Primary Endpoints of the Biventricular Pacing After Cardiac Surgery Trial

Henry M. Spotnitz, MD, Santos E. Cabreriza, MBA, Daniel Y. Wang, MD, T. Alexander Quinn, PhD, Bin Cheng, PhD, Lauren N. Bedrosian, BA, Linda Aponte-Patel, MD, and Craig R. Smith, MD

Department of Surgery, Columbia Presbyterian Medical Center, New York, New York; Department of Physiology and Biophysics, Dalhousie University, Halifax, Nova Scotia, Canada; Department of Biostatistics, Mailman School of Public Health of Columbia University, New York, New York; and University of Massachusetts Medical School, Worcester, Massachusetts

Temporary postoperative pacing can affect recovery from cardiac surgery by heart rate acceleration [1, 2] and cardiac resynchronization [1–4]. Cardiac resynchronization (CRT) is a well-established treatment for congestive heart failure with dilated cardiomyopathy affecting the left ventricle (LV) [5–9]. Clinical indications for resynchronization with “permanent” biventricular pacing (BiVP) include LV ejection fraction (EF) depressed to 0.35 or less and QRS duration (QRSd) greater than 120 milliseconds [5–10]. While many possible mechanisms exist for resynchronization efficacy, the mechanism in dilated cardiomyopathy appears to be a reversal of regional LV dyssynchrony due to delayed electrical conduction and myocardial fibrosis [11–13]. Biventricular pacing synchronizes atrial and ventricular contraction with programmable interventricular delay (AVD) and synchronizes pacing of the right ventricle and LV free wall with programmable interventricular delay (VVD). BiVP usually employs endocardial leads in the right atrium, apex of the right ventricle, and LV free wall through the coronary sinus. Effective CRT reverses LV remodeling, increases stroke volume, decreases mitral regurgitation [11], and may or may not decrease QRSd [12, 13] without increasing myocardial oxygen consumption [14]. Development of BiVP involved surgically implanted epicardial leads [15], and surgical investigators have examined benefits of temporary BiVP for LV dysfunction after cardiopulmonary bypass with mixed results [3, 4, 16–28]. However, aside from limited examination of lead location [18, 24, 28] and VVD [25], formal optimization of BiVP had not been attempted in temporary pacing. We initiated the Biventricular Pacing after Cardiac Surgery (BiPACS) trial hoping that optimization would improve
the results of temporary postoperative BiVP and improve understanding of high nonresponse rates in permanent CRT [29–31].

**Patients and Methods**

The BiPACS protocol was conducted at the Columbia University Medical Center between April 1, 2007 and February 29, 2012. A substudy at the University of California at Los Angeles contributed 3 completed studies with endpoints. Our study protocol was approved by the Columbia Institutional Review Board and was conducted under an Investigational Device Exemption from the Food and Drug Administration. We have described details of recruitment [3, 13, 32] and phase I [3], II [4], and III [3, 13, 32] testing, summarized below.

---

**Fig 1. Biventricular Pacing after Cardiac Surgery trial protocol.** Pacing was optimized 1 hour after weaning from bypass (phase I), 1 hour later after chest closure (phase II), and on the day after (phase III). Patients were randomized after phase I. Optimization included 7 atrioventricular delays, 6 LV lead locations, and 9 interventricular delays. Each parameter was tested for 10 (phase I), 20 (phase II), or 30 seconds (phase III) in duplicate and random sequence. Optimization parameters: aortic flow in phase I, mean arterial pressure in phase II, and mean arterial pressure followed by cardiac index in phase III. Primary endpoint: thermal dilution cardiac index prior to phase III. (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 = tricuspid dysplasia.)

---

**Fig 2. Biventricular Pacing after Cardiac Surgery trial epicardial temporary pacing sites.** (A) Anterior view. (B) Posterior view. (Circ = circumflex; IL = inferolateral; IM = inferomedial; OM = obtuse margin; PDA = posterior descending artery; RA = right atrium; RV = right ventricle; All locations except for RA and RV are left ventricular (LV) pacing sites; black labelled LV sites are LV1 group; yellow labels identify LV2 group.)
Adult patients undergoing elective open-heart surgery on cardiopulmonary bypass were screened for eligibility to enroll. All gave written, informed consent prior to the day of surgery, obtained by qualified study coordinators and investigators, with permission of the attending surgeon.

Preoperative data included the following: LVEF, by echocardiogram or left ventriculogram. Also included were heart rhythm, QRSd, and intraventricular blocks by electrocardiogram; surgery performed; and demographics.

Inclusion criterion No.1 was symptomatic surgical heart disease with LVEF 0.40 or less, and QRSd 100 milliseconds or greater. Alternatively, patients undergoing combined mitral and aortic valve surgery qualified, irrespective of LVEF or QRSd. Exclusion criteria included atrial fibrillation, second- or third-degree atrioventricular block, congenital heart disease, intracardiac shunts, or...

Table 1. Patient Characteristics, BiPACS Trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Patients (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>68 ± 11</td>
</tr>
<tr>
<td>Ejection fraction (±SD)</td>
<td>0.32 ± 0.14</td>
</tr>
<tr>
<td>QRS duration (msec ± SD)</td>
<td>119 ± 25</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>74</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, SOC/BiVP</td>
<td>2:23/2:22</td>
</tr>
<tr>
<td>Aortic cross-clamp time, SOC/BiVP</td>
<td>1:22/1:30</td>
</tr>
<tr>
<td>Type of surgery:</td>
<td></td>
</tr>
<tr>
<td>CABG/AVR, CABG/MVR, CABG/AVR/MVR, CABG/AVR/MVR/TVR</td>
<td>19</td>
</tr>
<tr>
<td>AVR/MVR, AVR/TVR, MVR/TVR</td>
<td>16</td>
</tr>
<tr>
<td>CABG</td>
<td>16</td>
</tr>
<tr>
<td>AVR</td>
<td>9</td>
</tr>
<tr>
<td>MVR</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative complications*</td>
<td></td>
</tr>
<tr>
<td>Biventricular Pacing (BiPACS)</td>
<td>10/30</td>
</tr>
<tr>
<td>Standard of Care (SOC)</td>
<td>10/31</td>
</tr>
<tr>
<td>30-day surgical mortality rate</td>
<td></td>
</tr>
<tr>
<td>Biventricular Pacing (BiPACS)</td>
<td>6.5%</td>
</tr>
<tr>
<td>Standard of Care (SOC)</td>
<td>0%</td>
</tr>
<tr>
<td>Pacing failure</td>
<td>12/61</td>
</tr>
</tbody>
</table>

* Sepsis/infection, renal failure, respiratory failure/complications, bleeding requiring reoperation, cerebrovascular accident.

AVR = aortic valve surgery; BiPACS = biventricular pacing after cardiac surgery; BivP = biventricular pacing; CABG = coronary artery bypass; MVR = mitral valve surgery; SOC = standard of care; TVR = tricuspid valve surgery.
heart rate greater than 120 beats/minute after bypass [3, 4, 13, 32–34].

**Study Design and Optimization Protocol**

The study protocol is illustrated in Figure 1. On bypass, temporary epicardial pacing leads were sewn to the right atrial appendage, anterior right ventricle, and 2 of 6 possible LV sites (Fig 2). Randomization and testing were defined by forms in sealed envelopes. These forms, prepared prior to enrollment of the first patient, also assigned LV1 to the basal LV obtuse margin or distal circumflex region. The LV2 was (1) basal near the posterior descending artery, midway from apex to base (2) medial or (3) lateral, or (4) at the LV apex. This was based on previous studies [18]. The LV1 was used preferentially during phase I. An InSync III biventricular pacemaker (Medtronic, Inc, Minneapolis, MN) was used for pacing, and electromagnetic (Carolina Medical Electronics, East Bend, NC) or ultrasonic (Transonics Systems Inc, Ithaca NY) probes measured aortic flow [35–37].

Biventricular pacing optimization was conducted after separation from bypass and stabilization, usually after protamine administration. Pacing rate was 90 beats per minute or 10 beats per minute above intrinsic atrial rate. In phase III, intrinsic heart rate was also optimized. Aortic flow, arterial pressure, and electrocardiogram lead II were digitized and recorded [2, 3]. Parameters were tested twice over 10-second intervals. The AVD was optimized first at the paced atrial rate and VVD = 0 milliseconds. Seven AVDs were tested between 90 to 270 milliseconds with 30 millisecond increments. The optimum AVD was selected graphically, based on flow. Optimization of 3 pacing sites and 9 VVDs were conducted similarly [3, 13, 32]. The validated AVD, VVD, and pacing site defined an optimum protocol, which was compared with atrial pacing and no pacing over 30-second intervals. The aortic flow probe was then removed, and the temporary pacing leads were externalized.

Stable patients with properly functioning BiVP were then randomized to BiVP or standard of care. Randomly permuted blocks of 4, 6, and 8 were used, with a treatment allocation ratio of 1:1.

Pacing in BiVP patients continued until phase II optimization, conducted in all patients during or after chest closure using mean arterial pressure. Optimization was similar to phase I, with testing intervals increased to 20
The newly optimized protocol was then applied to BiVP patients [4, 33] until phase III on the first postoperative day. The clinical endpoint, cardiac index, was measured by thermal dilution immediately prior to phase III testing. Five cardiac outputs were measured. The highest and lowest were discarded. The remaining 3 were averaged and divided by body surface area to determine cardiac index.

Phase III testing was conducted in the intensive care unit over 3 hours, using mean arterial pressure and 30-second intervals. Testing was expanded to include intrinsic heart rate. The newly defined optimum was tested against atrial pacing and no pacing, using thermal dilution cardiac output. Phase III results are currently in review. At the conclusion of phase III, research equipment was removed, cleaned, and sterilized. Temporary wires were removed by the clinical management team. The protocol allowed continuation of pacing, but this was not requested.

Statistical Analysis
Differences in cardiac index between groups were assessed by an independent 2-sample t test. Differences in mean arterial pressure between the optimized BiVP and no pacing in phases I, II, and III were assessed by paired t test. Statistical analysis was performed with SAS 9.1 software (SAS Institute, Inc, Cary, NC).

Study Termination and Patient Population
Our trial was terminated on February 29, 2012 for slow accrual (Fig 3) prior to reaching the endpoint target of 196. Our Consolidated Standards of Reporting Trials diagram is presented in Figure 4. Population characteristics are in Table 1. Screening involved 6,346 patients at the Columbia University Medical Center and the University of California at Los Angeles. This identified 682 eligible patients. We enrolled 111 patients and studied 47 in phase I, 43 in phase II, and 27 in phase III. Sixty-one patients were randomized, and 47 endpoints were analyzed.

Patients were excluded for missing LVEF (1,116), QRSd (668), or both (353). At Columbia, LVEF and QRSd were available in 3,572. Criteria were met for LVEF in 2,749 (77%) and for QRSd in 1,813 (51%). Sixty-nine qualified because of planned combined aortic and mitral surgery alone. Other exclusions were preoperative arrhythmia or heart block (167), reoperation (136), planned off-pump surgery (43), other common exclusions (79), and physician refusal (80). Sixty-six patients declined.

Results
Bypass and cross-clamp times were not significantly different between groups (Table 1). Overall surgical mortality was 3.2%, morbidity was 33%; pacing failed in 20%. There were no unanticipated adverse events.

Cardiac index measurements are presented in Figure 5. Two data points are from the University of California at Los Angeles. Data groups include ALL patients (47), combined aortic-mitral surgery (15), aortic valve surgery with or without coronary bypass (10), mitral valve surgery with or without coronary bypass (8), and isolated coronary bypass (13). Overall, cardiac index was 12% higher in BiVP patients versus standard of care; not statistically significant ($p = 0.136$). Cardiac index was 60% higher in BiVP patients in the AVR subgroup ($p = 0.018$). Combining aortic valve and aortic and mitral surgery yielded 11 standard of care patients and 14 BiVP patients, with cardiac index 29% higher in BiVP patients ($p = 0.0138$, Fig 6).

Mean arterial pressure during post-optimization comparisons in all patients was significantly higher with BiVP than with no pacing (Fig 7). The benefit was 6.3% in
phase I, 3.1% in phase II, and 3% in phase III ($p = 0.0024$ by linear mixed effects testing).

**Comment**

The present results suggest that effects of temporary perioperative pacing on cardiac index are load dependent; aortic valve surgery patients most likely to benefit. We found BiVP ineffective after primary coronary bypass or primary mitral surgery, consistent with previous studies [16–28].

Increased cardiac index on the first postoperative day could reflect increased heart rate, LV resynchronization, or both. Our protocol does not distinguish these possibilities. Our current and previous BiPACS data [3] suggest that resynchronization is more important than heart rate in phase I, with rate effects of increasing importance in phase III [3].

Previous studies by others also suggest that BiVP benefit is maximal early after cardiopulmonary bypass, decreasing over the next 24 to 48 hours. Intrinsic QRSd reportedly decreases over the same time period [23], and our unpublished data concur with this. Decreasing QRSd and BiVP effectiveness after bypass suggest that ischemia-reperfusion injury [38] is involved in postsurgical efficacy of BiVP, rather than conduction-related dyssynchrony [12, 14, 28]. Interestingly, we and others have failed to demonstrate dyssynchrony in BiPACS responders by echocardiography, except in patients selected for preoperative dyssynchrony [28]. The pathophysiology of early post-bypass BiVP thus appears to be related to ischemia-reperfusion injury, distinct from mechanisms in permanent CRT; single ventricle may represent a unique exception to this argument [39].

Are the changes in cardiac index and mean arterial pressure in BiPACS clinically important? We have previously demonstrated decreasing vasoactive inotropic score and increased urine output with BiVP during phases I and II [33]. As yet unpublished observations of decreasing intrinsic heart rate in the BiVP group further suggest that pacing might suppress atrial and ventricular arrhythmias in the postoperative period. We plan further studies of secondary endpoints.

The mechanism of post-bypass BiVP benefits is undefined [18, 26, 28, 35, 40]. Previous studies reported pressure-volume loops during BiVP without optimization [18, 26]. Our laboratory studies suggest that BiVP can synchronize pressure development across the interventricular septum, bringing pressure work from the less compromised ventricle to the assistance of the distressed ventricle [35]. Those studies did not involve cardioplegia and cardioplegic arrest, however. The possibility remains that BiVP reverses effects of conduction delays and dysynchrony at the cellular level, analogous to effects of CRT at the macroscopic level. Resolution of this question requires further study.

The BiPACS trial [3, 4, 13, 32–34] and previous studies [16–28] suggest that future pacing research should focus on aortic valve surgery and should distinguish benefits of rate acceleration from resynchronization. This may confirm whether the complexity of BiVP is justified, or whether accelerated heart rate alone is sufficient.

Earlier BiPACS data suggest that VVD optimization is usually less important than AVD optimization [2, 34]. The optimum BiPACS AVD is 180 milliseconds, with a broad range [2, 3, 34]. We have not found important effects of lead location, although more sophisticated studies of this question are needed. Future studies of perioperative BiVP could potentially be conducted with standard temporary pacemakers, allowing AVD optimization but eliminating VVD optimization. This would reduce cost and complexity and eliminate the need for an investigational device exemption. Without such studies, it is not clear whether frequent AVD optimization is necessary. Self-optimizing temporary pacemakers currently in development could advance this area of investigation. Improved reliability of temporary pacing leads is needed, as 6 to 8 functional contacts are needed, reflected in 20% BiPACS pacing failure. A recommended configuration based on BiPACS would be bipolar leads on the right atrial appendage, anterior right ventricle, and LV obtuse margin of the LV, with heart rate 90 beats per minute, AVD 180 milliseconds, and VVD of zero. The AVD should

![Fig 6. Combined aortic valve and aortic and mitral valve surgery subgroup. Cardiac index is 29% higher with biventricular pacing. (BiVP = biventricular pacing; SOC = standard of care.)](image-url)
be optimized on arrival in the intensive care unit. If no effect of varying AVD between 90 and 240 milliseconds is demonstrable, 180 would be the logical choice.

In conclusion, cardiac index was not significantly increased by BiVP versus standard of care 18 hours postoperatively in the BiPACS trial. Cardiac index was 29% higher in an aortic valve surgery subgroup, and mean arterial pressure was higher with BiVP versus no pacing at 3 tested time points in all patients. The AVD optimization merits continuing and increased attention. Additional study is needed to distinguish rate and resynchronization effects. Our data indicate that clinical benefits are achievable in selected patients with well-designed postoperative pacing protocols.

This study was funded by National Institutes of Health RO1 HL080152 to Dr Henry Spotnitz. Dr Wang was supported by National Institutes of Health T32 HL007854. Dr Rusanov was supported by a Guidant Pacemaker fellowship and by National Institutes of Health Training Grant 5T32GM008464-17. Dr Henry Spotnitz is the George H. Humphreys, II, Professor of Surgery.

We gratefully acknowledge investigators at the Columbia site: Primary Investigators: George Berberian, MD, David Rabkin, MD, Marc Richmond, MD, Alex Rusanov, MD. Coordinators: Vinay Yalamanchi, BA, Ashley Whyte, BA, Lauren Maskin, MD, Brianne Blumenthal, MD, Suzanne Karl, BA, Alexandra Murata, BS, Mira Gendy, BS, Bryan Velez de Villa, BS, Max Cohen, Cecilia Basbus, MD, Wanda Tuong, BS. Additional Investigators: Cara Garofalo, MD, Josh Kanter, MD, Alistair Phillips, MD, John Artrip, MD, Alex Beyentovich, MD, Rabin Gerrarj, MD, Manoj Saxena, MD, Ajay Mirani, MD, Mathew Martinez, MD, Sean Mazer, MD, Michelle Spotnitz, MD, Alan Weinberg, MS, Vinod Havalad, MD, Steve Horwitz, MD, Robin Brusen, MS. CT Fellows: Mona Flores, MD, Steve Xydas, MD, Ryan Davies, MD, Jeff Morgan, M.D., Mark Russo, MD, Isaac George, MD, George Comas, MD. P&S Students: Catherine Albright, MD, Matthew Spotnitz, MD, Erin George, MD, Barry Breaux, BA, Jamal Shillingford, BA, Benjamin Rubinstein, BA, Huy Nguyen, BA. Jiagie Lu, BA. Other Students: Justin Booth, MS, Justin Bryyles, BS, Jon Kenny, MD, Jason Prasso, MD, Lauren Kelly, BA, Rana Sahar, BA, Chris Johnson, Casey Wong, MD, Giselle Brown, MS, Anthony Pensiero, Alice Wang, MD. Surgeons: Michael Argenziano, MD, Jonathan Chen, MD, Ralph Mosca, MD, Yoshifumi Naka, MD, Mehmet Oz, MD, Jan Quaegebeur, MD, Allan Stewart, MD, Mathew Williams, MD. Cardiologists: Allen Hordof, MD, Hasan Garan, MD, Jose Dizon, MD. Other Faculty: Jeffrey Holmes, MD, PhD, Alan Weinberg, MS, Eric Rose, MD. Administrators: May Deutsch, Isabel Leger, Erika Harris. Physician Assistants: Debra Savarese, PA.

University of California at Los Angeles: Principal Investigator: Richard J. Shemin, MD. Investigators: Reshma Biniwale, MD, Yousef Odeh, MD, Peyman Benharash, MD. Study Coordinators: Nancy Satou, RN, Shannon Aulakh, BS, Msagana Tamrat, BS, Tayeba Makiabi, BS.

References
and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. Circulation 2005;111:2146–50.