, Milford, Mass) and recorded on a personal computer (iMac; Apple Computer, Inc, Cupertino, Calif; Figure 1). CO was measured by integrating aortic volume flow tracings over 1 respiratory cycle with MacLab software (ADInstruments, Inc) and custom-designed routines in Matlab (The MathWorks, Inc, Natick, Mass).

BiVP optimization was performed by optimizing AVD, followed by VVD. All pacing settings during optimization were conducted over 10-second intervals and were tested twice. The use of a rapid optimization protocol measuring changes in cardiac mechanics over brief intervals has been described previously.[14,27] AVD optimization was performed during sequential RA BiVP, with a VVD of 0 ms. AVD was varied in 30-ms increments, ranging from 90 to 270 ms, in randomized order. AVDs that were longer than the patient's intrinsic paced AVD were not tested. The AVD yielding the highest CO was selected as the optimum AVD. AVD optimization data from a representative patient are shown in Figure 2. VVD optimization was then performed with the optimum AVD by varying the VVD by 20-ms increments, ranging from –80 ms (LV first) to +80 ms (RV first) in randomized order. CO as a function of VVD was plotted, and the VVD yielding the highest CO was selected as the optimum VVD (Figure 3), thereby defining the optimum BiVP parameters for the patient. Optimized BiVP was then compared with RA pacing (AAI mode) at the same heart rate and with NSR with no pacing, in randomized order, and over 30-second intervals. The aortic flow probe was then removed, and the temporary pacing leads were externalized for further BiVP optimization in subsequent phases of the BiPACS trial.

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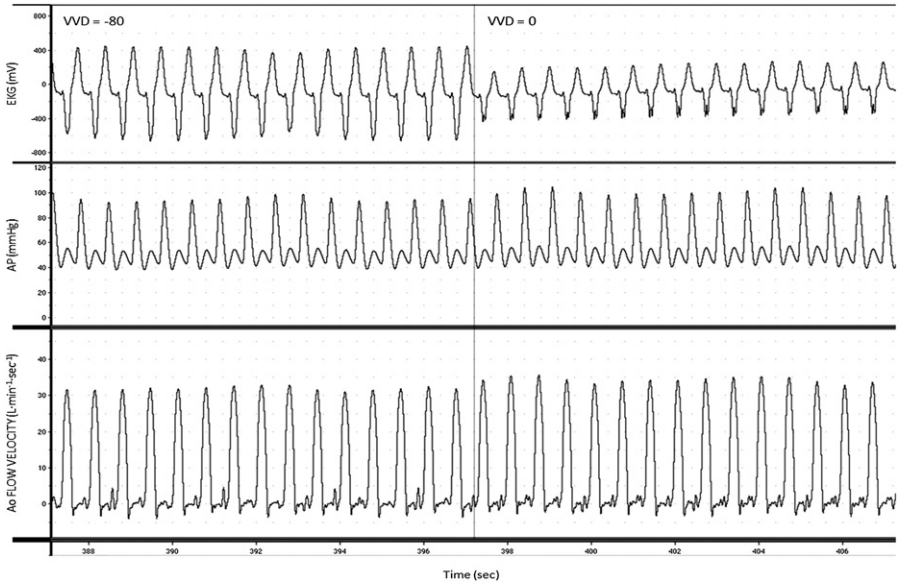

FIGURE 1. Intraoperative recordings from a representative patient displaying changes in electrocardiograms *(EKG)*, arterial pressure *(AP)*, and aortic *(Ao)* flow velocity during biventricular pacing optimization. *VVD*, Interventricular delay.

Statistical Analysis

For AVD and VVD optimization data and for the comparison among optimized BiVP, AAI, and NSR, descriptive statistics were calculated for each group. Differences among multiple groups (3) were tested by using blocked 1-way analysis of variance. Post hoc comparisons to assess pairwise differences between groups were performed with the Tukey test adjusted for multiple comparisons. Differences between 2 groups were tested by using a 2-way paired Student's *t* test. Statistical analysis was performed with SAS 9.1 software (SAS Institute, Inc, Cary, NC).

RESULTS

Patient flow for the BiPACS trial and this substudy covers recruitment from April 1, 2007, to June 2, 2009. The number of patients screened was 2261, and 60 were enrolled. Thirty-three patients received the intended testing in phase 1 and were subsequently randomized to BiVP (experimental group) or standard of care (control group). There were no adverse events during phase 1. The number of these patients for whom the primary end point was measured was 13 in the BiVP group and 13 in the standard-of-care group. The study has not been completed, however, and therefore no analysis of primary and secondary outcomes has been done, and the present study only describes the results for phase 1. Accordingly, the data after randomization and the period of follow-up are not relevant and are not summarized.

Among the 33 patients who received phase 1 testing in the BiPACS trial, 13 were eliminated from this substudy because of frequent ventricular ectopy, an intra-aortic balloon pump, or noisy aortic flow tracings. Ultimately, of the 20 patients included in this substudy, there were 13 without second- or third-degree atrioventricular block

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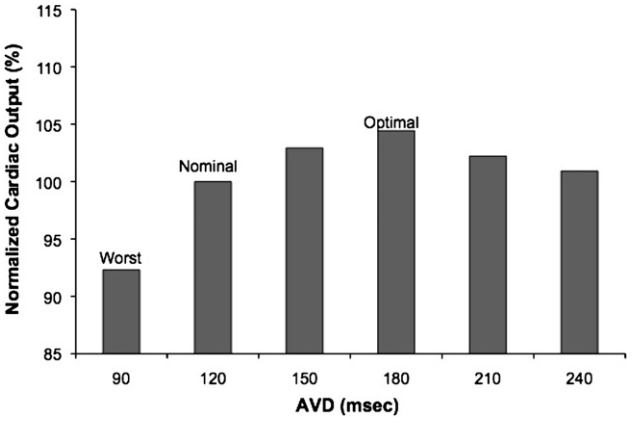

FIGURE 2. Cardiac output versus atrioventricular delay *(AVD)* from a representative patient during AVD optimization.

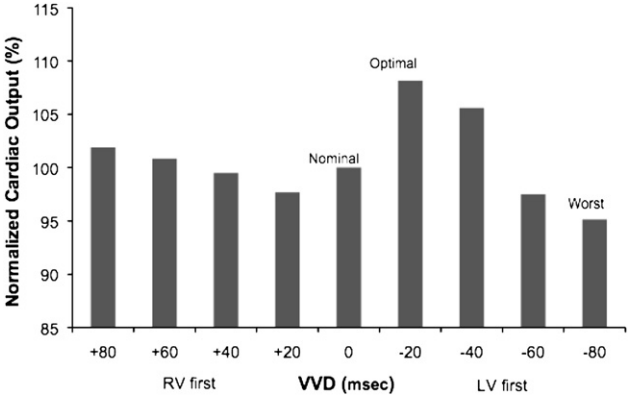

FIGURE 3. Cardiac output versus interventricular delay *(VVD)* from a representative patient during VVD optimization. *LV*, Left ventricle; *RV*, right ventricle.

who completed comparison of optimized BiVP, AAI, and NSR. Baseline clinical characteristics are shown in Table E1.

The majority of patients underwent valvular surgery, including double-valve cases, as well as combination valve and coronary artery bypass grafting (CABG) surgery. Average age was 67 ± 12 (standard deviation) years, and 75% were male. LVEF averaged 33% ± 15%, and average QRS duration was 116 ± 19 ms. Nine patients underwent combined CABG and aortic valve replacement, mitral valve replacement, or both. Five underwent combined aortic and mitral valve surgery, 3 underwent aortic surgery alone, and 3 underwent isolated CABG.

Results of AVD and VVD optimization are shown in Figure 4. The intrinsic paced AVD was greater than 150 ms in all patients and greater than 270 ms in 10 patients. The mean optimum AVD was 171 ± 8 versus 111 ± 11 ms (standard error of the mean) for the mean worst AVD ($P < .001$). The optimum AVD was greater than 150 ms in 10 patients and greater than 120 ms in all but 2 patients. Comparison of mean CO for the optimized, worst, and nominal (120-ms) AVD settings showed significant differences among groups ($P < .001$). In pairwise comparisons mean CO was different in both the optimum and worst groups compared with that at an AVD of 120 ms. BiVP with the optimum AVD differed from the worst AVD ($P < .001$), with a mean increase in CO of 14% (range, 2%–34%). The optimal AVD differed from an AVD of 120 ms ($P < .001$), with a mean increase in CO of 7% (range, 0%–34%).

VVD optimization after AVD optimization yielded significant differences in CO when comparing the optimum, worst, and nominal (0-ms) VVD settings ($P < .001$, Figure 4). In pairwise comparisons both the optimum and worst VVDs differed from the nominal VVD. BiVP with the optimum VVD differed from the worst VVD ($P < .001$), increasing CO by 10% (range, 4%–29%), and from the nominal VVD ($P < .001$), increasing CO by 5.0% (range, 0%–29%).

Distributions of optimal and worst AVDs and VVDs are shown in Figures E1 and E2, respectively. An AVD of 90 ms yielded the lowest CO in the majority of patients. In all but 2 patients, the optimal AVD was greater than 120 ms, and in 3 patients an AVD of 120 ms was the worst setting. VVD optimization resulted in a pattern of optimum and worst VVD settings, ranging from RV-first to LV-first pacing, likely reflecting heterogeneity in the types of IVCD among patients. In 2 patients the nominal VVD yielded the lowest CO.

Comparison of optimized BiVP with AAI and NSR is shown in Figure 5. The differences among the 3 groups were significant ($P = .003$), as were pairwise comparisons between optimized BiVP versus AAI and NSR ($P = .003$ and .019, respectively). Optimized BiVP resulted in an increase in mean CO by 13% versus AAI at the same heart rate (CO of 5.5 ± 0.6 vs 4.9 ± 0.6 L/min) and by 10% versus NSR (5.0 ± 0.5 L/min). The paced heart rate was greater in the BiVP and AAI groups (97 ± 3 beats/min) compared with that seen in the NSR group (80 ± 4 beats/min, $P < .001$).

DISCUSSION

Defining the best modality and method for permanent BiVP optimization to improve BiVP response rates and heart failure outcomes is an active area of investigation. To our knowledge, the BiPACS trial is the first randomized clinical trial to assess the role of temporary BiVP optimization at multiple time points in the perioperative cardiac surgery setting. In this substudy, which focused on intraoperative BiVP in the immediately post-CPB period, we found that BiVP optimization increased CO compared with both AAI and NSR (no pacing), with significant contributions from optimization of both AVD and VVD (Figure 4). The difference in CO between the best and worst

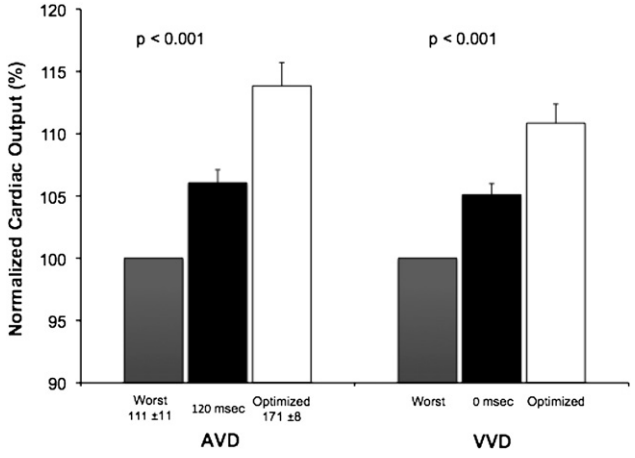

FIGURE 4. Biventricular pacing optimization profiles for atrioventricular delay *(AVD)* and interventricular delay *(VVD)*. Mean cardiac outputs are normalized to a scale of 100, with the worst parameter as the reference group. *Error bars* depict 1 standard error of the mean.

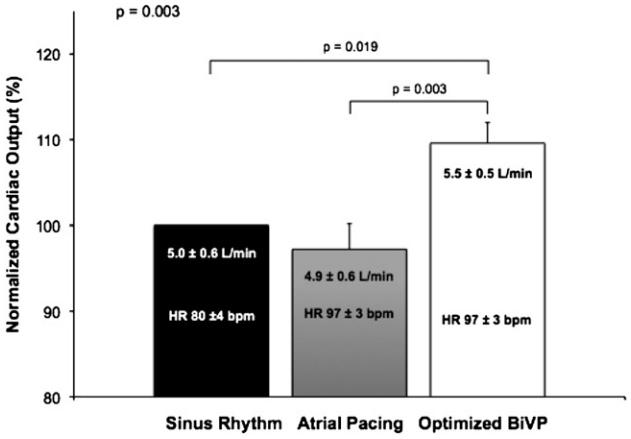

FIGURE 5. Comparison of cardiac output with optimized biventricular pacing *(BiVP)* versus right atrial pacing or sinus rhythm. *Error bars* depict 1 standard error of the mean. *HR*, Heart rate.

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settings was considerable, ranging as high as 34% in an individual patient. Moreover, in 5 patients programming a nominal AVD or VVD resulted in the least effective BiVP setting, which supports a rationale for routine optimization in all patients undergoing temporary BiVP.

AVD optimization represents a balance between optimizing LV filling and atrial emptying and minimizing diastolic mitral regurgitation. Nominal out-of-the-box AVD settings are typically programmed to short intervals, such as 120 ms, to ensure biventricular capture. However, empiric use of short AVDs might routinely underestimate the optimal AVD.[28] Longer intrinsic paced AVDs in the post-CPB period allowed for testing of AVDs greater than or equal to 240 ms in the majority of patients. AVD optimization alone resulted in a 14% increase in CO between the best and worst settings and a 7% increase compared with an AVD of 120 ms. In all but 2 patients, the optimum AVD was longer than 120 ms (see Figure E1). Indeed, in the immediate post-CPB period, factors contributing to impaired diastolic function, such as myocardial ischemia and edema, might necessitate the use of longer AVDs in patients with impaired LV function. In this study atrio-BiVP was achieved by pacing from the RA. RA pacing alters interatrial delay and the timing of left atrial–LV contraction, which implies that the optimum AVD would differ in right atrially paced, biatrially paced, and atrially sensed BiVP modes.[29,30]

Modulation of VVD has been shown to reduce ventricular dyssynchrony and improve hemodynamic parameters.[9,10] In the present study VVD optimization increased CO by 10% and 5% compared with the worst and nominal settings, respectively, underscoring the additional benefit of VVD optimization, even after AVD has been optimized. Whether the sequence in which AVD and VVD are optimized affects the determination of optimized BiVP parameters is uncertain and warrants further study.

Optimized BiVP improved CO by 13% compared with AAI at the same heart rate, indicating that the mechanism of hemodynamic benefit in BiVP was not explained solely by an increased paced rate compared with the patient's intrinsic sinus rate (Figure 5). This finding is consistent with previous studies of temporary BiVP.[13,17]

In this study the mean preoperative LVEF (33.4%) was higher and the mean QRS (115.7 ms) was narrower than in permanent BiVP trials (see Table E1).[2-5] Although the criteria for permanent BiVP implantation are established,[1] the predictors of acute response to temporary perioperative BiVP have yet to be defined and are an area of ongoing investigation. Cardiac surgery and extracorporeal circulation cause transient myocardial depression and edema and might exacerbate conduction abnormalities. Patients with preexisting LV dysfunction are among the highest-risk cardiac surgery patients and are an appropriate group in which to assess the benefit of temporary BiVP. Recent evidence suggests that ambulatory patients with CHF and narrow QRS complexes do not benefit from permanent BiVP, despite exhibiting echocardiographic evidence of dyssynchrony.[31] Whether this applies to temporary perioperative BiVP remains to be seen, especially in a heterogeneous population of ischemic and valvular cardiac surgery patients.

The mechanism by which BiVP acutely reduces dyssynchrony and improves hemodynamics is not fully understood, particularly in perioperative ventricular failure. We have previously described animal models of acute right- and left-sided heart failure and found BiVP to be beneficial in those settings.[32-34] The mechanism of action appears to be synchronization of pressure development across the interventricular septum, which allows the less impaired ventricle to assist the failing one.[34] These findings provide a further rationale for studying temporary BiVP in the perioperative setting and will serve as a guide for future studies examining the mechanism behind the effect demonstrated in this study.

Another area of uncertainty lies in selecting the best metric by which to assess BiVP optimization, including measures of ventricular dyssynchrony, mitral inflow, stroke volume, and dP/dt_{max}. The present study optimized BiVP based on CO, which is an important short-term end point for end-organ perfusion, particularly in critically ill postoperative patients with low output states. Further study is needed to evaluate the relationship between hemodynamic responses to temporary BiVP, changes in ventricular synchrony, and patients' outcomes.

Outcomes data, including morbidity, mortality, intensive care unit length of stay, and hospital costs are important secondary objectives of the BiPACS trial. Although the absolute changes in CO reported here during BiVP are relatively modest, the clinical effect might be important if amplified by a reduced requirement for β-agonists and vasopressors, with secondary improvements in peripheral organ function, fluid requirements, and incidence of arrhythmias.

Accumulating data indicate differences between patients in the BiPACS trial and those undergoing permanent BiVP for chronic heart failure. The optimal BiPACS trial protocol changes over time, and the effect also changes, with benefits being primarily rate related on postoperative day 1 but primarily related to stroke volume increases in the early post-CPB period. Absolute increases in CO during BiVP also tend to be larger in BiPACS trial patients with higher preoperative ejection fractions, contradicting observations made in patients with chronic heart failure.[35] These differences suggest that the effects of BiVP in BiPACS trial are primarily mediated through effects on reversible myocardial injury rather than chronic dysfunction. These differences provide a rationale for expanding the selection of patients in our trial beyond the current recommendations for permanent BiVP. Digital transesophageal echocardiographic data capable of defining changes in regional wall motion abnormalities is an important research goal of the BiPACS trial.

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The BiPACS trial is being done under an Investigational Device Exemption from the Food and Drug Administration because, as this is written, there is no biventricular pacemaker approved for temporary pacing in the operating room. Similarly, until our trial is completed, we will not have definitive information regarding optimum LV lead locations. Empirically, temporary BiVP can be implemented by adding a temporary bipolar lead configuration to the lateral basal segment of the LV. These leads can be connected to the output terminals of a standard external temporary pacemaker in conjunction with bipolar temporary RV leads connected to the same terminals. This will result in BIVP with a VVD of zero. AVD can then be optimized empirically by using mean aortic pressure or aortic flow criteria. Our current observations indicate that the optimum AVD might be as long as 300 ms in the early postoperative period, particularly in patients with atrial latency in excess of 100 ms (Rusanov et al, unpublished data).

In conclusion, optimization of temporary BiVP improves CO in patients undergoing cardiac surgery with preoperative evidence of LV systolic dysfunction and an IVCD. Individualized optimization of AVD and VVD each contributes to the overall benefit of optimized BiVP, and optimization should be considered a routine step in temporary BiVP protocols. Temporary BiVP to treat low output states after cardiac surgery is a promising area of investigation. Further studies with larger numbers of patients will better define patient selection criteria and refine optimization techniques.

We thank the BiPACS trial patients and investigators and the Columbia University Division of Cardiothoracic Surgery for their participation. Lauren Bedrosian, our study coordinator 2009–2010, and Giselle Brown provided important assistance with manuscript preparation.

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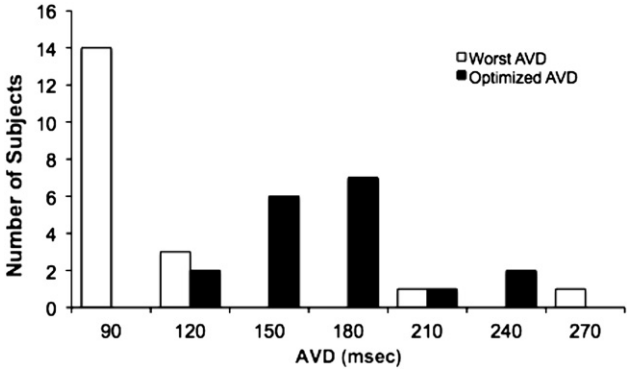

FIGURE E1. Distribution of optimal and worst atrioventricular delay *(AVD)* settings determined during AVD optimization.

TABLE E1. Baseline characteristics

No. of patients	
Total	20
Optimization analysis	20
Optimized BiVP vs AAI vs sinus rhythm	13
Age (y ± SD)	67.6 ± 12.2
Ejection fraction (% ± SD)	33.4 ± 15.4
QRS duration (ms ± SD)	115.7 ± 19.1
Male sex (%)	75
Type of operation	
CABG/AVR, CABG/MVR, CABG/AVR/MVR	9
AVR/MVR	5
CABG	3
AVR	3

BiVP, Biventricular pacing; *AAI*, atrial pacing; *SD*, standard deviation; *CABG*, coronary artery bypass grafting; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement or repair.

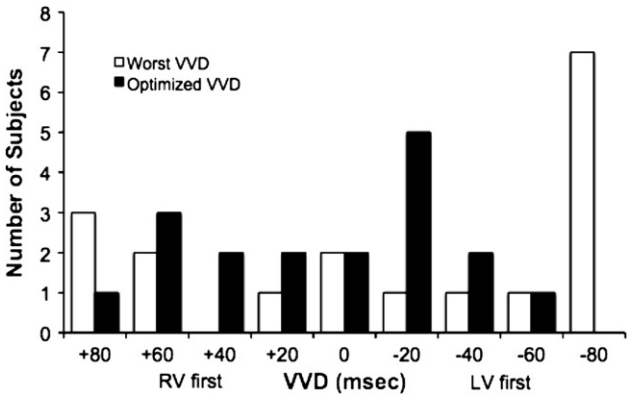

FIGURE E2. Distribution of optimal and worst interventricular delay *(VVD)* settings determined during VVD optimization. *LV*, Left ventricle; *RV*, right ventricle.

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