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Primary Endpoints of the Biventricular Pacing after Cardiac Surgery Trial

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Abstract

Background—To determine whether optimized biventricular pacing increases cardiac index in patients at risk of left ventricular dysfunction after cardiopulmonary bypass. Procedures included coronary artery bypass, aortic or mitral surgery and combinations. This trial was approved by the Columbia University Institutional Review Board and was conducted under an Investigational Device Exemption.

Methods—Screening of 6,346 patients yielded 47 endpoints. With informed consent, 61 patients were randomized to pacing or control groups. Atrioventricular and interventricular delays were optimized one (Phase I), two (Phase II), and 12–24 hours (Phase III) after bypass in all patients. Cardiac index was measured by thermal dilution in triplicate. Two-sample t-test assessed differences between groups and subgroups.

Results—Cardiac index was 12% higher (2.83 ± 0.16 (S.E.M.) vs. 2.52 ± 0.13 liters/minute/square meter) in the paced group, less than predicted and not statistically significant ($p=0.14$). However, when aortic and aortic/mitral surgery groups were combined, cardiac index increased 29% in the paced group (2.90 ± 0.19 , $n=14$) vs. controls (2.24 ± 0.15 , $n=11$) ($p=0.0138$). Using a linear mixed effects model, t-test revealed that mean arterial pressure increased with pacing vs. no pacing at all optimization points (Phase I 79.2 ± 1.7 vs. 74.5 ± 1.6 mmHg, $p=0.008$, Phase II 75.9 ± 1.5 vs. 73.6 ± 1.8 , $p=0.006$, Phase III 81.9 ± 2.8 vs. 79.5 ± 2.7 , $p=0.002$)

Conclusions—Cardiac index did not increase significantly overall but increased 29% after aortic valve surgery. Mean arterial pressure increased with pacing at three time points. Additional studies are needed to distinguish rate from resynchronization effects, emphasize atrioventricular delay optimization, and examine clinical benefits of temporary postoperative pacing.

Keywords

Pacemaker; CPB; Myocardium; Heart failure; Physiology/heart

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Introduction

Temporary postoperative pacing can affect recovery from cardiac surgery by heart rate acceleration [1,2] and/or cardiac resynchronization [1–4]. Cardiac resynchronization (CRT) is well-established treatment for congestive heart failure in patients 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 35% or less and QRS duration (QRSd) > 120 milliseconds [5–10]. While many possible mechanisms exist for resynchronization efficacy, the mechanism in dilated cardiomyopathy appears to be reversal of regional LV dyssynchrony due to delayed electrical conduction and myocardial fibrosis [11–13]. BiVP synchronizes atrial and ventricular contraction with programmable atrioventricular 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 via 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 4/1/07 and 2/29/12. A substudy at the University of California at Los Angeles contributed two 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.

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: LVEF, by echocardiogram or left ventriculogram; heart rhythm, QRSd, and intraventricular blocks by electrocardiogram (EKG); surgery performed; and demographics.

Inclusion criterion #1 was symptomatic surgical heart disease with LVEF < 40%, and QRSd > 100 milliseconds. Alternatively, patients undergoing combined mitral and aortic valve surgery qualified, irrespective of LVEF or QRSd. Exclusion criteria included atrial fibrillation, 2° or 3° atrioventricular block, congenital heart disease, intracardiac shunts, or heart rate > 120 beats/min 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 two of six possible LV sites. 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. 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]. 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].

BiVP 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. 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 three pacing sites and nine VVDs was 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, using randomly permuted blocks of 4, 6, and 8, with a treatment allocation ratio of 1:1.

Pacing in BiVP patients continued until phase II optimization, conducted in all patients during/after chest closure using mean arterial pressure. Optimization was similar to phase I, with testing intervals increased to 20 seconds [4]. 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 three were averaged and divided by body surface area to determine cardiac index.

Phase III testing was conducted in the intensive care unit, over three 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 independent two-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 2/29/12 for slow accrual (Figure 2) prior to reaching the endpoint target of 196. Our CONSORT diagram is presented in figure 3. 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/mitral surgery alone. Other exclusions were preoperative arrhythmia/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 4. Two data points are from the University of California at Los Angeles. Data groups include ALL (47), patients (ALL), 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 vs. 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/mitral surgery yielded 11 Standard of Care patients and 14 BiVP patients, with cardiac index 29% higher in BiVP patients ($p=0.0138$, Figure 5).

Mean arterial pressure during post-optimization comparisons in all patients was significantly higher with BiVP than with no pacing (Figure 6). 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 24–48 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 post-surgical 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 postbypass 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 postbypass 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 dyssynchrony at the cellular level, analogous to effects of CRT at the macroscopic level. Resolution of this question requires further study.

BiPACS [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 six to eight functional contacts are needed, reflected in 20% BiPACS pacing failure. A recommended configuration based on BiPACS would be bipolar leads on the RA appendage, anterior RV, and LV obtuse margin of the LV, with heart rate 90 beats per minute, AVD 180 milliseconds, and VVD of zero. AVD should 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 vs. 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 vs. no pacing at three tested time points in all patients. 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.

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References

1. Rafie R, Qamruddin S, Ozhand A, Taha N, Naqvi TZ. Shortening of atrioventricular delay at increased atrial paced heart rates improves diastolic filling and functional class in patients with biventricular pacing. *Cardiovasc Ultrasound*. 2012 Jan 24;10:2–11. [PubMed: 22269022]
2. Tse HF, Siu CW, Lee KL, et al. The incremental benefit of rate-adaptive pacing on exercise performance during cardiac resynchronization therapy. *J Am Coll Cardiol*. 2005; 46:2292–7. [PubMed: 16360061]
3. Wang DY, Richmond ME, Quinn TA, et al. Optimized temporary biventricular pacing acutely improves intraoperative cardiac output after weaning from cardiopulmonary bypass: a substudy of a randomized clinical trial. *J Thorac Cardiovasc Surg*. 2011; 141:1002–8. [PubMed: 20800242]
4. Rubinstein BJ, Wang DY, Cabreriza SE, et al. Response of mean arterial pressure to temporary biventricular pacing after chest closure during cardiac surgery. *J Thorac Cardiovasc Surg*. 2012; 144:1445–52. [PubMed: 22920599]
5. Strickberger SA, Conti J, Daoud EG, et al. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation*. 2005; 111:2146–2150. [PubMed: 15851622]
6. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. *Circulation*. 2008; 117:e350–408. [PubMed: 18483207]
7. Cazeau S, Leclercq C, Lavergn. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001; 344:873–80. [PubMed: 11259720]
8. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002; 346:1845–53. [PubMed: 12063368]
9. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005; 352:1539–49. [PubMed: 15753115]
10. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation*. 1999; 99:1567–73. [PubMed: 10096932]
11. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003; 107:1985–1990. [PubMed: 12668512]

12. Kass DA. Predicting cardiac resynchronization response by QRS duration: the long and short of it. *J Am Coll Cardiol*. 2003; 42:2125–7. [PubMed: 14680738]
13. Spotnitz ME, Richmond ME, Quinn TA, et al. Relation of QRS shortening to cardiac output during temporary resynchronization therapy after cardiac surgery. *ASAIO J*. 2010; 56:434–40. [PubMed: 20592584]
14. Nelson GS, Berger RD, Fetters BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. 2000; 102:3053–9. [PubMed: 11120694]
15. Foster AH, Gold MR, McLaughlin JS. Acute hemodynamic effects of atrio-biventricular pacing in humans. *Ann Thorac Surg*. 1995; 59:294–300. [PubMed: 7847940]
16. Tanaka H, Okishige K, Mizuno T, et al. Temporary and permanent biventricular pacing via left ventricular epicardial leads implanted during primary cardiac surgery. *Jpn J Thorac Cardiovasc Surg*. 2002; 50:284–289. [PubMed: 12166267]
17. Weiss U, Isgro F, Werling Ch, Lehmann A, Saggau W. Impact of atrio-biventricular pacing to poor left-ventricular function after CABG. *Thorac Cardiovasc Surg*. 2002; 50:131–135. [PubMed: 12077683]
18. Dekker AL, Phelps B, Dijkman B, et al. Epicardial left ventricular lead placement for cardiac resynchronization therapy: Optimal pace site selection with pressure-volume loops. *J Thorac Cardiovasc Surg*. 2004; 127:1641–1647. [PubMed: 15173718]
19. Flynn MJ, McComb JM, Dark JH. Temporary left ventricular pacing improve haemodynamic performance in patients requiring epicardial pacing post cardiac surgery. *Eur J Cardiothorac Surg*. 2005; 28:250–3. [PubMed: 15923120]
20. Dzemali O, Bakhtiyar F, Dogan S, Wittlinger T, Moritz A, Kleine P. Perioperative biventricular pacing leads to improvement of hemodynamics in patients with reduced left-ventricular function-interim results. *Pacing Clin Electrophysiol*. 2006; 29:1341–1345. [PubMed: 17201840]
21. Schmidt C, Frielingsdorf J, Debrunner M, et al. Acute biventricular pacing after cardiac surgery has no influence on regional and global left ventricular systolic function. *Europace*. 2007; 9:432–6. [PubMed: 17434890]
22. Evonich RF, Stephens JC, Merhi W, et al. The role of temporary biventricular pacing in the cardiac surgical patient with severely reduced left ventricular systolic function. *J Thorac Cardiovasc Surg*. 2008; 136:915–21. [PubMed: 18954630]
23. Pichlmaier M, Bagaev E, Lichtenberg A, et al. Four-chamber pacing in patients with poor ejection fraction but normal QRS durations undergoing open-heart surgery. *Pacing Clin Electrophysiol*. 2008; 31:184–91. [PubMed: 18233971]
24. Muehlschlegel JD, Peng YG, Lobato EB, Hess PJ Jr, Martin TD, Klodell CT Jr. Temporary biventricular pacing post-cardiopulmonary bypass in patients with reduced ejection fraction. *J Card Surg*. 2008; 23:324–30. [PubMed: 18598321]
25. Hamad MA, van Gelder BM, Bracke FA, van Zundert AA, van Straten AH. Acute hemodynamic effects of cardiac resynchronization therapy in patients with poor left ventricular function during cardiac surgery. *J Card Surg*. 2009; 24:585–590. [PubMed: 19740303]
26. Hanke T, Misfeld M, Heringlake M, Schreuder JJ, Wiegand UK, Eberhardt F. The effect of biventricular pacing on cardiac function after weaning from cardiopulmonary bypass in patients with reduced left ventricular function: a pressure-volume loop analysis. *J Thorac Cardiovasc Surg*. 2009; 138:148–56. [PubMed: 19577072]
27. Eberhardt F, Heringlake M, Massalme MS, et al. The effect of biventricular pacing after coronary artery bypass grafting: a prospective randomized trial of different pacing modes in patients with reduced left ventricular function. *J Thorac Cardiovasc Surg*. 2009; 137:1461–7. [PubMed: 19464465]
28. Straka F, Pirk J, Pindak M, et al. The hemodynamic effect of right ventricle (RV), RT3DE targeted left ventricle (LV) and biventricular (BIV) pacing in the early postoperative period after cardiac surgery. *Pacing Clin Electrophysiol*. 2011; 34:1231–40. [PubMed: 21714792]
29. Birnie DH, Tang ASL. The problem of non-response to cardiac resynchronization therapy. *Curr Opin Cardiol*. 2006; 21:20–26. [PubMed: 16355025]

30. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*. 2008; 117:2608–16. [PubMed: 18458170]
31. Mollema SA, Bleeker GB, van der Wall EE, Schalij MJ, Bax JJ. Usefulness of QRS duration to predict response to cardiac resynchronization therapy in patients with end-stage heart failure. *Am J Cardiol*. 2007; 100:1665–1670. [PubMed: 18036366]
32. Spotnitz ME, Wang DY, Quinn TA, et al. Hemodynamic stability during biventricular pacing after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2011; 25:238–42. [PubMed: 20638864]
33. Nguyen HV, Havalad V, Aponte-Patel L, Murata AY, Wang DY, Rusanov A, Cheng B, Cabreriza SE, Spotnitz HM. Temporary biventricular pacing decreases the vasoactive-inotropic score after cardiac surgery – A substudy of a randomized clinical trial. *J Thorac Cardiovasc Surg*. 2012 Jul 27. Epub ahead of print.
34. Rusanov A, Wang DY, Cabreriza SE, et al. Effect of atrioventricular conduction prolongation on optimization of paced atrioventricular delay for biventricular pacing after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2012; 26:209–16. [PubMed: 22000982]
35. Quinn TA, Cabreriza SE, Richmond ME, Weinberg AD, Holmes JW, Spotnitz HM. Simultaneous variation of ventricular pacing site and timing with biventricular pacing in acute ventricular failure improves function by interventricular assist. *Am J Physiol Heart Circ Physiol*. 2009; 297:H2220–6. [PubMed: 19855057]
36. Berberian G, Cabreriza SE, Quinn TA, Garofalo CA, Spotnitz HM. Left ventricular pacing site-timing optimization during biventricular pacing using a multielectrode patch. *Ann Thorac Surg*. 2006; 82:2292–4. [PubMed: 17126159]
37. Berberian G, Quinn TA, Kanter JP, et al. Optimized biventricular pacing in atrioventricular block after cardiac surgery. *Ann Thorac Surg*. 2005; 80:870–5. [PubMed: 16122446]
38. Buckberg GD. Controlled reperfusion after ischemia may be the unifying recovery denominator. *J Thorac Cardiovasc Surg*. 2010; 140:12–8. [PubMed: 20416890]
39. Bacha EA, Zimmerman FJ, Mor-Avi V, et al. Ventricular resynchronization by multisite pacing improves myocardial performance in the postoperative single-ventricle patient. *Ann Thorac Surg*. 2004; 78:1678–1683. [PubMed: 15511455]
40. Yu Y, Kramer A, Spinelli J, Ding J, Hoersch W, Auricchio A. Biventricular mechanical asynchrony predicts hemodynamic effect of uni- and biventricular pacing. *Am J Physiol Heart Circ Physiol*. 2003; 285:H2788–96. [PubMed: 14613916]

Figure 1.

BiPACS protocol. Pacing was optimized one hour after weaning from bypass (phase I), one hour later after chest closure (phase II), and on the following day (phase III). Patients were randomized after phase I. Optimization included seven atrioventricular delays, six LV lead locations, and nine 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. ICU = intensive care unit. MAP = mean arterial pressure. SOC = Standard of Care.

Figure 2.
BiPACS epicardial temporary pacing sites.
Circ = circumflex. IL = inferolateral. IM = inferomedial. OM = Obtuse Margin. PDA = posterior descending. 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.

Figure 3. BiPACS recruitment was terminated for slow accrual on 2/29/12. STEPS = speckle tracking echocardiography post surgery trial. UCLA = University of California at Los Angeles.

Figure 4. BiPACS patient flow. Enrollment was 111 of 6,346 screened. Sixty-one were randomized. Primary endpoints were obtained in 47. AVR/MVR = combined aortic and mitral valve surgery. BiVP = biventricular pacing group. SOC = Standard of Care group.

Figure 5.

Cardiac index endpoint is 12% higher in all BiVP patients, not statistically significant. In the AVR subgroup CI is 60% higher (p=0.018). ALL = all patients. AVR = aortic valve surgery. AVR/MVR = combined aortic and mitral surgery. BiVP = biventricular pacing. CABG = coronary artery bypass. CI = cardiac index. SOC = Standard of Care.

Figure 6. Combined aortic valve and aortic/mitral valve surgery subgroup. Cardiac index is 29% higher with biventricular pacing. BiVP = biventricular pacing. SOC = Standard of Care.

Figure 7.

Linear effects model t-test reveals mean arterial pressure increase with optimized biventricular pacing vs. no pacing in all patients. AAI = atrial pacing. BiVP = biventricular pacing. NoP = no pacing.

Table 1**Patient Characteristics, BiPACS trial**

Number of Patients:	
Total:	61
Age (years $\pm$ SD)	68 $\pm$ 11
Ejection Fraction (% $\pm$ SD)	32 $\pm$ 14
QRS duration (msec $\pm$ SD)	119 $\pm$ 25
Male gender (%)	74
Cardiopulmonary Bypass Time, SOC/BiVP	2:23/2:22
Aortic Cross-clamp Time, SOC/BiVP	1:22/1:30
Type of Surgery:	
CABG/AVR, CABG/MVR, CABG/AVR/MVR, CABG/AVR/MVR/TVR	19
AVR/MVR, AVR/TVR, MVR/TVR	16
CABG	16
AVR	9
MVR	1
Postoperative Complications *	
BiVP	10/30
SOC	10/31
30 Day Surgical Mortality Rate	
BiVP	6.5%
SOC	0%
Pacing Failure	12/61

* 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.