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ORIGINAL ARTICLE

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Ventricular force-frequency relationships during biventricular or multisite pacing in congenital heart disease

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Abstract

Background: Traditional indices to evaluate biventricular (BiV) pacing are load dependent, fail to assess dynamic changes, and may not be appropriate in patients with congenital heart disease (CHD). We therefore measured the force-frequency relationship (FFR) using tissue Doppler-derived isovolumic acceleration (IVA) to assess the dynamic adaption of the myocardium and its variability with different ventricular pacing strategies.

Methods: This was a prospective pilot study of pediatric and young adult CHD patients with biventricular or multisite pacing systems. Color-coded myocardial velocities were recorded at the base of the systemic ventricular free wall. IVA was calculated at resting heart rate and with incremental pacing. FFR curves were obtained by plotting IVA against heart rate for different ventricular pacing strategies.

Results: Ten patients were included (mean: 22 ± 7 years). The FFR identified a best and worst ventricular pacing strategy for each patient, based on the AUC at baseline, submaximal, and peak heart rates ($P < .001$). However, there was no single best ventricular pacing strategy that was optimal for all patients. Additionally, the best ventricular pacing strategy often differed within the same patient at different heart rates.

Conclusion: This novel assessment demonstrates a wide variability in optimal ventricular pacing strategy. These inherent differences may play a role in the unpredictable clinical response to BiV pacing in CHD, and emphasizes an individualized approach. Furthermore, the optimal ventricular pacing varies with heart rate within individuals, suggesting that rate-responsive ventricular pacing modulation may be required to optimize ventricular performance.

KEYWORDS

biventricular pacing, cardiac resynchronization therapy, congenital heart disease, force-frequency relationship, multisite pacing, ventricular function

1 | INTRODUCTION

Cardiac pacemakers play an important role in the care of pediatric and young patients with congenital heart disease (CHD). However, chronic single-site pacing, especially from the right ventricle (RV), has been associated with decreased left ventricular (LV) function due to electromechanical dyssynchrony.[1-3] Biventricular (BiV) pacing may restore electromechanical synchrony, and improve ventricular function.[4,5] Unlike the adult population, where the most common underlying etiology is ischemic cardiomyopathy, BiV pacing is most frequently utilized in young patients with ventricular dyssynchrony secondary to conventional RV pacing or complex structural malformations and who have a relative heterogeneity in their

All authors take responsibility for all aspects of reliability and freedom from bias of the data presented and their discussed interpretation

response.[6-8] It is not clear whether this heterogeneity of response is due to lack of effect, or failure to optimize the BiV pacing sequence, the latter being dependent on adequate methods to dynamically assess functional responses to changes in ventricular pacing. In this regard, the traditional noninvasive methods to assess response to pacing may not be appropriate in children.

Isovolumic acceleration (IVA) is a noninvasive tissue Doppler-derived index that is relatively load-independent and has good reproducibility and allows us to study the ventricular force-frequency relationship (FFR) that provides a dynamic assessment of the myocardial function.[9-11] Prior studies of FFR in patients with BiV pacing have utilized invasive or load-dependent parameters and have been limited to adults.[12-14] In this pilot study, we assessed the changes in the ventricular FFR derived from noninvasively obtained IVA during different pacing configurations in a young population to better delineate the dynamic ventricular myocardial performance.

2 | METHODS

This was a prospective cross-sectional study of patients followed at our institution who were ≥ 5 years of age with BiV or multisite pacemaker for at least 6 months. Patients with ventricular lead problems or those who declined to participate were excluded from the study. Informed consent was obtained from all patients or parents of patients < 18 years of age, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Transthoracic echocardiography was performed with the use of a Vingmed GE ultrasound scanner (GE, Milwaukee, Wisconsin). In a 4-chamber equivalent view, the systemic ventricle free wall was imaged and color-coded myocardial velocities by tissue Doppler imaging (TDI) were recorded at the base immediately below the insertion of the atrioventricular valve leaflets during different pacing strategies for an individual patient. This included atrial pacing for those without AV block, BiV pacing without ventricular-ventricular delay (VV-0), BiV pacing with LV paced 20 m/s before the RV (LV+20), and BIV with LV paced 20 m/s after the RV (LV-20 interval), then by single lead pacing (RV, LV). Myocardial velocities were first obtained at a baseline heart rate, followed by incrementally paced heart rates (+10 bpm incremental increase) to a maximum of 160 bpm for each pacing modality. Echopac software (GE Vingmed) was used to analyze the stored TDI data by the principal investigator. The sample volume was placed at the center of the myocardium at the basal free wall. Myocardial velocities during peak isovolumic contaction (IVC) and systolic ejection (S wave) were recorded. IVA was calculated by dividing the peak velocity by the time interval from onset of the isovolumic wave (zero crossing) during IVC to the time at peak velocity of this wave. Using IVA at incrementally paced heartbeats, the FFR curves were constructed.[9,15] (Supplemental Figure S1).

Data were entered into a REDCap database, and exported to SAS 9.4 for analyses (SAS, Cary, North Carolina). The AUC was calculated for each FFR curve at baseline, submaximal heart rate (100 bpm), and maximal heart rate. AUC was instead of absolute IVA values to take into account the variability of the IVA at different heart rates in between the set points of heart rate (baseline, submaximal and maximal). With each patient acting as his/her own control, the best and worst pacing strategies were identified for each individual. A paired *t* test was used to compare the IVA at baseline with AUC at submaximal and maximal heart rates.

3 | RESULTS

A total of 12 patients satisfied the inclusion criteria and underwent the study. Of these patients, one did not have interpretable data for offline analysis and one was unable to complete the study due to pain with pacing from a lead which was not in regular use. These two patients were hence excluded from the analysis. The remaining 10 patients were predominantly young adults (mean age: 22 ± 7 years) with 40% being female. The patients had a heterogeneous mixture of underlying CHD (Table 1). The majority of the patients had a biventricular physiology (80%). Among the patients with biventricular physiology, the RV was the systemic ventricle in two patients and the LV was systemic in the remainder. Three patients had multisite pacing with two ventricular leads on the same ventricle. Two of these patients had single ventricle physiology (both systemic LV), while two patient had a second RV lead that was in place as a backup secondary to complete heart block without adequate ventricular escape and device dependency. Excluding the patient who had a backup lead, the remaining had BiV pacing for ventricular dysfunction. Six patients had had a favorable response to BiV pacing either by clinical improvement in symptoms or echocardiographic improvement in ventricular function.

The FFR curves constructed by plotting IVA against heart rate for each pacing modality in individual patients are shown in Figure 1. Based on the AUC of the FFR curves of each pacing modality in a patient, a worst and best modality was identified at baseline, submaximal, and maximal heart rates which were all significantly different ($P < .001$) (Figure 2). There were not only interpatient differences in the best pacing modality at different heart rates, but also significant intrapatient variability as to the best pacing strategy at different heart rates. (Table 2). At baseline, the best and worst IVA differed by 0.7 ± 0.3 m/s^2 while the AUCs by submaximal heart rate (100 bpm) and maximal heart rate differed by 25 ± 19 and 176 ± 136, respectively.

4 | DISCUSSION

We have measured for the first time noninvasively, ventricular FFR (a load-independent marker of myocardial performance) in pediatric and young adult CHD patients with BiV pacing, demonstrating a wide inter- and intrapatient variability in the optimal ventricular pacing configuration.

The abnormal ventricular morphology in young patients with CHD makes the assessment of ventricular function difficult by traditional measurements. Furthermore, the QRS complex may be

TABLE 1 Clinic characteristics of the patients

	Age	Sex	Cardiac Diagnosis	Surgical Procedures[a]	Systemic Ventricle	RV Lead Location	LV lead Location	Indication for CRT
1	22	M	CHB	None	LV	RV myocardium	CS	V. Dysfunction
2	26	M	CCTGA, Ebstein's	Tricuspid valve replacement	RV	Epi–RV	Epi–post LV	V. Dysfunction
3	27	M	AV septal defect	AV septal defect repair	LV	Low RVOT	MCV	V. Dysfunction
4	31	F	Esbtein's anomaly	Tricuspid valve replacement	LV	Epi–RV	Epi–LV	Wide QRS, prophylactic
5	23	M	CCTGA, Ebstein's	Tricuspid valve replacement	RV	LV apex[a]	CS	Prophylactic
6	28	F	Marfan's/dilated aorta	Aortic root/valve replacement	LV	RV apex	RVOT	V. Dysfunction[b]
7	16	F	HLHS	Fontan palliation	Single	Epi–RV apex	Epi–RV AV groove	V. Dysfunction
8	11	F	CHB	None	LV	Epi–RV	Epi–posterior LV	V. Dysfunction
9	19	M	VSD, coarctation, BAV	Aortic valve replacement	LV	RV apex	CS	V. Dysfunction
10	13	M	DILV	Fontan palliation	Single	Epi–posterior LV	Epi–LV apex	V. Dysfunction

Abbreviations: AV, atrioventricular; BAV, bicuspid aortic valve; CHB, congenital heart block; CCTGA, congenitally corrected transposition of great arteries; CS, coronary sinus; DILV, double inlet left ventricle; HLHS, hypoplastic left heart syndrome; LV, left ventricle; MCV, middle cardiac vein; RV, right ventricle; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

[a]Subpulmonary ventricle.

[b]Placed as backup lead secondary to device dependency.

intrinsically abnormal due to the underlying disease or interventions making an end point of narrowing of the QRS complex questionable. Indeed, EF, QRS duration, and LV end-diastolic dimension were not found to predict which CHD patients might respond to BiV pacing.[16] Measurement of markers of cardiac output such as dP/dT and aortic VTI by echocardiography lack sensitivity, and are burdened by load dependency.[17,18] Studying the intrinsic myocardial function, with IVA derived FFR, in such conditions might be a more accurate parameter.[19,20] The FFR is a fundamental property of the myocardium that reflects increased calcium cycling with increasing frequency of the stimulation.[11] Prior studies have used load-dependent or invasive parameters (dP/dT, pressure-volume analysis) to study the FFR in adults and they have not been studied in pediatrics or CHD.[12,13]

Our pilot study highlights the unpredictability of contractile responses to BiV pacing in CHD patients. Not only does our data provide a rationale for the unpredictable clinical responses previously discussed, but it also highlights the fundamental differences with findings in adults who have acquired heart disease, making extrapolation of adult guidelines for CRT to patients with CHD inappropriate. In some pacing strategies, there was little or no advantage to BiV pacing in some patients, while the same setting was optimal in others. Furthermore, different pacing strategies appeared to be more advantageous at different heart rates, such that an individual may have superior contractility with one strategy at lower heart rates, but improved peak force generation at an optimal heart rate with a different pacing strategy. While speculative, and clearly requiring study in a larger group of patients, this raises the intriguing possibility of rate-responsive ventricular pacing modulation algorithms to optimize submaximal and maximal performance in individual patients. What is clear from the currently available data is that "traditional indices" of response to CRT may be inappropriate in patients with CHD, and more detailed assessments of contractile response may be required both to optimize pacing and to maximize the chronic remodeling responses, before a patient is deemed a nonresponder.

This proof-of-principle study has several necessary limitations. This pilot study was limited by the small sample size, and larger studies are obviously required to validate our findings. Although IVA measured at a single anatomic point might be considered not to represent the global function due to the dyssynchronous contraction, LV longitudinal function correlates well with the global ventricular strain in ischemic heart disease.[21] However, this is an important limitation of the present study and further studies are required to accurately correlate IVA with invasive measurement of ventricular function in the setting of ventricular dyssynchrony. The issue of comparing IVA in systemic LV and systemic RV in this study is offset by each patient acting as his/her own control and the knowledge that functional adaptation of the RV myocardium in the systemic condition alters its mechanistic properties to be more similar to the LV.[15] Finally, the changes in the myocardial performance in this study were restricted to force changes with stimulation frequency and might not completely represent all the physiological changes seen with exertion. Changes in FFR are fundamental to improved contractility

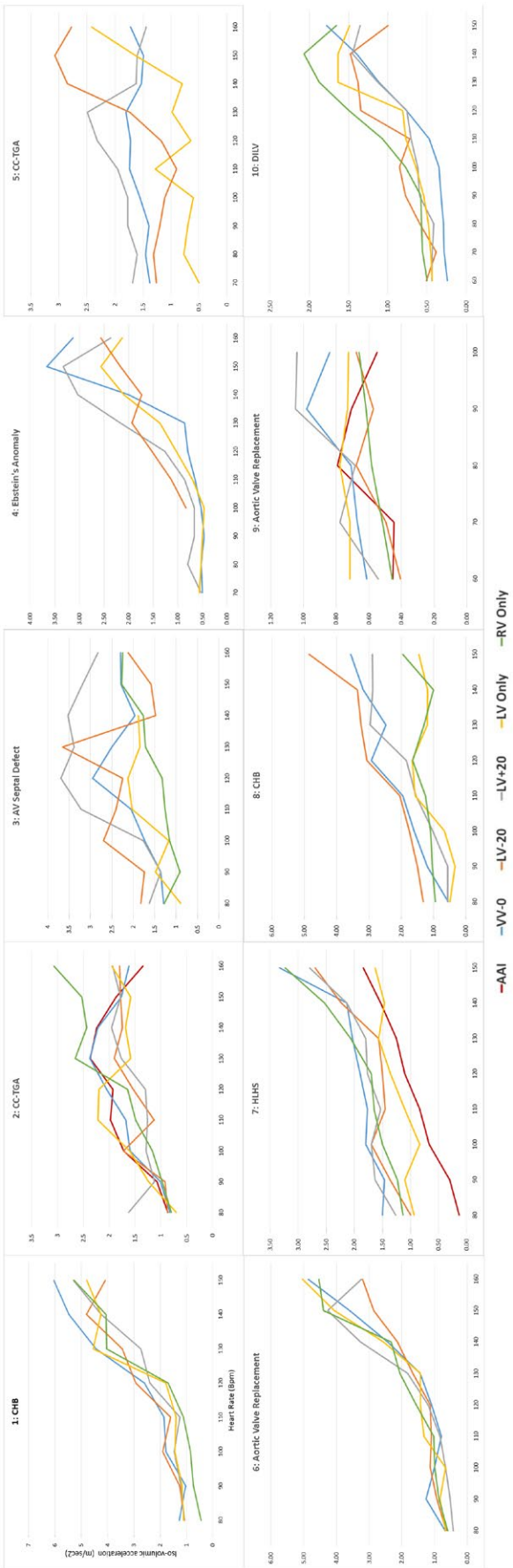

FIGURE 1 Ventricular force-frequency relationship obtained using different pacing modalities for each patient. The ventricular FFR for each patient is demonstrated with different pacing modality color-coded. Abbreviations: CHB, congenital heart block; CC-TGA, congenitally corrected transposition of great arteries; HLHS, hypoplastic left heart syndrome; DILV, double inlet left ventricle. Note: In patient #5: LV, systemic ventricle; RV, subpulmonary ventricle

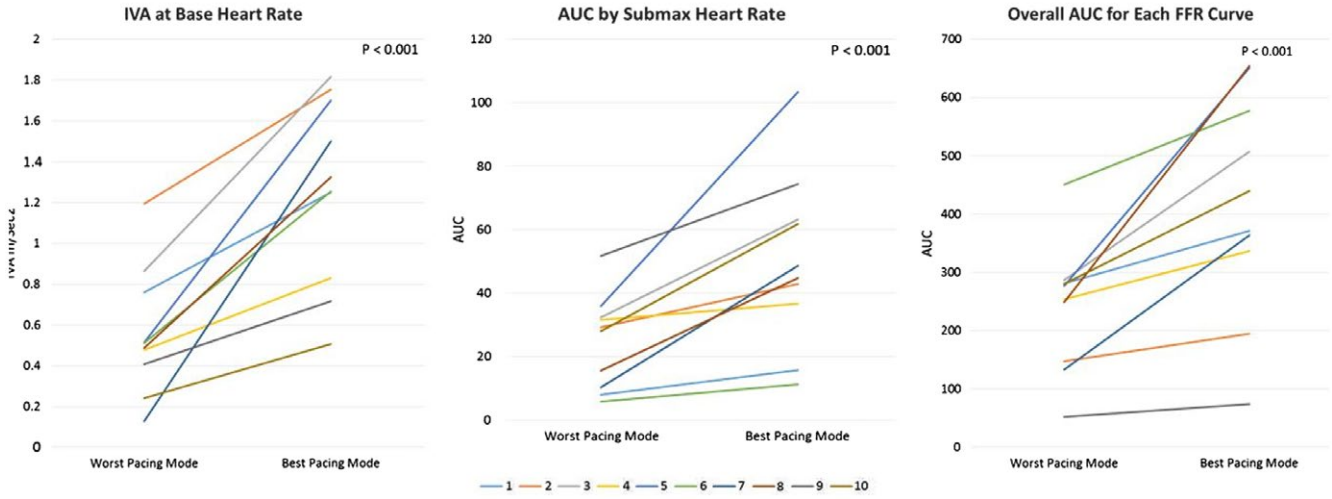

FIGURE 2 Comparison of IVA at baseline, AUC at submaximal, and overall AUC between best and worst ventricular pacing strategies. The graph demonstrates a significant difference between different ventricular pacing strategies at baseline, submaximal, and maximal heart rates. Abbreviations: AUC, area under the curve; IVA, isovolumic acceleration.

TABLE 2 Inter- and intrapatient variability defined by AUC

	Best mode at base heart rate	Best AUC from baseline through submaximal heart rate	Best AUC from baseline through maximal heart rate
1	VV-0	VV-0	VV-0
2	LV+20	LV	RV
3	LV-20	LV+20	LV+20
4	LV	RV	VV-0
5	LV+20	LV+20	RV
6	VV-0	LV	LV
7	VV-0	VV-0	VV-0
8	LV-20	LV-20	LV-20
9	LV	AAI	LV+20
10	LV-20	RV	VV-0

Abbreviations: AUC, area under the curve; LV, left ventricle; RV, right ventricle; VV, ventricle-ventricle delay.

upon exercise, accounting for approximately 40% of exercise-induced increase in stroke volume; however, future studies should assess the relationship between optimized FFR and exercise performance, perhaps with individualized changes in ventricular pacing modulation to optimize the peak force generation where appropriate.

5 | CONCLUSION

Noninvasive IVA-derived FFR offers a novel assessment of acute changes in BiV pacing parameters in patients with CHD and demonstrates a wide variability in optimal ventricular pacing emphasizing an individualized approach. Furthermore, the optimal strategy for ventricular pacing varies with heart rate within individuals, suggesting that rate-responsive modulation of pacing parameters may be required to optimize ventricular performance.

CONFLICT OF INTEREST

No conflict of interest specific to the work involved in this manuscript.

AUTHOR CONTRIBUTIONS

SB: Concept/design, Data collection, Data analysis/interpretation, Drafting article. ANR: Concept/design, Critical revision of article, Data analysis/interpretation. PRK: Statistics, Critical revision of the article. TKK: Critical revision of the article. DSS: Critical revision of the article. RJC: Concept/design, Drafting article, Critical revision of the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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