Closed Loop Stimulation Improves Ejection Fraction in Pediatric Patients with Pacemaker and Ventricular Dysfunction

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Background: *The aim of this prospective study was to evaluate the effect of the closed loop stimulation (CLS) on the ejection fraction in pediatric patients, affected by complete atrioventricular block (CAVB) or CAVB and sinus node dysfunction (SND), with a previously implanted pacemaker (PM) and ventricular dysfunction. The role of electrical therapy in the treatment of pediatric patients with congenital atrioventricular (AV) blocks has been shown. Conventional right ventricular pacing seems to affect ventricular function. Up to now, the feasibility and the long-term results of biventricular pacing in pediatric patients were not entirely clear.*

Methods: *In eight pediatric patients with a previously implanted single or dual chamber PM, ventricular dysfunction, and CAVB or SND and CAVB, a dual chamber PM INOS^{2+}-CLS (Biotronik GmbH, Berlin, Germany) was implanted. The effect of the physiological modulation of CLS pacing mode on the ejection fraction was evaluated by Echo-Doppler examination. Measurements were performed before the substitution of the old PM and for up to 2 years of follow-up.*

Results: *All patients showed correct electrical parameters at implantation and during follow-up. The mean value of the ejection fraction measured before the replacement of the old PM was 36 $\pm$ 7%, while after 2 years it was 47 $\pm$ 1% ($P < 0.003$). No patient showed any worsening of the ejection fraction, while only one showed no improvement.*

Conclusions: *DDD-CLS pacing seems to improve ventricular function in pediatric patients with CAVB and/SND in spite of the use of the apical right conventional stimulation. (PACE 2007; 30:33–37)*

pediatric age, physiological pacing, ventricular dysfunction

Introduction

The effectiveness of electrical therapy in the treatment of complete atrioventricular block (CAVB) has been shown, but there is concern about age and time duration of right ventricular apical site pacing.[1–5] Experience has underlined that a subset of these particular patients develops ventricular dysfunction. Literature seems to show that ventricular stimulation, in spite of its necessity, might impair ventricular function.[6–10]

Recently, some authors have demonstrated that in adult patients a biventricular stimulation reduces the consequences of right apical stimulation (paradoxical septal motion, synchronism of contraction of the two ventricles, decreased cardiac output, structural myocellular remodeling).[11] However, in children, the use of this pacing system is still controversial and the data are still limited.[12]

In the last decade, several studies have showed the efficacy of closed loop stimulation (CLS) system in the modulation of the heart rate using an indirect measure of the ventricular contractility.[13–15] Closed loop stimulation is a new sensor concept for rate adaptive pacing measuring changes in the unipolar right ventricular impedance, which correlates to changes of the right ventricular contractility and reflects the autonomic innervations of the heart. This system responds to both physical and non-physical stressors, providing physiological pacing rate and preserving the physiological course of the systolic and diastolic pressure.[16–18]

The aim of this prospective study was to evaluate the effect of CLS system on the ejection fraction in pediatric patients with a previously implanted pacemaker (PM) and ventricular dysfunction affected by CAVB or CAVB and sinus node dysfunction (SND).

Method

Since June 2003, in our Institution, all patients with ventricular dysfunction and a previously percutaneously implanted single or dual chamber PM

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Table I.

Clinical Characteristics of the Study Population

Patient No.	EF Pre-CLS	EF Post-CLS	Delta	PM Pre-CLS	Atrial Pacing	Other Cardiopathy	Drug Tx	Age 1st Implant	Age CLS Implant
1	31	50	63%	VVI	70%	PS Interv. Def. Left Isom	NO	9 months	19
2	38	48	26%	DDD	42%	PA Interv. Def.	Ace inh. Digoxin	4	17
3	29	33	14%	DDD	60%	MR pAVSD	Digoxin Warfarin	6	14
4	32	44	37%	VVI	44%	ToF	NO	1	11
5	29	50	72%	VVI	59%	– –	Ace inh. Digoxin Warfarin	9	14
6	48	57	19%	AAI	71%	TAPVR	NO	10	15
7	34	34	0%	DDD	65%	–	NO	2	16
8	47	63	34%	VVI	78%	MR	NO	2	14
Total	37	47	27%	–	61%	–	–	4	15

PS = pulmonary stenosis; PA = pulmonary atresia; MR = mitral regurgitation; ToF = Tetralogy of Fallot; TAPVR = total anomalous pulmonary venous return; pAVSD = partial atrioventricular septal defect; EF = ejection fraction; PM = pacemaker; CLS = closed loop stimulation pacemaker.

(depending on the clinical characteristics of the patients) for CAVB (3 patients with a previous VVI PM) or CAVB and SND (5 patients, 1 with a previous VVI PM, 3 with a DDD PM, and another with an AAI PM) underwent PM upgrading or replacement with a dual chamber PM INOS^{2+}-CLS (Biotronik GmbH, Berlin, Germany). The technical details about the system upgrading in our Institution have already been reported.[19]

The characteristics of dual chamber PM INOS^{2+}-CLS have already been described.[13–18] Briefly, it performs a CLS pacing mode that is a physiological stimulation according to an indirect evaluation of ventricular contractility. Such evaluation is obtained using the values of intracardiac impedance measured by a subthreshold pulse train delivered in unipolar fashion between the ventricular catheter tip and the device. Echocardiographic examinations were performed before and after INOS^{2+}-CLS implant at every follow-up visit. We observed the evolution of the left ventricle ejection fraction, calculated in 4 chamber and 2 chamber views by the Biplane Simpson-modified method ($V = (A1+A2)h+A3h/2+\pi h^3/6$)*. Ejection fraction was derived from these volumes, and left ventricular mass was estimated using the area-length method. A video recording of each examination was re-examined twice by both investigators to reduce the operator dependence of the exam. To reduce any methodical errors, we performed accurate and repeated echo recordings.[20–22]

We compared the ejection fraction data obtained before the implantation of INOS^{2+}-CLS with those performed after 2 years of follow-up.

For statistical analysis, it has been assumed that the series of values of the ejection fraction before and after the INOS^{2+}-CLS implant had a normal distribution. Thus the mean value and the standard deviation were used to describe such series, and the parametric *t*-test to two tails for coupled data was used to verify the significance of the difference.

*V = ventricle volume, during the systole and the diastole; A1,A2,A3 = cross-sectional areas of the left ventricle, calculated in mitral annulus, near the papillary musculars and near the apex; h = apical-base diameter/3.

Results

Since 2003, in our study population of 341 pediatric patients who underwent PM implantation, 8 subjects (5 boys) fulfilled the criteria for enrollment. The mean age at the first PM implant was 4 years (range 0–10 years), while it was 15 years (range 11–19 years) at the CLS replacement time (for detailed clinical characteristics, see Table I). All devices were implanted using endocardial leads. Three patients had been submitted to medical therapy before the CLS replacements, which was not modified during the 2 years of follow-up (see Table I).

The PM parameters were programmed according to the clinical conditions of the patients with a lower rate range of 50–70 bpm and an upper CLS rate range of 140–160 bpm. All electrical values of sensing, impedance, and pacing threshold were in the standard range during replacement and follow-up.

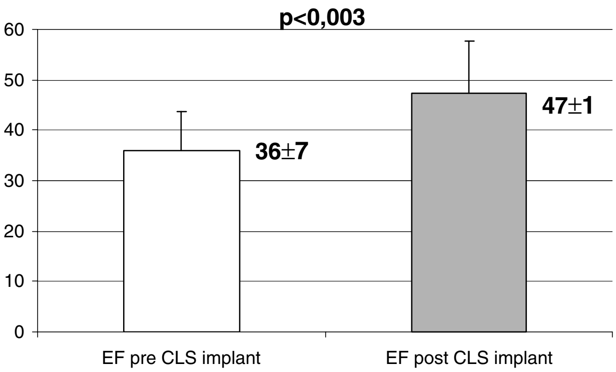

Figure 1. *Mean Value of ejection fraction before CLS implant and after 2 years.*

The ventricular pacing percentage was 100% in all patients. The mean value of atrial pacing percentage was 61% (see Table I).

No complications, intolerance to the stimulation, or dysfunctions of the systems were observed.

After 2-year follow-up, all patients were in good clinical conditions. The ejection fraction showed a significant increase in all patients except for the one case where no difference was recorded (for details, see Table I and Fig. 1).

Discussion

CAVB and SND, in pediatric age, have a very low incidence with a benign prognosis.[1] PM implantation, sooner or later, is the primary treatment,[1,2] and ventricular pacing seem to be very effective at least in the mid-term follow-up.[4,5]

In literature, a single or a dual chamber PM implantation is reported with the ventricular electrode generally located in the right ventricular apex.[19] Nevertheless, up to now, the effects of this type of stimulation after a long-term follow-up are still on debate. In fact, while Tantengco et al.,[23] Cron et al.,[24] Thackray et al.,[25] and Faris et al.[26] suggest that such stimulation can cause progressive cardiac muscular disarray with progressive biventricular dilatation and dysfunction, other authors reported series of children who did not develop any ventricular dysfunction.[1–6]

PM implant in patients with dilated cardiomyopathy is a very different problem. Some recent trials carried out in adult patients[27,28] have demonstrated that interventricular and intraventricular desynchronization are able to cause a ventricular dysfunction with a reduced ejection fraction, and that a device able to resynchronize the contractility of both ventricles can improve the ejection fraction and the New York Heart Association (NYHA) class. Therefore, very recently, international guidelines recommend to choose a biventricular PM in adult patients with ventricular dysfunction and signs of lack of ventricular synchronization.[29]

Although biventricular stimulation has been tried in particular pediatric patients with very interesting results during the short-term follow-up,[23,30–32] the general opinion is that the use of multiple transvenous leads in pediatric patients is not to be recommended. In fact, due to the physiological growth, many complications may occur later, such as lead dislocation or rupture, deep venous thrombosis, and very difficult lead extraction.[12,19,32–34]

Probably, in pediatric patients, an interesting solution of this problem may come from the evaluation of the effectiveness of an alternative site of ventricular stimulation. In fact, a normalization of the left ventricular function was reported in patients affected by ventricular dysfunction, locating the tip of the ventricular lead in the basal segment of the interventricular septum.[35]

In our study, we tried to increase the ejection fraction of a group of previously implanted pediatric patients with ventricular dysfunction, using a new type of pacing mode, the CLS pacing mode.

Closed loop control is a physiological principle that allows any system to react to external influences to restore the equilibrium.[13–15,19] The ideal method for obtaining a physiological PM system would be the integration of the pacing device into the natural cardiocirculatory system.[19] This concept has been realized in the CLS pacing mode, which converts information from the circulation applied to the right ventricle into a concordant heart rate. Based on this relationship, the INOS2 CLS PM detects changes in myocardial contraction dynamics through intracardiac impedance measurement and transfers them into individual pacing rates.[24,36,37] Therefore, CLS PM responds physiologically to all cathecolaminergic situations even to mental or emotional stimuli, unlike accelerometric rate responsive PM. This important feature could allow the heart to reduce the parietal stress, due to a chronotropic incompetence, during these particular situations and consequentely to reduce fatigue and increase the performance with time.

As is well known, the ejection fraction, used alone, is not the best index to evaluate the ventricular function. In the adult population, it has often been associated with other echocardiographic parameters, like the volume across the aortic valve, index of the single heart beat ejection. But, up to now, in children, there were no guidelines about the usefulness of these parameters. Moreover, in a growing heart, it is very difficult to use parameters, like volumes or diameters, to evaluate the effectiveness of a therapy on ventricular function.

The results of this study show a real increase of ejection fraction in our patients and seem to confirm a similar experience conducted in adult subjects by Cron et al.[24] This author, very recently, observed a reduction of the NYHA class in adult patients implanted with a CLS PM.

In our opinion, the positive effects of the CLS mode could depend on the capability to regulate the heart rate measuring the impedance of the ventricular walls, indirect expression of the strain of the muscular fibers and, therefore, of sympathetic activity.[13–15,19,24,36–38]

In our population, before CLS implantation, all patients, except 1, showed an increase of the ejection fraction. In the 5 patients, in whom we realized an upgrading of the stimulation system, we cannot totally exclude that the increase of the ejection fraction was a consequence of this procedure, and, actually, the highest increase of ejection fraction was found in these particular patients. But, if this is true, it is also true that a good result was found also in the patient who underwent an upgrading from AAI to DDD in which the ventricular desynchronization should have had, according to most recent reports, a negative inotropic effect. Moreover, as is well known, literature reports that pediatric patients, with normal cardiac function, have no advantages, in terms of cardiac output, with a dual chamber stimulation in comparison to a single chamber stimulation.[39–42]

In conclusion, our experience, in such a limited series of patients, seems to show that CLS pacing mode, with the conventional right ventricular stimulation in pediatric subjects, with an already implanted PM and ventricular dysfunction affected by CAVB or CAVB and SND, can improve the ventricular function in the mid-term follow-up. It is clear that a randomized, controlled study, with a larger series of patients, shall be necessary to confirm these preliminary data.

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