Received: 7 October 2019 | Accepted: 15 March 2020

DOI: 10.1111/pace.13908

PACE WILEY

DEVICES

Left ventricular (LV) pacing in newborns and infants: Echo assessment of LV systolic function and synchrony at 5-year follow-up

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

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Background: Small retrospective studies reported that left ventricular (LV) pacing is likely to preserve LV function in children with isolated congenital complete atrioventricular block (CCAVB). The aim of this study was to prospectively evaluate LV contractility and synchrony in a cohort of neonates/infants at pacemaker implantation and follow-up.

Methods: Patients with CCAVB who underwent LV pacing were evaluated with electrocardiogram and echocardiogram in a single-center, prospective study. Data were collected at implantation, at 1-month and every year of follow-up, up to 5 years. LV ventricular dimensions (diameters and volumes), systolic function (ejection fraction [EF] and global longitudinal strain [GLS]), and synchrony were evaluated. Data are reported as median (25th-75th centiles).

Results: Twenty consecutive patients with CCAVB underwent pacemaker implantation (12 single-chamber pacemaker [VVIR] and eight dual-chamber pacemaker [DDD]) with epicardial leads: 17 on the LV apex and three on the free wall. Age at implantation was 0.3 months (1 day-4.5 months). Patients showed good clinical status, normal LV dimensions, preserved systolic function, and synchrony at 60 (30-60) months follow-up. EF increased to normal values in patients with preimplantation EF <50%. Presence of antibodies and pacing mode (DDD vs VVIR) had no impact on the outcome.

Conclusions: LV pacing preserved LV systolic function and synchrony in neonates and infants with CCAVB at 5-year follow-up. LV EF improved in patients with low preimplantation EF. Pacing mode or the presence of autoantibodies did not demonstrated an impact on LV contractility and synchrony.

KEYWORDS

alternative pacing sites, cardiac pacing, children, congenital atrioventricular block, heart failure

1 | INTRODUCTION

Permanent cardiac pacing is challenging in neonates and infants with congenital complete atrioventricular block (CCAVB). Indeed, pacing-induced ventricular dyssynchrony may cause left ventricular (LV) remodeling and dysfunction in 5-30% of infants.[1-5] Epicardial LV pacing has been shown to preserve ventricular function and synchrony in retrospective studies.[6-9] Early results have been already presented

Abbreviations: bpm, beats per minute; CCAVB, congenital complete atrioventricular block; DDD, dual-chamber pacemaker; ECG, electrocardiogram; EF, ejection fraction; GLS, global longitudinal strain; IVMD, interventricular mechanical delay; LV, left ventricular; LVA, left ventricular apex; LVFW, left ventricular free wall; n.v., normal value; SDI, systolic dyssynchrony index; SPWMD, septal to posterior wall motion delay; VVIR, single-chamber pacemaker.

in our previous prospective study on LV pacing in a small cohort of patients.[10] On this ground, in the present study, we report the outcome of a larger group of neonates and infants with CCAVB treated with LV epicardial pacing through a longer follow-up period.

2 | METHODS

Between 2010 and 2018, all consecutive neonates and infants referred to the Cardiac Arrhythmias Unit of Bambino Gesù Children's Hospital (Rome) for CCAVB requiring pacemaker implantation were enrolled in this single-center, prospective study. The study population included patients with CCAVB without other congenital heart defects. The following data were recorded: demographic characteristics, including age and size of patients, pacing system implanted, electrocardiographic and echocardiographic findings at implantation and during follow-up, and clinical status at the most recent follow-up.

The study complies with the Declaration of Helsinki. The research protocol was approved by the locally appointed ethics committee. Informed consent was obtained from the guardians of all patients.

2.1 | Implant procedure, pacemakers, and leads

All patients routinely underwent electrocardiogram (ECG) and echocardiogram evaluation before implantation.

The surgical technique used for pacing system implantation at our Center was already described.[10] Briefly, a midline sternotomy or a subxiphoid incision is performed and the pacing leads are sewn to the epicardial surface of the heart. The epicardial leads are tunneled to the abdomen, and the pacemaker is placed in a pocket created beneath the posterior fascia of the rectus abdominis. Indications for pacing were in accordance with the guidelines of the European Society of Cardiology.[11]

The sites of lead implantation were the left ventricular apex (LVA) beyond left anterior descending coronary artery at a minimum distance of 5 mm, and the left ventricular free wall (LVFW) toward the apex. Unipolar (Medtronic 4965) or bipolar (Medtronic 4968) steroid-eluting leads were directly affixed and sutured to the epicardium. The location of the stimulating electrode (cathode) was considered the site of implantation of bipolar leads.

Dual-chamber (DDD) and single-chamber (VVIR) pacemakers were implanted. At our Center, DDD are implanted in neonates/infants with a body weight ≥3 kg and VVIR in neonates <3 kg. Lower rates at implantation range from 60 to 130 beats per minute (bpm). In fact, DDD pacing with normal sinus node function requires slow minimum rates (60-90 bpm) to allow spontaneous sinus rhythm (atrial sensing-ventricular pacing). On the other hand, VVIR pacing requires minimum rates of 100-130 bpm to give an adequate rate to the newborn. Upper rates range from 160 to 200 bpm, and 160 bpm is the upper limit of small VVIR pacemakers (St Jude Abbott Microny) implanted in these patients. Instead, faster rates (170-200 bpm) are used in DDD pacing. In patients with DDD pacemakers, the sensed atrioventricular delay was optimized using Doppler echocardiography for mitral flow measurements (median: 100; 25th-75th centiles: 80-120 ms), and adapted to increases in heart rate (shortest 60, 50-90 ms).

2.2 | Follow-up

All patients were followed up at 1 and 6 months after implantation with clinical evaluation and telemetric pacemaker interrogation. Thereafter, the same evaluation was repeated every 6 months.

During in-hospital controls, a standard 12-lead ECG was recorded. Parameters recorded included sinus rate, ventricular rate in native rhythm and paced ventricular rate after implantation, QRS complex (QRS) duration, and JT interval corrected (JTc) duration. QRS and QT interval (QT)/JT interval (JT) duration were measured manually from standard ECG recorded at a paper speed of 25 mm/s and corrected according to Bazett's formula.[10,12] Paced ventricular rate was measured either in DDD, that is, atrial sensing-ventricular pacing, or in VVIR. In DDD pacing mode, sinus rate and paced ventricular rate are coincident.

Echocardiographic evaluation was generally performed once a year during follow-up. Standard M-mode, two- and three-dimensional parameters, and Doppler measurements were obtained.[10] Two-dimensional parameters included LV dimensions expressed as absolute values (left ventricular end diastolic diameter) and weight-related *Z*-scores, interventricular dyssynchrony, LV dyssynchrony, and global longitudinal strain (GLS).[13-14] Normal GLS in adults ranges from −15.9% to −22.1%, and in children it is age related: -18.3 ± 1.9 at 1 year and -22.5 ± 1.3 at 5 years of age.[15-16] Interventricular dyssynchrony was measured with the interventricular mechanical delay (IVMD), as the time from QRS onset to aortic flow onset minus QRS onset to pulmonary flow onset (normal value [n.v.] <40 ms). LV dyssynchrony was calculated with the septal to posterior wall motion delay (SPWMD; n.v. < 130 ms). Three-dimensional echocardiography was used to measure LV volumes (end diastolic and end systolic, left ventricular end diastolic volume and left ventricular end systolic volume, respectively), ejection fraction (EF) (normal: ≥55%, subnormal: <55%, and depressed: <45%). It also provided regional time-volume curves for the evaluation of LV dyssynchrony, assessed through systolic dyssynchrony index (SDI) calculation (normal: <5.5, mild: ≥5.5, moderate: ≥11, and severe LV systolic dyssynchrony: ≥15.5).[17] Synchrony indexes and LV EF were evaluated after implantation and at every-year follow-up. The assessment of interventricular and intraventricular dyssynchrony was not performed routinely prior to pacemaker implantation.

2.3 | Statistical analysis

Demographic and clinical data were reported as absolute numbers and percentages for categorical variables. Continuous variables were expressed as median and 25th-75th centiles. Differences across groups have been evaluated through Chi square or Fisher exact test for unmatched categorical data, or by McNemar test for matched categorical data. Comparison of continuous independent variables was performed by Wilcoxon Rank sum (Mann-Whitney) test and Kruskal-Wallis test. Wilcoxon signed-rank test or Friedman test was used

TABLE 1 Demographic and implantation data

	Number
Patients	20
Females	15
Age (months)	0.35 (1 day-4.5 months)
Weight (kg)	3.0 (2.4-6.4)
Height (cm)	50 (46-69)
Antibodies (yes)	9
Antibodies (not)	7
Ventricular rate (bpm)	55 (52-70)
Sinus rate (bpm)	140 (50-160)
QRS duration (ms)	60 (50-60)
JTc duration (ms)	390 (340-440)
LVEDD (mm)	21 (19-28)
LVEDD *Z*-score	0.9 (0.4-2.2)
LVEDV (mL)	13 (5-16)
LVESV (mL)	3 (2-6)
Ejection fraction (%)	59 (40-64)
VVIR pacing	12
DDD pacing	8
Paced QRS (ms)	80 (70-98)
Paced JTc (ms)	365 (345-370)
Ventricular lead, bipolar-unipolar	12-8
Lower rate (bpm)	90 (80-110)
Upper rate (bpm)	160 (160-190)

Abbreviations: bpm, beats per minute; DDD, dual-chamber pacemaker; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; VVIR, single-chamber pacemaker.

for continuous dependent variables. Multiple comparisons were performed by Dunn test. Spearman's Rho evaluated correlation between continuous variables.

All statistical analyses were conducted using StataSE 12.0 (StataCorp., College Station, TX, USA). A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographic characteristics

Between 2010 and 2018, 20 patients (15 females) with CCAVB underwent pacemaker implantation with epicardial ventricular leads placed in the left ventricle (Table 1). Autoantibodies (anti-SSA/Ro and anti-SSB/La) were detected in nine out of 16 patients with congenital CCAVB. In four patients, autoantibodies were not investigated.

3.2 | Pacemaker implantation and follow-up

Data at implantation are reported in Table 1. Age at implantation was 0.3 months (1 day-4.5 months). Ten patients were implanted below 10 days of age: four patients were implanted on the day of birth, three on the second day of life, and two on the third day. Native QRS was narrow in all but three patients who had broad QRS escape rhythm. The majority of patients had normal LV EF before pacemaker implantation. Only four patients showed an EF <50% before pacemaker implantation. Leads were implanted in LVA in 17 patients. At the beginning of this experience, LVFW was the implant site in three smaller patients, whereas LVA was the implant site in four larger patients (3.1 [2.6-8.0] kg and 6.0 [3.6-9.1] kg, respectively). Afterward, leads were always implanted on the LVA. Twelve patients received VVIR pacemakers (activity sensor) and eight DDD pacemakers.

Follow-up duration was 60 (30-60) months. Patients showed a percentage of ventricular pacing of 99.9% (range, 99-100%). All patients showed normal growth and were in good clinical status at follow-up, without drug treatment. No sign of congestive heart failure or dilated cardiomyopathy was observed in the whole cohort. A tendency toward decrease of sinus rate and paced rate at ECG was recorded as probable effect of growth (sinus rate) and of pacemaker programming (pacing rate). ECG data and echocardiographic findings are summarized in Table 2. Paced QRS duration, 80 (70-98) ms, was significantly longer than native QRS, 60 (50-60) ms, $P = .0009$. Echocardiography examination revealed normal LV dimensions, preserved LV systolic function, and synchrony throughout follow-up. Systolic function and synchrony parameters did not show significant differences at subsequent follow-up (Table 2). However, EF improved in all patients with low EF, reaching normal values. GLS was within normal limits in all patients. Figure 1 shows GLS measurements in two patients, one with LVA pacing and one with LVFW pacing. The presence of autoantibodies had no effect on LV systolic function.

3.3 | Comparison between pacing modes

DDD and VVIR pacing modes were compared. Patients implanted with VVIR pacemaker (12 patients, VVIR group) were younger than those with DDD pacemaker (eight patients, DDD group): 0.06 (0.03-1.3) months versus 7.0 (0.2-17.2) months, respectively ($P = .03$). VVIR group showed lower height and weight at implantation than DDD group: 46 (45-49) cm versus 69 (52-75) cm, $P = .002$, and 2.5 (2.0-3.0) kg versus 7.4 (4.3-8.9) kg, $P = .0006$. Native QRS of VVIR group was 50 (50-60) ms versus 60 (52-103) ms in DDD group ($P = .052$, not significant). As DDD group included older patients, LV dimensions were significantly larger than those of VVIR group. *Z*-score, instead, was not significantly different between groups. Heart rate, sinus rate, presence of antibodies, JTc, and EF were also not significant. Paced QRS was 80 (70-90) ms in VVIR group and 95 (73-100) ms in DDD group ($P = .1$). Lower pacing rate at pacemaker implantation was significantly higher for VVIR, 100 (90-120) bpm, than for DDD patients, 80 (80-88) bpm ($P = .001$). On the other hand, upper pacing rate was lower for VVIR, 160 (160-160) bpm, than for DDD patients, 190

TABLE 2 Echo and ECG data during follow-up

	1 month	1 year	2 years	3 years	4 years	5 years
Patients	20	20	17	15	15	14
Paced ventricular rate (bpm)	110 (92-120)	100 (95-117)	94 (86-108)	90 (80-110)	84 (80-98)	80 (75-90)
Sinus rate (bpm)	128 (110-148)	118(110-137)	95 (90-120)	105 (99-110)	100 (95-120)	101 (90-120)
QRS (ms)	80 (70-98)	90 (80-110)	90 (80-110)	95 (85-110)	100 (80-110)	100 (82-110)
JTc (ms)	365 (345-370)	350 (330-360)	340 (330-359)	340 (320-350)	330 (325-345)	330 (320-350)
LVEDD (mm)	24 (18-27)	27 (25-29)	29 (25-32)	33 (31-34)	35 (32-39)	36 (32-40)
LVEDD *Z*-score	0.3 (−0.1-0.9)	−0.1 (−0.7-0.5)	0.1 (−1.3-1.1)	0.1 (−0.1-0.7)	0.3 (−1.0-1.3)	0.2 (−0.9-0.9)
LVEDV (mL)	12 (5-20)	13 (11-16)	20 (15-23)	27 (18-30)	31 (23-41)	38 (29-43)
LVESV (mL)	4 (2-8)	6 (4-6)	8 (6-9)	10 (8-13)	11 (9-15)	14 (12-18)
EF (%)	60 (57-65)	59 (55-65)	60 (59-62)	59 (54-61)	62 (59-66)	59 (57-61)
GLS (%)	Not available	−23 (−25-−21)	−25 (−27-−24)	−24 (−25-−22)	−23 (−24-−21)	−24 (−26-−21)
IVMD (ms)	6 (5-16)	7 (3-15)	10 (4-28)	11 (3-28)	19 (8-24)	7 (1-14)
SPWMD (ms)	110 (70-130)	92 (70-106)	99 (70-106)	80 (74-100)	84 (47-102)	60 (30-90)
SDI	4.2 (2.7-6.7)	4.3 (2.7-6.1)	4.0 (2.0-10.0)	2.8 (1.5-5.2)	2.4 (1.7-3.6)	3.3 (2.5-4.3)

Note. Data examined did not show significant differences between subsequent follow-up times.
Abbreviations: bpm, beats per minute; EF, ejection fraction; GLS, global longitudinal strain; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular and diastolic volume; LVESV, left ventricular end systolic volume; IVMD, interventricular mechanical delay; NA, not available; SDI, systolic dyssynchrony index; SPWMD, septal to posterior wall motion delay.

(165-198) bpm ($P = .014$). During follow-up, systolic function (EF and GLS) and synchrony (SPWMD, IVMD, and SDI) did not show significant differences between the two groups. EF, GLS, and synchrony data did not vary significantly during follow-up in the two groups, as demonstrated in the whole cohort.

3.4 | Pacing system complications

Three leads of 28 (11%) fractured during the follow-up: one atrial and two ventricular. For the atrial fracture (after 2 years), the DDD PM was downgraded to VVIR without reoperation and the patient was censored from the comparison DDD-VVIR. The 2 ventricular leads fractured after 3 and 4 years. The two fractures were located proximally to the generator, and were repaired without any other changes of the pacing system. Two patients (10%) experienced early postoperative system infection: one mediastinitis (VVIR pacemaker) and one abdominal pacemaker pocket infection (DDD), both successfully treated with antibiotics, without system removal.

4 | DISCUSSION

In the last few years, alternative pacing sites in pediatric pacing have been more commonly used, either with endocardial pacing in the right ventricle[18,19] or with epicardial pacing in the LV. Retrospective studies in children have consistently shown that LV pacing is safe and effective in preserving LV synchrony and function.[8-9,20-22]

In 2015, our group published the first prospective study on this issue,[10] demonstrating a favorable clinical outcome of LV epicardial pacing at physiological rates in 10 neonates and infants with CCAVB with preserved ventricular contractility and synchrony at short-term follow-up.

Departing from those results, the present study showed that LV pacing seems effective in preserving LV contractility and synchrony in a larger cohort of newborns and infants also at longer follow-up. The 10 patients of the previous study completed the 5-year follow-up. All patients showed good clinical status during follow-up, without any signs or symptoms of heart failure or dilated cardiomyopathy. LV dimensions were in the normal range in all patients, without LV remodeling. Systolic function, assessed by EF and GLS, was preserved. It can be argued that EF is not a perfect index of contractility, being influenced by LV loads and volumes.[23] To obtain more relevant details about contractility, volumes and strain measurements were recorded. Two-dimensional speckle-tracking echo and the derived myocardial strain are good clinical tools and allow a different assessment of myocardial contraction than traditional methods as fractional shortening and EF. Myocardial strain expresses the inhomogeneous and complex contraction patterns of the different orientated cardiac fibers as percentage of regional ventricular deformation. Fiber orientation is circumferential in mid-wall layer and longitudinal in the endocardial and epicardial layers. Therefore, myocardial strain quantitatively characterizes left ventricle function. It has been demonstrated to be more effective than traditional methods in predicting early subclinical left ventricle dysfunction.[24]

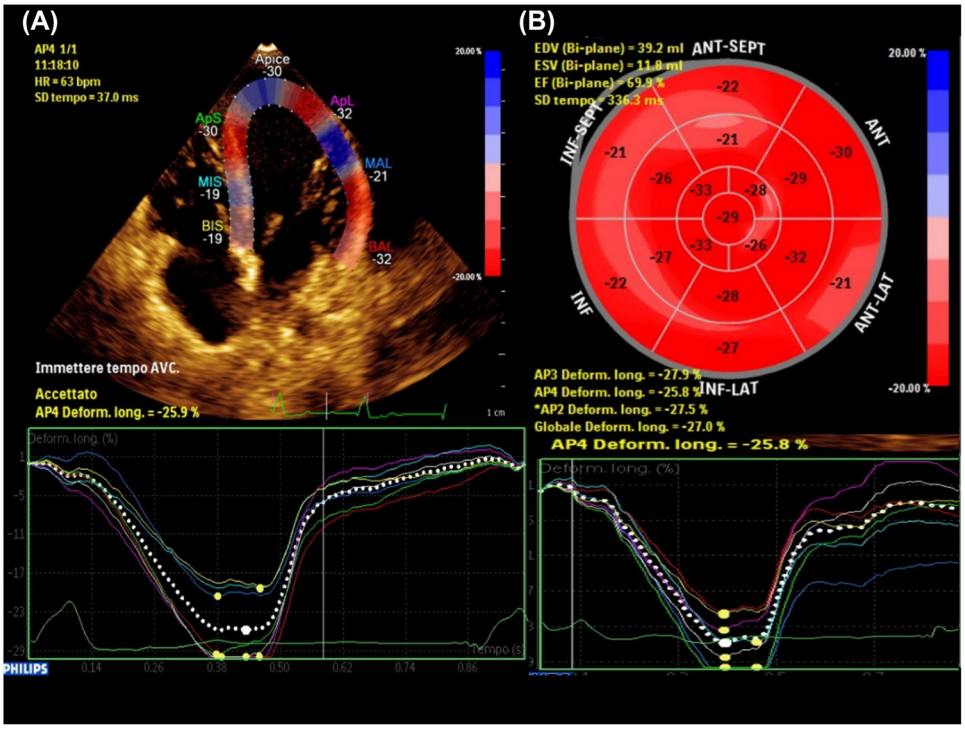

FIGURE 1 A, Two-dimensional speckle tracking global longitudinal strain (GLS) derived from the weighted average of the seven segments processed from the apical four-chamber view (top panel; BAL, basal anterolateral; MAL, mid anterolateral; ApL, apicolateral; ApS, apicoseptal; MIS, mid inferoseptal; BIS, basal inferoseptal) and the corresponding strain curves (bottom panel) of a patient with left ventricular apical pacing (Epiq 7G, QLab 10.4, aCMQ module; Philips Healthcare North America, Andover, MA, USA). B, Typical strain pattern in Bull's eye plot of peak systolic strain (top panel) of 17-segment model and longitudinal strain curves (bottom panel) calculated from segmental averaging of the three apical views: four, three, and two chambers in a patient with left ventricular free wall pacing. The image is uniformly red in color, which represents normal peak systolic strain in all segments with values given for each subsegments. ANT-SEPT, anteroseptal; ANT, anterior; ANT-LAT, anterolateral; INF-LAT, Inferiorlateral; INF, inferior; INF-SEPT, Inferiorseptal (Epiq 7G, QLab 10.4, aCMQ module; Philips Healthcare North America) [Color figure can be viewed at wileyonlinelibrary.com]
[Color figure can be viewed at wileyonlinelibrary.com]

LV pacing from LV apex (preferred site) or from the low free wall (used in three cases at the beginning of this experience) seems to produce a sequence of activation close to normal, probably due to the homogeneous spread of activation from the apex/low lateral wall toward the base, as expected in absence of delay of activation between septum and left free wall.[10] Moreover, in the small group of patients with reduced EF before pacemaker implantation, EF increased and normalized after LV pacing. Consequently, a positive functional effect of LV pacing can be predicted in infants or small children with CCAVB and impaired LV function. In addition, the effect on LV function is independent from pacing mode used, VVIR or DDD. A simple VVIR pacemaker is generally enough to preserve heart rate and LV function in low-birthweight infants with CCAVB and structurally normal heart.[25] DDD pacing is reserved to newborns/infants with larger body dimensions (≥3 kg in our experience) to reduce the risk of surgical complications. System infection was not significantly different in single- and dual-chamber systems. It occurred in two patients (10%), one with VVIR and one with DDD pacemaker.

Previous studies described pacing-induced cardiomyopathy in neonates and infants. The incidence of dilated cardiomyopathy in neonates with CCAVB treated with permanent pacing is reported at around 5-11%.[2-4] Moak et al found that congestive heart failure is likely to occur in the first 2 years in these patients.[3] A previous study from our group[5] demonstrated the appearance in the first year of life of dilated cardiomyopathy and heart failure in 32% of neonates/infants paced for CCAVB because of high-rate RV-pacing-induced electromechanical dyssynchrony. Therefore, in newborns/infants with CCAVB, the risk of pacing-induced dilated cardiomyopathy and heart failure is high and presents early, in the first 1-2 years of age. Consequently, the results of the current study are relevant, showing that LV pacing does not cause impairment of LV systolic function, at least for the first 5 years of life/pacing. With LV pacing, high pacing rates, as in DDD pacing, had no deleterious effects on LV function, unlike the worse outcome detected with right ventricular free wall pacing.[5]

In this study, the presence of SSA/SSB antibodies was not predictive for dilated cardiomyopathy, as reported by previous studies.[2-5] Further, in the study of Udink ten Cate et al, patients with CCAVD that did not implant a pacemaker did not develop dilated cardiomyopathy.[4] Thus, the pacing site, RV free wall or LV apex/low free wall, seems to be the most important determinant of LV function in children with CCAVB, regardless of the serological pattern. Pacing mode (DDD

or VVIR) did not demonstrate an impact on LV function in newborns/infants, as described earlier in older age groups.[2,22]

5 | LIMITATIONS

The limitations of this study are as follows: the single-center study, the relatively small number of patients (common to most pediatric studies), and the follow-up not longer than 5 years. Moreover, echo-derived measurements have been used as sole criteria of ventricular function. Indeed, echo measurements can be biased and subjective to individual interpretation. EF is not a perfect index of contractility, as it is influenced by LV loads and volumes.[23] Then, volumes and strain measurements were registered[24] to better assess contractility. The automated quantification of myocardial strain reduces the measurement errors, the interobserver variability, and intraobserver variability and improves accuracy and reproducibility of this method. It can be questioned that no patient underwent direct hemodynamic contractility measurements. However, the hemodynamic assessment is an invasive test that in this cohort was not necessary due to the good clinical status of patients and possible procedural risks. Cardiac magnetic resonance is another effective noninvasive functional tool, but it is not allowed with epicardial leads.

6 | CONCLUSIONS

In a cohort of neonates and infants with CCAVB, LV pacing demonstrated at 5-year follow-up:

1. to be effective in maintaining good clinical status;
2. to preserve LV systolic function and synchrony;
3. that high DDD pacing rates did not show deleterious effects on LV function; and
4. to increase EF in patients with impaired LV function before pacemaker implantation.

These findings provide additional pacing and electrocardiographic and echocardiographic data that may improve our knowledge of pacing physiology in small children with CCAVB.

AUTHOR CONTRIBUTIONS

Massimo Stefano Silvetti and Fabrizio Drago were associated with concept/design, data analysis/interpretation, drafting article, critical revision of article, and approval of article. Giulia Muzi, Marta Unolt, Carolina D'Anna, and Corrado Di Mambro assisted in data collection, data analysis/interpretation, drafting article, critical revision of article, and approval of article. Fabio Anselmo Saputo was associated with data collection, data analysis/interpretation, and approval of article. Sonia Albanese and Antonio Ammirati assisted in data collection, data analysis/interpretation, critical revision of article, and approval of article. Lucilla Ravà was associated with data analysis/interpretation, statistics, critical revision of article, and approval of article.

ACKNOWLEDGMENT

The authors thank Dr Elisa Del Vecchio for her valuable collaboration in the editorial revision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Silvetti MS, Muzi G, Unolt M, et al. Left ventricular (LV) pacing in newborns and infants: Echo assessment of LV systolic function and synchrony at 5-year follow-up. *Pacing Clin Electrophysiol*. 2020;43:535–541. https://doi.org/10.1111/pace.13908