Feasibility of Temporary Biventricular Pacing after Off-Pump Coronary Artery Bypass Grafting in Patients with Reduced Left Ventricular Function

In selected patients undergoing cardiac surgery, our research group previously showed that optimized temporary biventricular pacing can increase cardiac output one hour after weaning from cardiopulmonary bypass. Whether pacing is effective after beating-heart surgery is unknown. Accordingly, in this study we examined the feasibility of temporary biventricular pacing after off-pump coronary artery bypass grafting.

The effects of optimized pacing on cardiac output were measured with an electromagnetic aortic flow probe at the conclusion of surgery in 5 patients with a preoperative mean left ventricular ejection fraction of 0.26 (range, 0.15–0.35). Atrioventricular (AV) and interventricular (IV) delay settings were optimized in randomized order.

Cardiac output with optimized biventricular pacing was 4.2 ± 0.7 L/min; in sinus rhythm, it was 3.8 ± 0.5 L/min. Atrial pacing at a matched heart rate resulted in cardiac output intermediate to that of sinus rhythm and biventricular pacing (4 ± 0.6 L/min). Optimization of atrioventricular and interventricular delay, in comparison with nominal settings, trended toward increased flow.

This study shows that temporary biventricular pacing is feasible in patients with preoperative left ventricular dysfunction who are undergoing off-pump coronary artery bypass grafting. Further study of the possible clinical benefits of this intervention is warranted.

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Cardiac resynchronization therapy in the form of biventricular pacing (BiVP) results in long-term improvements in left ventricular (LV) function and in heart-failure morbidity and mortality rates.1-4 Consequently, it has become the standard of care for select patients with advanced congestive heart failure (CHF), reduced LV function, and intraventricular conduction delay (IVCD).5 Biventricular pacing acutely raises stroke volume and maximal first derivative of pressure (dP/dt max) and reduces intraventricular dyssynchrony, without increasing myocardial oxygen consumption.6,7 Accordingly, considerable interest has developed in regard to the acute hemodynamic effects of temporary BiVP in patients at risk of low-output states after cardiopulmonary bypass (CPB).8-24

In patients with reduced preoperative LV function and IVCD, we recently reported a 10% to 13% increase in intraoperative cardiac output when BiVP was performed after weaning those patients from CPB.24 It was also shown that the benefit of BiVP was amplified by the optimization of pacemaker settings such as atrioventricular delay (AVD) and interventricular delay (VV). Whether these effects extend to patients who undergo surgery without CPB and cardioplegic arrest is unclear. Accordingly, we evaluated the effects of temporary BiVP on cardiac output in patients undergoing off-pump coronary artery bypass grafting (CABG). We compared optimized BiVP to right atrial pacing (AAI) and to sinus rhythm.

Patients and Methods

Patients were recruited from November 2007 through November 2008. Nine patients were enrolled, 5 of whom were studied. Two patients were not studied because of conversion to on-pump CABG, and 2 others were not studied at the attending surgeon’s discretion. Baseline clinical characteristics are shown in Table I. Mean patient
age was 69 years (range, 59–74 yr); LV ejection fraction (LVEF), 0.26 (range, 0.15–0.35); and QRS duration, 114 ms (range, 100–140 ms).

The study protocol was approved by the Columbia University Medical Center Institutional Review Board. Adult patients scheduled for elective off-pump CABG were screened for eligibility. All subjects provided written, informed consent. Inclusion criteria included a preoperative LVEF of $\leq 0.40$ and a QRS duration of $\geq 100$ ms. Exclusion criteria included 2nd- or 3rd-degree atrioventricular block, sinus tachycardia exceeding 120 beats/min, atrial fibrillation, congenital heart disease, or intracardiac shunts. Preoperative data obtained by chart review included LVEF, as measured by echocardiogram or left ventriculogram; heart rhythm; QRS duration; conduction blocks from electrocardiogram tracings; and demographic information.

**Optimization Protocol**

Temporary epicardial pacing leads were attached to the right atrial appendage, to the anterior right ventricle (RV), and to 2 randomized sites of 6 possible sites on the LV. The first site, LV1, was either a basal obtuse marginal site or a circumflex site. The other site, LV2, was selected at random, as disclosed by a randomization form, from any of 4 locations—the apex of the heart, the inferior medial aspect, the inferior lateral aspect, or the posterior descending artery. In the final analysis, we used data collected from LV1. The leads were connected to an InSync® III cardiac resynchronization therapy (CRT) pacemaker (Medtronic, Inc.; Minneapolis, Minn) mounted in an external housing unit; adequate sensing and pacing were confirmed. At the conclusion of CABG, an electromagnetic flow probe (Carolina Medical Electronics, Inc.; King, NC) was placed on the ascending aorta. Electrocardiographic, arterial pressure, and aortic flow data were acquired with a PowerLab analog-to-digital converter (ADInstruments, Inc.; Colorado Springs, Colo) and recorded on a personal computer (Fig. 1). Aortic flow tracings were integrated over 1 respiratory cycle to determine cardiac output with the aid of MacLab software (ADInstruments) and custom-designed routines in MATLAB® (The MathWorks, Inc.; Natick, Mass).

Biventricular-pacing optimization was conducted during stable dosing of vasoactive medications and fluids, as described previously.24–25 The pacing rate was held constant at 90 beats/min. Atrioventricular-delay optimization was performed by varying AVD in randomized order over 10-second intervals from 90 to 270 ms in 30-ms increments, while VVD was held constant at 0 ms. Only AVDs shorter than the patient’s intrinsic atrioventricular interval during atrial pacing were tested. Each setting was tested twice. Interventricular-delay optimization using the optimal AVD was performed by varying VVD from –80 ms (LV first) to +80 ms (RV first) in randomized order in 20-ms increments. Optimized BiVP was defined as the combination of AVD and VVD producing the maximum cardiac output. Optimized BiVP (DDD 90) was then compared with atrial pacing (AAI 90) and with sinus rhythm over 30-second intervals, in randomized order. This protocol, described in detail previously in the Biventricular

**TABLE I. Baseline Clinical and Operative Characteristics of the 5 Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Preoperative LVEF</th>
<th>QRS (ms)</th>
<th>Conduction Delay</th>
<th>No. of Distal Anastomoses</th>
<th>Arterial Conduit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>M</td>
<td>0.35</td>
<td>100</td>
<td>IVCD</td>
<td>4</td>
<td>BIMA</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>0.20</td>
<td>102</td>
<td>LAFB</td>
<td>3</td>
<td>LIMA</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>0.15</td>
<td>128</td>
<td>LBBB</td>
<td>1</td>
<td>LIMA</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>M</td>
<td>0.35</td>
<td>140</td>
<td>RBBB</td>
<td>4</td>
<td>LIMA</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>M</td>
<td>0.25</td>
<td>102</td>
<td>IVCD</td>
<td>3</td>
<td>LIMA</td>
</tr>
</tbody>
</table>

BIMA = bilateral internal mammary arteries; F = female; IVCD = nonspecific intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LIMA = left internal mammary artery; LVEF = left ventricular ejection fraction; M = male; RBBB = right bundle branch block.

![Fig. 1](image-url) From a representative patient: intraoperative recordings during biventricular-pacing optimization. Change in pacemaker settings (at the horizontal center) is associated with changes in the electrocardiogram and in hemodynamics.
Pacing After Cardiac Surgery (BiPACS) trial,\textsuperscript{24} required a total of 7.5 minutes of testing.

\section*{Statistical Analysis}

Descriptive statistics were calculated for demographic information and for BiVP optimization data. In comparison of AAI, BiVP, and no pacing, cardiac output was normalized as percent change versus no pacing. For the evaluation of cardiac output changes during AVD optimizations (Fig. 2), the lowest cardiac output value was determined for each patient during the optimization run, and the remaining data were expressed as a percentage of this value. Statistical analysis was performed with SAS 9.2 software (SAS Institute, Inc.; Cary, NC).

\section*{Results}

Atrioventricular-delay optimization yielded optimal AVDs, ranging from 120 to 210 ms (mean, 162 ms; Table II). The worst AVDs tended to be at the extreme of the tested settings (90 ms in 3 patients, 270 ms in 1 patient, and 210 ms in 1 patient). The effect of AVD on normalized cardiac output is illustrated in Figure 2. The curve is relatively flat in the range of 150 to 180 msec, the change averaging less than 1%. Optimization was associated with trends in cardiac output noted among the best, worst, and nominal (AVD 120 ms) settings. There was a trend toward increased cardiac output with the best versus nominal AVD, and a trend toward increased cardiac output with the best versus the worst AVD.

Interventricular-delay optimization after optimizing AVD resulted in optimal VVDs ranging from –60 ms (LV first) to +40 ms (RV first; Table II). The worst VVDs ranged from –80 to +80 ms. There was a trend toward slightly increased cardiac output with optimized VVD compared to nominal VVD.

Optimized BiVP resulted in a mean cardiac output of 4.2 ± 0.7 L/min (mean ± SEM), compared with sinus rhythm (3.8 ± 0.5 L/min) and with AAI pacing (4 ± 0.6 L/min) (Fig. 3). In all patients, optimized BiVP resulted in a comparable or higher cardiac output than did other pacing modes (Fig. 4). Post hoc pairwise comparisons showed trends toward increased cardiac output with optimized BiVP in comparison with sinus rhythm and with AAI pacing at a matched heart rate (Table II). The mean heart rate during sinus rhythm was 65 beats/min (range, 56–76 beats/min), while all patients were paced at 90 beats/min during AAI pacing and BiVP.

No adverse events, including arrhythmias, bleeding, hemodynamic instability, or aortic injury, occurred during testing.

\section*{Discussion}

Despite improvements in perioperative management, LV dysfunction remains a strong predictor of low-output syndrome after cardiac surgery.\textsuperscript{26} Perioperative use of inotropic agents to increase cardiac output has been linked to increased cardiac morbidity and mortality rates.\textsuperscript{27} In light of this, temporary BiVP has emerged as a promising procedure to support cardiac output and improve hemodynamics after weaning from CPB.\textsuperscript{8–24} Possible mechanisms of action include optimizing ventricular filling or reversing ventricular dysynchrony and depressed contractility\textsuperscript{13,22,28} after the ischemia and reperfusion associated with CPB.

Off-pump CABG also involves recovery from ischemia-reperfusion injury, although the inflammatory effects of CPB are minimized.\textsuperscript{29,30} To our knowledge, the present study is the first to test the intraoperative effects of optimized BiVP after beating-heart surgery. Although our cohort of patients was small, we found that optimized BiVP after off-pump CABG resulted in cardiac output in all patients comparable to or higher than the output associated with either sinus rhythm or atrial pacing (Figs. 3 and 4). An increase in cardiac output of approximately 10%, seen in other studies,\textsuperscript{9,24,26} is similar to that seen in our studies of intraoperative BiVP optimization in patients within an hour of CPB for cardiac surgery. In the present study, heart rates increased by pacing improved cardiac output; whereas in patients undergoing on-pump surgery, any benefits from increasing heart rate appeared to be offset by decreases in stroke volume,\textsuperscript{26} which possibly indicates a need for longer diastolic filling times in those patients.

Our findings underscore the importance of pacing optimization and its potential to maximize the effect of BiVP. Cardiac output was changed by 5% to 17% sim-
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PLY by altering AVD timing. In studies of permanent CRT, suboptimal AVD selection was found to reduce cardiac output by up to 15%. As in treating patients after CPB, the “out-of-the-box” AVD frequently used in permanent CRT devices (i.e., 120–130 ms) was found to be suboptimal, and a longer AVD (mean, 174 ms) was needed to optimize cardiac output. This might reflect a postoperative increase in interatrial conduction delay, necessitating longer AVDs to optimize left atrial–LV contraction timing. Biatrial pacing might shorten the optimal AVD by minimizing interatrial conduction delay. Atrial latency has prolonged optimal AVD in earlier studies that used right atrial but not left atrial leads. The potential benefits of biatrial pacing were not examined in the present study because of resistance to left atrial leads among our surgical teams and institutional review board.

Additional questions about our protocol concern our preference for basal rather than apical sites in the design and final data analysis. The medical literature supports potential advantages of both apical and basal sites. In the BiPACS trial, basal sites were superior to other sites 14:2 in head-to-head comparison, but that trial was inadequately powered to resolve this question. A much larger study will ultimately be needed to resolve this issue.

The optimization of atrioventricular delay contributed the predominant benefit of BiVP optimization in this study. Atrioventricular-delay optimization not only affects ventricular filling but might reduce intraventricular dyssynchrony via fusion with intrinsic conduction. Indeed, after optimizing AVD, simultaneous BiVP (VVD, 0 msec) appeared to be as effective as sequential BiVP (optimized VVD).

Further work is needed to refine the patient-selection criteria for BiVP after cardiac surgery. Prior studies in a diverse range of patient populations and operations have
revealed a variable response to postoperative BiVP. Patients with chronic cardiomyopathy and low LVEF are more predictable and are likely to develop QRS prolongation or dyssynchrony and to respond to permanent BiVP. The effects of temporary BiVP early after routine cardiac surgery could involve unusual mechanisms. Our BiVP studies to date have not manifested the regional dyssynchrony seen in other populations during the early postoperative period. Acute heart failure might be ameliorated by pressure support from the uncompromised ventricle transmitted across the interventricular septum. Furthermore, the effects of temporary BiVP have been shown to change over time in the early post-bypass period, both in our studies and in those of others. This supports the view that the pathophysiology of BiVP after cardiac surgery involves ischemia-reperfusion injury, rather than chronic dyssynchrony.

No correlation between BiVP response and preoperative QRS duration or type of conduction delay was seen in study (Tables I and II). Of note, recent data from studies of permanent CRT suggest that traditional CRT criteria cutoffs for LVEF, QRS duration, and New York Heart Association functional class might be suboptimal predictors of CRT benefit. The BiPACS trial is attempting to determine whether changes in contractility and systemic resistance after responsiveness to BiVP therapy over 24 hours after CPB.

Our study is limited by small sample size. Although our patients were selected for their reduced preoperative LVEF, the mean postoperative cardiac output during sinus rhythm was relatively good at 3.8 L/min with minimal vasoactive medication (Table II). The present study was designed for feasibility testing over 7.5 minutes. Formal clinical trials are indicated when appropriate U.S. Food and Drug Administration-approved perioperative pacemakers become available. Pacing should be maintained as long as patients require inotropic support. Biventricular-pacing optimization can be affected by chest closure, depth of anesthesia, and positive-pressure ventilation. For this reason, an automatic, self-optimizing pacemaker should be a clinical goal.

In conclusion, in patients who manifested reduced preoperative LVEF and IVCD before undergoing off-pump CABG, optimization of temporary postoperative BiVP resulted in trends toward increased cardiac output. Our data indicate that the role of temporary BiVP after off-pump CABG warrants further study.

**Acknowledgments**

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**References**


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