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Optimized Multisite Ventricular Pacing in Postoperative Single-Ventricle Patients

Vinod Havalad,

Department of Pediatrics, Advocate Children's Hospital, 1775 Dempster Street, Park Ridge, IL, USA

Santos E. Cabreriza,

Department of Surgery, Columbia University, New York, NY, USA

Eva W. Cheung,

Department of Pediatrics, Columbia University, New York, NY, USA

Linda Aponte-Patel,

Department of Pediatrics, Columbia University, New York, NY, USA

Alice Wang,

Department of Surgery, Columbia University, New York, NY, USA

Bin Cheng,

Department of Biostatistics, Columbia University, New York, NY, USA

Daniel Y. Wang,

Department of Medicine, Columbia University, New York, NY, USA

Eric Silver,

Department of Pediatrics, Columbia University, New York, NY, USA

Emile A. Bacha, and

Department of Surgery, Columbia University, New York, NY, USA

Henry M. Spotnitz

Department of Surgery, Columbia University, New York, NY, USA

Abstract

Ventricular dyssynchrony is associated with morbidity and mortality after palliation of a single ventricle. The authors hypothesized that resynchronization with optimized temporary multisite pacing postoperatively would be safe, feasible, and effective. Pacing was assessed in the intensive care unit within the first 24 h after surgery. Two unipolar atrial pacing leads and four bipolar ventricular pacing leads were placed at standardized sites intraoperatively. Pacing was optimized to maximize mean arterial pressure. The protocol tested 11 combinations of the 4 different ventricular lead sites, 6 atrioventricular delays (50–150 ms), and 14 intraventricular delays. Optimal pacing settings were thus determined and ultimately compared in four configurations: bipolar, unipolar, single-site atrioventricular pacing, and intrinsic rhythm. Each patient was his or

her own control, and all pacing comparisons were implemented in random sequence. Single-ventricle palliation was performed for 17 children ages 0–21 years. Pacing increased mean arterial pressure (MAP) versus intrinsic rhythm, with the following configurations: bipolar multisite pacing increased MAP by 2.2 % (67.7 ± 2.4 to 69.2 ± 2.4 mmHg; $p = 0.013$) and unipolar multisite pacing increased MAP by 2.8 % (67.7 ± 2.4 to 69.6 ± 2.7 mmHg; $p = 0.002$). Atrioventricular single-site pacing increased MAP by 2.1 % (67.7 ± 2.4 to 69.1 ± 2.5 mmHg; $p = 0.02$, insignificant difference under Bonferroni correction). The echocardiographic fractional area change in nine patients increased significantly only with unipolar pacing (32 ± 3.1 to 36 ± 4.2 %; $p = 0.02$). No study-related adverse events occurred. Multisite pacing optimization is safe and feasible in the early postoperative period after single-ventricle palliation, with improvements in mean arterial pressure and fractional area shortening. Further study to evaluate clinical benefits is required.

Keywords

Pediatrics; Single-ventricle physiology; Congenital heart disease; Cardiac critical care; Cardiac resynchronization therapy; Heart failure

Introduction

Biventricular pacing (BiVP) benefits individuals with heart failure by conserving energy lost from ventricular dyssynchrony while increasing stroke volume and cardiac output. These benefits are mediated by early stimulation of late-activating regions of the myocardium.

In clinical trials, BiVP improved event-free survival and quality of life for adults with cardiomyopathy and congestive heart failure [1]. In addition, BiVP can improve left ventricular function while reducing myocardial oxygen demand [10].

At our center, clinical trials conducted with adult patients at risk for left ventricular dysfunction showed that temporary BiVP increased urine output and reduced the vasoactive-inotropic score (VIS) during 3 h immediately after cardiopulmonary bypass (CPB) [11]. Our trial also demonstrated the hemodynamic benefits of atrioventricular delay (AVD) and interventricular delay optimization [14, 17]. Thus, optimized temporary BiVP may provide an alternative method for increasing cardiac output without the cost of increasing myocardial oxygen demand.

In pediatrics, temporary BiVP also can ameliorate ventricular dysfunction after CPB [6, 12, 18]. In particular, the functional single ventricle (SV), which results from various congenital heart defects, may benefit from multisite ventricular pacing (MSVP) after CPB, analogous to BiVP in two-ventricle anatomy. Tissue Doppler and speckle-tracking echocardiography demonstrate impaired systolic and diastolic function as well as dyssynchrony in patients with SV physiology [5, 9]. This ventricular dysfunction correlates with morbidity and mortality after SV palliation.

In 26 patients with SV, Bacha et al. [2] demonstrated increased cardiac output and systolic blood pressure and reduced QRS duration with temporary MSVP. However, the pacing protocols were not systematically optimized.

The current study examined the feasibility of optimization of AVD, intraventricular delay (IVD), and pacing site during MSVP after SV palliation. We hypothesized that optimized MSVP would safely increase postoperative mean arterial pressure (MAP) without inotrope dosage increases, afterload reduction, or volume infusion.

Materials and Methods

In the intensive care unit (ICU), MSVP was optimized within 24 h after palliative surgery for SV under a protocol approved by the Columbia University Institutional Review Board. With permission of the attending surgeon and informed consent from parents or legal guardians, pediatric patients undergoing SV palliation were screened for eligibility and recruited before the day of surgery by qualified and trained study investigators.

The inclusion criteria for the study specified patients 0–21 years of age with SV palliation. The exclusion criteria ruled out inability to place pacing leads safely and lack of a functional peripheral arterial line.

Temporary epicardial pacing leads were sewn to the beating heart on the CPB after removal of the aortic cross-clamp. Paired unipolar leads were placed on the atrium, and four bipolar leads were placed on the SV, as defined in Fig. 1. The leads were secured with 4–0 Prolene to promote stable pacing.

Hemodynamically stable patients were studied in the pediatric cardiac intensive care unit (PCICU) within the first 24 postoperative hours. The preoptimization data included an electrocardiogram, vital signs, fluid balance, and inotrope and vasoactive medications.

Pacing was performed using a Medtronic InSync III (Medtronic, Inc., Minneapolis, MN, USA) and a permanent biventricular pacemaker mounted in a specially housed external unit, as described in our earlier publications [14, 17]. Pacing was programmed using a Medtronic CareLink Programmer (Medtronic, Inc.). Real-time arterial pressure was digitized using PowerLab (ADInstruments, Inc., Milford, MA, USA) and recorded on a personal computer (iMac; Apple Computer, Inc., Cupertino, CA, USA).

Optimization of MSVP was accomplished with sequential atrioventricular pacing, tracking the patient's own intrinsic atrial rate. At no point during testing was the pacemaker used to pace at a higher rate. All heart rates were sensed.

The pacing site was optimized first, followed by AVD and IVD. All settings were tested twice during 10-s intervals in a sequence individually randomized for each patient, as shown in Fig. 2. Our previous study protocols showed 10-s intervals to be sufficient for reaching a steady state [14, 17]. The average MAP for each setting then was compared graphically, and the optimal value for the parameter tested was selected.

Real-time data processing was used to calculate the average MAP using all beats in the last respiratory cycle of a timed interval. Cycles containing ectopic beats were removed from the calculation. The use of a rapid, real-time optimization protocol to measure changes in cardiac mechanics during brief intervals has been described previously [7]. The results were confirmed later by manual analysis.

Site optimization, with a default AVD of 90 ms and a default IVD of 0 ms (simultaneous multisite pacing), was tested using 11 different combinations of the four possible pacing sites. The site combination yielding the highest MAP, as measured by arterial catheter, was selected as the optimal pacing site and used for analysis throughout the remainder of the protocol.

Next, AVD was optimized using the optimal pacing site and a default IVD of 0 ms. Then AVD intervals, ranging from 50 to 150 ms, were randomly tested in 20-ms increments. Each setting was tested twice, and AVDs longer than the patient's intrinsic AVD were not tested. The optimal AVD then was selected and confirmed graphically.

With the optimal site combination and AVD interval in place, IVD was optimized. To accomplish this, random testing of IVD settings ranging from -60 to +60 ms was performed in 20-ms increments. The IVD was varied in two ways: with delay between stimulating from the basal sites (V1 and V2) to the apical sites (V3 and V4) and with delay between stimulating from the rightward sites (V1 and V3) to the leftward sites (V2 and V4) (Fig. 1). The optimal IVD then was selected and confirmed graphically.

Four conditions were compared during the final comparison: optimized multisite bipolar pacing (BiP), optimized multisite unipolar pacing (UniP), optimized single-site pacing (AV), and intrinsic rhythm (NoP). The BiP condition used the optimal site, AVD and IVD as determined by the study protocol. The UniP condition used the optimal AVD as previously described, and ventricular pacing was achieved by connecting the pacemaker to only one of the two available poles on each bipolar pacing lead at the optimal sites (IVD was not used in the UniP condition).

The aforementioned UniP configuration most closely approximated the technique described by Bacha et al. [2]. This technique also has been described as "extended bipolar pacing." The AV condition used only the optimal AVD setting because site and IVD optimization were not relevant to this configuration. The NoP condition served as the control for each patient.

In random order, each of the final comparison conditions was tested twice for 30-s periods. The total pacing time for the optimization protocol was a maximum of 12 min (Fig. 2). Once the protocol was completed, the pacing leads were retained or removed at the primary team's discretion.

Echocardiograms were collected under each of the final comparison conditions (BiP, UniP, AV, NoP). Images were acquired using a Vivid 7 cardiovascular ultrasound system (GE, Waukesha, WI, USA). Fractional area change (FAC), defined as percentage change in the ventricular cavity from end-diastole to end-systole, was measured for each patient in the

parasternal short view by a pediatric cardiologist (E.W.C.), who was blinded to the pacing condition.

Statistical Analysis

Historical data was used to determine that a sample size of 17 was needed for a power of 80 % to detect a 10 % improvement in MAP from 61.1 to 67.2 with a standard deviation of 8.4 for the difference. Statistical differences in MAP and FAC between the three settings were assessed using a mixed-effects model, which accounts for within-subject correlations due to repeated measures. Bonferroni adjustment was used to control the family-wise error rate due to multiple testing. As the result, a p value lower than 0.017 was considered statistically significant for this part of the analysis. Multiple linear regression models analyzed percentage change in MAP from NoP to UniP, AV, and MSVP. Explanatory variables included VIS, time on bypass, time until start of study, fluid balance (calculated using ICU flowsheets), age, and gender. Analysis was performed with SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

The inclusion criteria were fulfilled by 20 patients, identified between April 2011 and April 2012, who consented to participate in the study. Of these 20 patients, 17 completed the protocol. The remaining three patients were not studied due to hemodynamic instability ($n = 2$) or failure of the atrial pacing lead ($n = 1$).

The preoperative demographics and types of SV repair are presented in Table 1. Most of the patients (82 %) underwent a bidirectional Glenn, with a mean CPB time of 76 min. In 70 % of the cases, RV-dominant SV was present. The vasoactive-inotrope score was less than 10 for 88 % of the patients, with a mean value of 4.

Optimization analysis did not show a distinct site combination that was clearly superior. However, the apical pacing site (V4) was present in 94 % of the optimal combinations. For 59 % of the patients, AVDs shorter than 100 ms were optimal. On the average (using $n \pm$ standard error of the mean [SEM]), MAP showed an increase from 67.6 ± 2.6 to 71.1 ± 2.5 mmHg ($p < 0.0001$, Fig. 3) in the comparison of optimal and worst AVDs, a 5 % increase. A maximum increase of 17 % in MAP was observed with optimal AVD compared with the worst AVD in one patient. The IVD optimization did not show any significant benefit.

The final comparison data are shown in Fig. 4a. Pacing increased MAP in BiP and UniP configurations compared with NoP: 2.2 % with BiP (67.7 ± 2.4 to 69.2 ± 2.5 mmHg; $p = 0.013$), 2.8 % with UniP (67.7 ± 2.4 to 69.6 ± 2.7 mmHg; $p = 0.002$), and 2.1 % with AV (67.7 ± 2.4 to 69.1 ± 2.5 ; $p = 0.020$, insignificant difference subject to Bonferroni correction).

Fractional area change was analyzed in 9 of 17 patients (Fig. 4b). Poor image quality prevented analysis of the remaining patients. The average FAC increased in UniP compared with NoP (32.0 ± 3.1 % to 36.0 ± 4.2 %; $p = 0.024$). FAC during BiP (32.0 ± 3.1 % to 34.5

$\pm 4.0 \%$; $p = 0.137$) and AV ($32.0 \pm 3.1 \%$ to $32.0 \pm 4.0 \%$; $p = 1.00$) did not differ significantly from FAC during NoP.

Multiple linear regressions (Table 2) identified two factors positively affecting MAP response to unipolar pacing: positive fluid balance and decreasing age. Gender, bypass time, VIS, and study start time were not significant. In addition, preoperative QRS duration and ventricular function, as measured qualitatively by echocardiogram, did not affect the response to pacing.

Adverse Events

Adverse events such as pacing-induced arrhythmias, bleeding, and infection were not observed in the study patients.

Discussion

Currently, BiVP is a proven therapy for adults with cardiomyopathy and congestive heart failure. However, related studies in pediatrics have been limited. Whereas temporary MSVP has been studied postoperatively after SV surgery, the current study is the first to examine optimized MSVP. Our results demonstrate the feasibility of bedside optimization in the postoperative period. The absence of adverse events or complications from pacing lead placement or removal suggests that this procedure is safe with proper care.

The safety of the study protocol and the observation of statistically significant improvement in MAP support the development of a clinical trial to examine the potential benefits of MSVP for postoperative SV patients. The observed 2.8 % increase in MAP is small but likely indicates a 6 % increase in cardiac output based on prior data [13, 14, 17]. Clinical benefits in terms of VIS and urine output have resulted from similar hemodynamic effects in adults after CPB [11, 17]. A 12 % increase in FAC with optimized multisite unipolar pacing supports this assessment.

Fractional area change identified only the unipolar configuration as superior to intrinsic rhythm. The unipolar configuration is speculated to result in anodal stimulation and simultaneous depolarization of myocardial tissue among all pacing sites, leading to broader simultaneous activation across the ventricle. This simultaneous activation of large myocardial segments versus more localized activation with bipolar pacing may explain the observed advantage of unipolar pacing, seemingly indicating that a multisite configuration is optimal. However, further studies should include comparison with single-site pacing as well.

Our results also demonstrate the value of pacing optimization. Although site optimization was indeterminate, the apical pacing site was included in 16 of 17 optimal pacing configurations. This suggests that an apical ventricular lead should be included in the pacing configurations during future trials. The optimal AVD increased MAP an average of 5 % compared with the worst AVD, with a peak difference of 17 % in one individual. In addition, the optimal AVD was less than 100 ms in most patients compared with the adult BiVP population, for which the median optimal AVD was 150 ms during atrial pacing [14, 17]. The results of IVD optimization were insignificant. Thus, AVD optimization should be

included in future trials, but optimizing the pacing site and IVD in individual patients is unlikely to result in benefit.

Multiple linear regressions identified positive fluid balance and younger age as variables that predicted a positive response to multisite unipolar pacing. The importance of positive fluid balance may reflect impaired postoperative systolic function or reduced ventricular compliance [4]. The age effect may be related to the immature conduction circuits observed in younger children.

Three-dimensional echocardiography has demonstrated that MSVP can reverse dyssynchrony immediately after SV surgery [2, 18], whereas BiVP was found to be more effective on the day of surgery than on the following day in adults with acquired heart disease. Thus, perioperative resynchronization may affect two mechanisms of perioperative ventricular dysfunction. The first is intrinsic dyssynchrony present preoperatively in SV patients. The second is myocardial depression due to intraoperative ischemia and reperfusion, which may themselves cause transient regional dyssynchrony or global ventricular depression in the several days after surgical correction. Ischemia and reperfusion also can cause myocardial edema and increased diastolic stiffness [4], possibly implicating diastolic filling [16] in mechanisms of MSVP action.

Our study was limited by a sample size insufficient to determine the effect of SV repair technique on MSVP response. A larger study could examine differences in MSVP response in bidirectional Glenn versus Fontan repair or in RV versus LV dominance.

Our study also was limited by indirect measures of cardiac output. Mean arterial pressure reflects cardiac output only if vascular resistance is stable, allowing factors other than improved synchronization and ejection to affect assessment of MSVP. Echocardiographic FAC may be useful for this in future studies, although image quality limited its utility in the current study. The use of FAC, preferred for echocardiographic evaluation of right ventricular function, also is accepted for evaluation of SV function [15]. No reliable noninvasive options for measurement of cardiac output in SV patients were available at the time of this study. In addition, this was a pilot study, and prolonged pacing was not included in the protocol. In future studies involving prolonged pacing, other measurements of cardiac output and oxygen delivery, such as lactate level or urine output, would be valuable.

The modest hemodynamic changes demonstrated in this study did not clearly indicate whether optimized MSVP will result in clinical benefit. The multicenter insync randomized clinical evaluation (MIRACLE) trial reported stroke volume increases of 5–15 % that produced subjective and objective clinical benefits such as a quality-of-life 6-min hall walk distance [8]. However, these results may not be applicable to our patient population. A larger, randomized, blinded clinical trial, including longer periods of testing, is necessary to determine whether the hemodynamic improvement observed in this study has any effect on clinical outcome.

Optimized MSVP beneficially affects hemodynamics early after SV palliation, with increases in MAP and FAC. In the ICU, MSVP can be safely and effectively optimized at

the bedside. A larger randomized, controlled clinical trial is indicated to evaluate the potential clinical benefits.

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Fig. 1.
Schematic of ventricular pacing sites (original image from Gaca et al. [3])

Form ICU 1 - Phase I

Study: _____ Total Time: _____
 ICU Arrival Time: _____
 Study Start Time: _____

Inotropes: _____
 Afterload Reducing Agents: _____
 Antiarrhythmics: _____
 Sedatives: _____

- HR = _____ bpm
 - Vent Rate = _____
 - Sensed AVD = _____
 - Paced AVD = _____
 - Default AVD = 120 msec or _____
 - Intervals = 10 sec
 - Total Time ~ 3.6 mins

#	SITE	MAP
1	V1V3V4	
2	V1V4	
3	V1V2	
4	V1V2V3	
5	V1V2V4	
6	V2V4	
7	V3V4	
8	V1V2V3V4	
9	V2V3V4	
10	V1V3	
11	V2V3	
12	V1V3	
13	V1V2	
14	V3V4	
15	V1V4	
16	V2V3V4	
17	V1V2V4	
18	V1V2V3	
19	V2V4	
20	V1V3V4	
21	V1V2V3V4	
22	V2V3	

Opt Site = _____
 Default Site = V1V2V3V4

- HR = _____ bpm
 - LV Site = LV _____ = _____
 - AVD = OPT = _____ msec
 - Intervals = 10 sec
 - "+" = V1V2 first
 - "-" = V3V4 first
 - Total Time ~ 2.3 mins

#	IVD	MAP
33	+20	
34	+60	
35	+40	
36	-20	
36	0	
38	-40	
39	-60	
40	-60	
41	-40	
42	0	
43	+20	
44	+60	
45	+40	
46	-20	

Opt IVD1 = _____
 Default IVD1 = 0

- HR = _____ bpm
 - LV Site = LV1 = _____
 - VVD = 0 msec
 - Intervals = 10 sec
 - Total Time ~ 2 mins

#	AVD	MAP
23	130	
24	110	
25	70	
26	90	
27	150	
28	70	
29	90	
30	130	
31	150	
32	110	

Opt AVD = _____
 Default AVD = 120 or _____

- HR = _____ bpm
 - LV Site = LV _____ = _____
 - AVD = OPT = _____ msec
 - Intervals = 10 sec
 - "+" = V1V3 first
 - "-" = V2V4 first
 - Total Time ~ 2.3 mins

#	IVD	MAP
47	-40	
48	-60	
49	+20	
50	-20	
51	+40	
52	+60	
53	0	
54	-20	
55	+60	
56	+20	
57	-40	
58	+40	
59	0	
60	-60	

Opt IVD2 = _____
 Default IVD2 = 0

- LV Site = LV _____ = _____
 - AVD = OPT = _____ msec
 - IVD = OPT = _____ msec
 - Intervals = 30 sec
 - Total Time = 1:30

#	SETTIN MAP
61	NoP
62	UniP
63	P1
64	AV

Fig. 2.
 Sample optimization protocol

Fig. 3. Atrioventricular delay (AVD) optimization illustrating the difference in mean arterial pressure (MAP) between the optimal and worst AVD settings for all patients

Fig. 4.

a Mean arterial pressure during the final comparison, normalized to intrinsic rhythm ($n = 17$). **b** Fractional area change during the final comparison, normalized to intrinsic rhythm ($n = 9$)

Patient characteristics

Table 1

Patient ID	Age (months)	Gender	Diagnosis	Surgery	Dominant	CPB time (min)	VIS score
1	4	M	HLHS, Norwood-Sano	BDG	R	45	3
2	7	M	DIRV, BTS	BDG	R	73	6
3	10	F	HLHS, Norwood-Sano	BDG	R	132	10
4	36	M	Dextrocardia, DORV, BDG	Fontan	R	0	3
5	5	M	HLHS, hybrid procedure	Norwood, BDG	R	139	10
6	5	M	HLHS, Norwood-Sano	BDG	R	49	0
7	4	M	HLHS, Norwood-Sano	BDG	R	82	12
8	4	M	DILV, Norwood-BTS	BiI BDG	L	127	5
9	5	M	HLHS, Norwood-Sano	BiI BDG	R	83	0
10	4	M	HLHS, Norwood-Sano	BDG	R	82	5
11	4	F	HLHS, Norwood-Sano	BDG	R	87	5
12	14	M	HRHS	BDG	L	55	3
13	5	M	TA, TGA	BDG	L	81	0
14	45	F	TA, TGA	Fontan	L	68	0
15	3	F	TA, TGA	BDG	L	70	3
16	10	F	HLHS, Norwood-BTS	BDG	R	50	0
17	47	F	DORV	Fontan	R	63	8
Mean		12.5	35 % female	82 % BDG	70 % R	mean 76	mean 4

ID identification number, CPB cardiopulmonary bypass, HLHS hypoplastic left heart syndrome, BDG bidirectional Glenn procedure, DIRV double-inlet right ventricle, BTS Blalock-Taussig shunt, DORV double-outlet right ventricle, DILV double-inlet left ventricle, HRHS hypoplastic right heart syndrome, TA tricuspid valve atresia, TGA, transposition of the great arteries

Table 2

Summary of multiple regression analysis evaluating change in mean arterial pressure (MAP) from intrinsic state to unipolar pacing

Parameter	Estimated coefficient	SE	<i>p</i> value
Fluid balance	0.014	0.030	0.045
Age	−0.364	0.140	0.026
Gender, female	1.865	2.124	0.400
Bypass time	−0.013	0.030	0.678
VIS	−0.234	0.234	0.340
Time to start	0.346	0.174	0.075

Increase in MAP was positively associated with fluid balance and negatively associated with age

SE standard error, *VIS* vasoactive-inotropic score