Left ventricular epicardial pacing achieved hyper-responsiveness in young children with dilated cardiomyopathy with left bundle branch block

Sijuan Sun†, Xiaofeng Guo†, Yiwei Chen†, Jie Shen, Diqi Zhu, Zhifang Zhang†, Lijun Fu, Wei Ji* and Fen Li*

1Department of Cardiology, Shanghai Children’s Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China; and 2Department of Cardiology, Fujian Children’s Hospital, Affiliated Hospital of Fujian Medical University, Fuzhou, China

Abstract

Aims The management of heart failure (HF) in young children is challenging. The present study aimed to clarify the effect of left univentricular epicardial pacing on dilated cardiomyopathy with left bundle branch block (LBBB) in children.

Methods and results A total of five cases (30.86 ± 16.39 months, three female) of children weighing 5.8–15 kg with dilated cardiomyopathy and LBBB were included in this study. LBBB in one child occurred after device closure of peri-membranous ventricular septal defects, and the remaining four were idiopathically discovered early after birth. Before implantation, all children suffered from refractory HF and cardiac dilatation; the left ventricular ejection fraction was 33.48 ± 5.84% with Ross Heart Failure Classification III–IV. Electrical and mechanical dyssynchrony were observed in all children with QRS duration >140 ms and prolonged septal-to-left posterior wall motion delay. Left univentricular epicardial pacing was successfully implanted via left axillary minithoracotomy in the five children. Sensed atrioventricular delays (83 ± 15 ms) were optimized by velocity time integral of aortic blood flow before discharge. During the follow-up period (10.8 ± 2.68 months), the dilated failing heart was reversed significantly in terms of decreased left ventricular dimension (55.62 ± 3.46 vs. 38.94 ± 3.69 mm, \(P = 0.005\)), while the left ventricular ejection fraction improved to 60.18 ± 8.78% (\(P = 0.006\)).

Conclusions In young children with low body weight, if HF is caused by or related to LBBB, left ventricular epicardial pacing still has an excellent effect.

Keywords Heart failure; Children; Left bundle branch block; Cardiomyopathy; Left univentricular pacing

Introduction

The prognosis of dilated cardiomyopathy (DCM) with idiopathic or iatrogenic left bundle branch block (LBBB) is poor in young children, especially infants,\(^1\)–\(^3\) which is difficult to deal with effectively except for heart transplantation. However, donors for heart transplantation in infants and young children are scarce. The positive response of cardiac resynchronization therapy (CRT) in adult heart failure (HF) with LBBB\(^4\)–\(^5\) facilitated its application in the paediatric population but was limited in young children because of the slim vessel size for transvenous approach, and hence, the left ventricular (LV) univentricular epicardial pacing against LBBB would be a safe and reliable technique. Despite the successful reversal of LV dysfunction in children with right ventricular pacing-induced cardiomyopathy and a case of cardiomyopathy with post-surgical LBBB,\(^6\) data from paediatric DCM with idiopathic or iatrogenic LBBB after septal interventions are available.
yet lacking. Thus, the present study aimed to evaluate the preliminary results of LV univentricular epicardial pacing in this group of children.

**Methods**

Between March 2018 and October 2020, five children (male/female = 2/3, mean age: 30.86 ± 16.39 months) were admitted to Shanghai Children’s Medical Center because of DCM with LBBB [QS or rS in leads V1 or V2 and mid-QRS notching or slurring in two or more contiguous leads (V1, V2, V5, V6, I, and aVL)] and refractory HF. All children met the criteria for DCM: LV dilation and systolic dysfunction in the absence of coronary artery disease or abnormal loading conditions proportionate to the degree of LV impairment.7

Left bundle branch block in one child (Patient 5) occurred after device closure of peri-membranous ventricular septal defects, and the remaining four were idiopathic, among which two (Patient 1 and Patient 3) had LBBB since birth. All cases were subjected to Ross Heart Failure Classification8 from III to IV, the average LV ejection fraction (LVEF) was 33.48 ± 5.84%, and the QRS duration was >140 ms despite at least 3 months of optimal pharmacological therapy. The obvious symptoms of HF occurred several years after the onset or discovery of LBBB. Four children underwent cardiac magnetic resonance imaging before pacing, and focal late gadolinium enhancement was observed at various regions of LV myocardium in two patients, among which the most obvious were septal subendocardium in Case 1 and midwall of septum in Case 2. Other potential causes for HF, including congenital heart deformation, myocarditis or ischaemic cardiomyopathy, and inherited endocrine and metabolic diseases, were excluded. Parents denied family history of cardiomyopathy or sudden cardiac death in all children; also, genetic abnormalities were screened negative in four children by whole-exome sequencing (Table 1).

The epicardial electrode was implanted into the LV epicardium via a left axillary minithoracotomy performed by a team of thoracic surgeons, as described previously.5 Before the operation, the family members of the children were informed about the choice of treatment and the possible operation risks. This study was approved by the Ethical Committee of Shanghai Children’s Medical Center (No. SCMCIACUC-K2019020). In the operation, unipolar steroid-eluting epicardial leads (Medtronic CapSure Epi 4965, Medtronic Inc., Minneapolis, MN, USA) were successfully implanted on the left atrial appendage and the LV anterior to lateral base. In addition, LV pacing sites were placed distal to the areas of positive late gadolinium enhancement (LGE+), based on the magnetic resonance imaging (MRI) before surgery. Generator was buried under the superior left greater pectoral muscle (Figure 1, B). All children adopted DDD(R) mode; the pacing

**Table 1** Baseline characteristics of patients

| Patients | Sex/ Age (year) | Cause of LBBB | LBBB onset or discovery age (year) | Implantation age (Months) | LVEF (%) | ROSS Classification | MR finding | Genetic Screening | Follow-up duration (Month) |
|----------|----------------|---------------|-----------------------------------|--------------------------|---------|---------------------|------------|------------------|--------------------------|
| 1        | male 8.6       | idiopathic    | newborn                           | 19.6                     | 35      | III                 | LGE (+)    | negative         | 8                        |
| 2        | female 14      | idiopathic    | newborn                           | 51                       | 38.6    | III                 | LGE (+)    | negative         | 14                       |
| 3        | female 5.8     | idiopathic    | newborn                           | 9.7                      | 23.5    | IV                  | LGE (+)    | negative         | 12                       |
| 4        | male 2.5       | idiopathic    | newborn                           | 2                        | 34      | III                 | LGE (+)    | negative         | 8                        |
| 5        | female 14.8    | iatrogenic    |                                   |                          | 36.3    | III                 | -          | -                | 12                       |

LBBB, left bundle branch block; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

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threshold, sense, and impedance for LV leads were 0.5–2.0 V/0.4 ms, 2.0–3.0 mV, 300–700 Ω, respectively. Then, atrioventricular (AV) delays were optimized by LV stroke volume using echocardiography and set at 83 ± 15 ms before discharge from the hospital. Because velocity time integral of aortic blood flow was considered the surrogate of LV stroke volume, a higher velocity time integral indicates optimization of LV fusion and optimal LV performance (Figure 2). The re-examination of electrocardiography also showed shortened QRS duration in these patients (Figure 3). The strategy of LV epicardial pacing achieved hyper-responsiveness that improved cardiac function. The LVEF was improved (33.48 ± 5.84% vs. 60.18 ± 8.78%, P = 0.006) with decreased left ventricular end-diastolic dimension (55.62 ± 3.46 vs. 38.94 ± 3.69 ms, P = 0.005) in all children (Supporting Information, Videos S1 and S2). A remarkable decrease was also confirmed in both LV end-diastolic and end-systolic volumes (219.73 ± 47.79 vs. 105.18 ± 25.43 mL, P = 0.01). SPWMD was also reduced from 230 ± 81.55 to 97 ± 29.92 ms (P < 0.001) in all patients (Table 2, Figure 4).

Discussion

Compared with older children and adults, DCM in young children is a major concern because of the lack of appropriate devices for treatment and heart transplantation donors. Presently, none of the physiological pacing techniques are suitable for young children because of the uncertainty and security risks brought about by growth and development. However, the present study provides a novel idea, and the subjects included five young children with a minimum age

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**Figure 1** Chest X-ray of a 4-year-old girl (Case 2) (A) before and (B) 5 months after pacing showed decreased heart size.
of 10 months and a weight of 5.8 kg. During the follow-up, LV epicardial pacing exhibited hyper-responsiveness in the five paediatric DCM cases with LBBB. Similar to adult results, correction of LBBB has the potential to reverse myocardial remodelling in paediatric DCM.

Over the previous decades, data from both animal models and human adults' observational studies demonstrated that the dyssynchronous electrical activation of isolated LBBB results in abnormal and inefficient contraction of LV wall, poor myocardial perfusion, and thus ventricular remodelling. However, the precise causative correlation between LBBB and DCM in young children was still unaffirmed. In the current study, four children presented idiopathic DCM and LBBB, discovered immediately after full-term birth with normal heart structure and function but deteriorated during 1 or 2 years of follow-up. Similarly, another one suffered from new-onset iatrogenic LBBB with gradual dilation of LV volume and decreased contraction performance before implantation. Because the alternative aetiology for HF was excluded, the development of DCM and reverse remodelling of LV after pacing in these cases may provide evidence for the causative and harmful effect of LBBB in newborn and young children.

Figure 2  Echo-guided optimization of atrioventricular delay (AVd) by velocity time integral (VTI) of aortic blood flow in Case 5. (A) AVd=120ms/ VTI 20.8cm, (B) AVd=90ms/ VTI 23.7cm.
Another finding of these cases was the MRI evidence of LV myocardial fibrosis in two patients before pacemaker implantation. Only a few studies reported that LBBB induced LGE+ cardiomyopathy previously and is rarely detected in children with DCM compared with high prevalence in adults. Furthermore, LGE+ in LV midwall of adults DCM was less likely to exhibit LV reverse remodelling after CRT, predicting a high rate of the combined endpoint of all-cause death and hospitalization for cardiovascular events. On the contrary, the correction of LBBB by left univentricular epicardial pacing in the current study effectuated better than expected results in the two LGE+ children, inferring that the improvement of electrical activation has significant potential for the reversal of myocardial remodelling in paediatric LGE+ DCM. One of the reasons for the different outcomes may refer to the distinct pathological entities in the development of paediatric DCM, including less adverse myocardial remodelling and innate immune activation. This phenomenon clarified that the cause of HF in these children is LBBB, not idiopathic myocardial disease. Obviously, when LBBB is corrected, the myocardial function and potential of young children are much better than those of adults. In addition, LV leads were placed away from scarred myocardium guided by MRI, which might also increase the success rate of resynchronization therapy in our patients.

Limited by the small venous diameter and coronary sinus, the traditional transvenous lead is not applicable to young children with HF. As a specific CRT, left univentricular epicardial pacing and reserved intrinsic AV conduction in the right ventricle create haemodynamic benefits similar to

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**Figure 3** Electrocardiography showed improved QRS duration after left ventricular univentricular pacing in Case 1. (A) pre-implantation, (B) After-implantation.
Left ventricular epicardial pacing achieved hyper-responsiveness in young children

Table 2 Comparison of the clinical data between the pre-implantation and follow-up periods

|                  | Pre-implantation | Follow-up periods | P-value |
|------------------|------------------|-------------------|---------|
| HR (beat/min)    | 126.60±11.46     | 85.8±11.11        | 0.017*  |
| QRSd (ms)        | 154.40±6.99      | 113.40±19.51      | 0.013*  |
| NT-proBNP (pg/ml)| 8213.20±5493.88  | 195.40±59.62      | 0.031*  |
| CTR (%)          | 0.654±0.0095     | 0.585±0.043       | 0.013*  |
| SPWMD (ms)       | 230±81.55        | 97±29.92          | 0.005*  |
| LVDd (mm)        | 55.62±3.46       | 38.94±3.69        | 0.005*  |
| LVEDV (ml/m²)    | 219.73±47.79     | 105.18±25.43      | 0.01*   |
| LVEF (%)         | 33.48±5.84       | 60.18±8.78        | 0.006*  |

CTR = cardiothoracic ratio; HR, heart rate; LVDd = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; QRSd = QRS duration; SPWMD = Septal-to-posterior wall motion delay; *Significant in statistical analysis, p < 0.05.

Figure 4 Graphs (A–D) depict the change in measurement in left ventricular end-diastolic dimension (LVDd), left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), and septal-to-left posterior wall motion delay (SPWMD).

those of biventricular pacing.17 Also, successful improvement of cardiac function was reported in cases of children after the implantation.18 To achieve the best haemodynamic effect, during the follow-up measurement, we used LV stroke volume to optimize AV delays at the resting state of the children, which provides an optimal LV fusion, decreased QRS duration, and improved LV remodelling.

In addition to surgical procedures, the selection of LV lead position was another essential factor for successful pacing and better outcome in our patients. Although the 2013 guidelines from the European Society of Cardiology suggested the latest activated area as the promising position for transvenous LV lead in adults CRT,19 there is yet a lack of accepted consensus or large randomized controlled trials.
in children with HF. Because the lateral base was often the latest activated epicardial area of the LBBB activation pattern, considering the myocardial fibrosis on MRI, we chose the anterior to the lateral wall as the LV pacing site, which significantly improved the LV electrical and mechanical synchrony of our patients. Moreover, it is also the easiest place to implant LV electrodes in young children during cardiac surgery. Similar reverse remodelling of LV was reported in a 3-year-old girl with idiopathic DCM and LBBB with the implant at the LV posterior wall. Nevertheless, further studies are needed to confirm the best LV epicardial lead pacing site and predictor elements for CRT responders in this group of patients.

Additional studies with evidence from other imaging techniques, such as speckle tracing and three-dimensional echocardiography or MRI during the follow-up, are essential to evaluate the long-term impact of LV epicardial pacing in young children.

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Conflict of interest

None declared.

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Supporting information

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

Video S1: Apical four chamber view of case 1 before implantation.

Video S2: Three months after implantation, apical four chamber view of case 1 showed improved LV systolic function and decreased LV cavity.
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