Long term follow-up of children with heart block born from mothers with Systemic Lupus Erythematosus: a retrospective study from the database pediatric and congenital heart disease in University Hospitals Leuven.

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ABSTRACT

25 Background: Children from mothers with Systemic Lupus Erythematosus are frequently born with congenital heart block. This study aimed at evaluating long-term outcome because long-term data are scarce.

30 Methods: In the database pediatric and congenital heart disease (University Hospitals Leuven), 19 children from Systemic Lupus Erythematosus mothers and who were born with or developed atrio-ventricular block were identified. All records were reviewed for disease course and outcome.

35 Results: Median follow up time was 7 years (IQR 4.5-13 years). One child had no heart block at birth and developed only a first-degree block during follow-up. One had a second-degree heart block and developed a complete heart block. Seventeen patients (89%) were born with a complete heart block. Seventeen patients (89%) needed a definitive pacemaker. In all, epicardial leads were used at first implantation. Eighty-two percent received their pacemaker in the first year of life. The first battery had a median lifetime of 5 years (IQR 3.5-5 years), the second 6 years (IQR 4.5-6.3 years) and the third 5 years (IQR 5-6 years). 47% of patients needed a lead replacement due to lead problems. Only one pericardial tamponade after pacemaker implantation. No device or lead infections occurred. The left ventricular
40 systolic function at latest follow-up was normal for all. No patients died.

Conclusion: In children with heart block born from Systemic Lupus Erythematosus mothers, an early need for pacemaker implantation was documented. The overall battery life was acceptable, but there was a high need for lead replacement. Complication rate was low. Late outcome was good.

Key words: congenital heart block, neonatal lupus, pacemaker, epicardial

INTRODUCTION

Pregnant patients with Systemic Lupus Erythematosus are known to be at increased risk for miscarriage, intrauterine growth restriction, preterm delivery and perinatal fetal death (1).

Much has been reported concerning the outcome of mothers with Systemic Lupus Erythematosus during pregnancy. However, literature is scarce about the outcome of newborns from Systemic Lupus Erythematosus mothers suffering from heart block.

Congenital atrio-ventricular heart block is a rare illness, affecting 1 in 15.000 to 20.000 live births (2). The large majority of congenital heart block cases (60-90%) presenting in utero or in the neonatal period are due to neonatal lupus. The fetal heart is perfused with maternal anti-Ro/Anti-Sjögren's-syndrome-related antigen antibodies crossing the placenta (3,4).

Congenital heart block is a rare manifestation among neonatal lupus symptoms and the prevalence is now reported to be 1–2% in pregnant women with anti-SS-A antibodies (5).

Maternal antibodies, which start crossing the placenta as early as eleven weeks of gestation, are associated with the development of cardiac anomalies, rash and/or various liver and blood cell abnormalities in the newborn. Clearance of the antibodies occurs in the 6th to 8th month of postnatal life. In contrast to regenerative processes in the skin, the hepatobiliary, and the hematologic system, this regeneration does not occur in cardiac tissue. Indeed, definitive reversal of a third degree congenital heart block has never been observed (6). This is explained by disruption of the atrio-ventricular conduction system by the maternal antibodies. The latter cause inflammation with subsequent fibrosis and calcification, which leads to an irreversible complete atrio-ventricular block (6).

In 1998, Buyon et al published the first large series of auto-immune associated congenital heart block based on 'The Research Registry for Neonatal Lupus' in the United States. They found that autoantibody-associated CHB is not coincident with major structural abnormalities, carries a substantial mortality in the neonatal period and frequently requires pacing (7). The aim of our study was to evaluate children with congenital heart block born from mothers with Systemic Lupus Erythematosus evaluating 1/ The presence at birth and persistence during follow-up of heart block, 2/ The presence of associated structural cardiac abnormalities at birth and during follow-up, 3/ The need for, timing of and complications related to pacemaker implantation, 4/ Late effect on left ventricular systolic function and 5/ Survival.

MATERIALS AND METHODS

Study population

All patients were identified through the database of pediatric and congenital heart disease from the University Hospitals Leuven, updated until April 2014. The inclusion criteria for the present study were: 1/ born with or developed congenital heart block and 2/ born from a mother with Systemic Lupus Erythematosus. The study protocol was reviewed and approved by the Ethics Committee of the University Hospitals Leuven.

The search based on the key words of the inclusion criteria resulted in a list of 24 files. Five files had to be excluded because these patients did not meet the inclusion criteria, as these patients were born from a mother in whom the diagnosis of Systemic Lupus Erythematosus was not confirmed.

Variables

All patient files were reviewed for the presence at birth, development of, and degree of congenital heart block, the need for and timing of pacemaker implantation, possible complications and death. Echocardiography at first presentation and at latest follow up was reviewed for associated structural cardiac lesions and/or evaluation of left ventricular function. Moderate valvular insufficiency was noted when it was graded at least 2 out of 4. Mild valvular insufficiency was noted when it was graded less than 2 out of 4. Neonatal

myocarditis was defined as the presence of biventricular dysfunction and elevated cardiac
enzymes.

Statistical analysis

Mainly descriptive statistics were used. Because of the low number of patients, continuous
variables were reported by median and interquartile ranges (IQR). Proportions were
mentioned by numbers and percentages. To identify differences in consecutive battery
survival, Kaplan Meier analysis and log rank testing were done. Statistic analyses were
performed in Excel (Microsoft Office 2013) and by using Statistical Package for the Social
Sciences (version 20). A p value < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Demographics

The majority of the patients were female (68%, 13/19). Seventy-four percent of the patients (14/19) were from Caucasian origin.

The birth weight and gestational age at birth were missing in 4 files. The median birth weight was 2.345 kg (IQR 1.865-2.237 kg) and the median gestational age was 34 weeks (IQR 32.25-36.75 weeks). Some deliveries were induced early because of progressing heart block, threatening heart failure in the fetus, fetal hydrops or fetal distress caused by neonatal lupus.

Immune status of the mothers

Eighty-four percent (16/19) of mothers had a diagnosis of pure SLE, 11% (2/19) had a diagnosis of mixed SLE with Sjögren's syndrome, 5% (1/19) had a pure Sjögren's syndrome.

We tried to identify the specific immune status of the mothers, but in 16% (3/19) of files the immune status could not be identified, because it was not mentioned in their children's file and we were not able to get into contact with the mothers or their treating physician. All

the remaining 16 mothers (100%) tested positive for anti-Rho/SSA antibodies, 63% (10/16) tested positive for anti-La/SSB antibodies.

Prenatal and postnatal therapy

In 52% (10/19) of patients corticosteroids were administered before birth. In 16% (3/19) of patients corticosteroids were administered after birth. In one patient (1/19) terbutaline was given before birth. In none of our patients IV immunoglobulin therapy was given or plasmapheresis applied.

Heart block at birth and during follow-up

The median follow up time was 7 years (IQR 4.5-13 years). Only one patient (1/19, 5%) had no heart block at birth, but developed a first degree atrio-ventricular block as a neonate with a PR interval of 224ms. One patient (1/19, 5%) had a second degree block, but developed a complete heart block later on. All the other patients (17/19, 89%) were born with a complete heart block.

Associated congenital and structural heart disease at birth

In 58% of the patients (11/19) there was some kind of structural heart defect. Atrial septal defects (ASD) (4/19, 21%), ventricular septal defects (VSD) (3/19, 16%) and persistent ductus arteriosus (PDA) (6/19, 32%) were noted. One patient had a mon coronary system (1/19, 5%). Twenty-one percent of patients (4/19) had a moderate tricuspid insufficiency. One patient (1/19, 5%) had a moderate mitral insufficiency. There were patients with prominent right ventricular hypertrophy (2/19, 11%) and left ventricular hypertrophy (3/19, 16%). In 6

patients (6/19, 32%) there was a significant dilatation of the left ventricle, however, with normal function. Neonatal myocarditis was diagnosed in 3 patients (16%, 3/19).

Pacing

Temporary pacing

Before the definitive pacemaker implant, 6 patients (32%) needed temporary pacing with epicardial temporary leads and an external pacing system as a dedicated temporary pacing method. Two (11%) were bridged with transesophageal leads before the epicardial system was implanted. Both patients received their transesophageal pacing in a referral center, but detailed information about the technique could not be obtained. One patient was paced for 20 days, the duration of transesophageal pacing in the other patient is not known.

The reasons for temporary pacing were cardiogenic shock (17%), fetal hydrops (17%) or very slow ventricular escape rhythm with bradycardia < 70/min (67%).

Definitive pacemaker implantation

The patient with first degree heart block did not progress to a higher degree heart block and did not undergo pacemaker implantation at the current age of 21 years. One patient received epicardial leads, but had a sufficient escape rhythm, so that no pacemaker was implanted until today. All the other patients (17/19, 89%) received a definitive pacemaker, all with epicardial leads at first. In figure 1 the timing of the first pacemaker implantation is visualized, indicating that after the first year 82% of patients have received a pacemaker.

Forty-one percent (7/17) of pacemakers were implanted during the first month of life. The

earliest pacemaker implantation was done on the first day of life, the latest pacemaker implantation was done at the age of 7 years.

Complications immediately related to pacemaker implantation

One of the two patients who needed temporary transesophageal pacing developed an esophageal stenosis. This was the patient who received 20 days of transesophageal pacing. In the immediate post pacemaker and lead implantation period were four patients (4/17, 24%) in whom pericardial effusion was detected on routine echocardiography. One of them (1/17, 6%) had signs of pericardial tamponade and needed two repetitive punctures to drain the pericardial fluid. No other complications were found, more specifically, there were no reports of device or lead infections.

Battery replacement

Two patients were lost to follow up. The remaining 15 patients had one or more battery replacements. The patients received their first battery replacement after a median time of 5 years (IQR 3.5-5 years). Eight patients (53%) needed a second battery replacement, after their second battery had lasted for a median time of 6 years (IQR 4.5-6.3 years). Three patients (20%) received a third battery. Figure 2 is a Kaplan Meier plot where log rank testing was performed to identify differences between battery life of the first, the second and the third battery.

Eight patients (53%) had a dual chamber device implanted when battery replacement was needed: in five patients (33%) the second ventricular lead was used as a backup, two patients (13%) were paced in both ventricles because they had no underlying escape

rhythm, one patient (7%) received dual right ventricular pacing because a slow ventricular escape rhythm around 30 bpm.

Leads

All patients (17/17) received an epicardial pacing system at first. All leads were Medtronic Capsure Epi model 4965 steroid eluting leads. Two third of the patient population (71%, 12/17) was paced on the right ventricle. Three patients (18%) were paced on the left ventricle, two patients (12%) were paced on both ventricles.

During follow-up a total of 10 patients (59%) underwent lead replacement after a median time of 5 years (IQR 4-5 years). There were multiple reasons found for the lead replacements: (1) 6 patients (35%) had a lead fracture - two of them even had two fractures - , (2) 2 patients (12%) were diagnosed with lead dysfunction (high threshold without lead fracture), (3) 2 patients (12%) received an elective lead replacement during the procedure for battery replacement with upgrade to a dual chamber device. Table 1 shows an overview of the number of leads at implantation and at latest follow up.

Pacing mode at implantation and electrical analysis at latest follow-up

The majority of the patients (14/17, 82%) were programmed in VVI mode at first, only 2/17 patients (11%) were immediately programmed in DDD mode. From one patient no information concerning the pacing mode at first programming was found.

The pacing mode after implantation and at latest follow-up is summarized in table 1. A minority of the patients was still programmed in a VVI or VVI-R mode (5/17, 29%). There were 12 patients (71%) programmed in DDD, DDD-R or cardiac resynchronization therapy

mode. Nine of them (75%) received implantation of an atrial lead during follow-up, three of them (33%) received the atrial lead at the first lead implantation procedure, but in one patient the atrial lead was initially not used. The majority of the patients programmed in DDD/DDD-R mode had a cardiac resynchronization therapy -device (7/9, 78%), where the second ventricular lead was used as a backup but not functional. Three patients (18%) were programmed in biventricular pacing mode for safety at latest follow-up; two (12%) of them were programmed in cardiac resynchronization therapy biventricular pacing mode because they had no ventricular escape rhythm, one of them (6%) had dual right ventricular pacing because a very slow ventricular escape rhythm around 30 bpm.

Left ventricular systolic function and structural heart disease during follow-up

At birth, 26% of the patients (6/19) had some degree of decreased left ventricular ejection fraction. The echocardiography at latest follow-up was reviewed in all patients. For evaluation of the left ventricular function some records used an ejection fraction, other records used fractional shortening. One patient (5%) had a borderline left ventricular systolic function due to septal dyskinesia. All the other patients had a normal left ventricular systolic function at latest follow up. Two patients (11%) had a cardiac resynchronization therapy device with biventricular pacing mode. Indication for implantation of the biventricular device was not a decreased left ventricular function, but these patients had no escape rhythm and needed 100% pacing.

The ASD persisted in all four patients (100%). Two patients (2/4, 50%) underwent a surgical repair, one (1/4, 25%) received an ASD closure device. In one patient (1/4, 25%) the ASD

persisted and was not corrected during follow-up. All three VSD (100%) closed spontaneously. Of the PDA 67% (4/6) closed spontaneously, one (1/6, 17%) was closed with a Rashkind umbrella, one (1/6, 17%) was surgically closed.

The presence of moderate insufficiency of the mitral and tricuspid valve was in none of the patients graded higher than a mild insufficiency at latest follow-up. The left and right ventricular hypertrophy that was present at birth, normalized in all patients (100%) during follow-up. Left ventricular dilation (present in 6/19 patients at birth) persisted in four out of six patients (67%), in three of them (3/6, 50%) the dilation was only graded mild, in one (1/6, 17%) the dilation was graded moderate.

Survival during follow-up

None of our patients died.

DISCUSSION

Nineteen children with congenital heart block born from mothers with Systemic Lupus Erythematosus were identified through the database of pediatric and congenital heart disease in University Hospitals Leuven. Eighty-nine percent of patients presented immediately with a complete heart block at birth. After a median follow-up time of 7 years (IQR 4.5-13 years) 95% of patients had a complete heart block. Eighty-nine percent of patients needed a definitive pacemaker implantation, all with surgically placed epicardial leads at first. Complication rate immediately related to pacemaker implantation was low with only one pericardial tamponade. A high percentage of lead replacements in 59% of our patient population was noted. In 58% of patients, associated structural heart disease was present, and 16% of patients had a neonatal myocarditis. The left ventricular systolic function at latest follow-up was normal in all patients.

Demographics

The risks of premature and low weight baby rates are increased in mothers with Systemic Lupus Erythematosus. A recent Chinese study of 41 patients found a mean gestational age of 37.6 ± 3.3 weeks and a mean birth weight of 2.510 ± 0.757 kg (8). In our study the median birth weight and gestational age were considerably lower than in the higher mentioned study. This can be explained by the fact that some deliveries were induced early because of progressing heart block, threatening heart failure in the fetus, fetal hydrops or fetal distress.

Structural heart disease

Structural congenital heart disease has been reported in 16-42% of patients with congenital heart block (9). We found structural heart disease in 58% of the cases. It has been suggested

that cardiomyopathy may also be a separate manifestation of neonatal lupus (9). Neonatal myocarditis, for example is a manifestation of myocardial infiltration by the maternal antibodies and we found 16% of patients with myocarditis. Nevertheless we noticed a normal left ventricular function at latest follow-up in all patients, although in literature the outcome of neonatal lupus associated myocarditis is very poor with more than 80% of patients needing a heart transplant or dying (10). One of the three patients with neonatal myocarditis (33%) received prenatal therapy with corticosteroids, one of the three patients (33%) received postnatal therapy with corticosteroids, one (33%) received no therapy.

We cannot exclude that there could be a selection bias because our study started from the database of pediatric and congenital cardiology – while most studies are based on Systemic Lupus Erythematosus registries. This could explain for the higher prevalence of structural heart disease in our population.

Pacing

Battery survival

We describe an early timing of pacemaker implantation with the majority of pacemakers implanted during the first year of life (75%) and even 40% during the first month. Battery life is known to be relatively shorter in neonates compared with children and adults because of the fast heart rate and complete pacemaker dependency. Also in newborns the smallest battery possible is implanted. A retrospective study in 22 neonates who underwent epicardial pacemaker implantation because of congenital heart block or sinus node

dysfunction reported a median battery life of 4.1 years (11), which is little shorter than the median time of 5 years for the first battery replacement in our analysis.

Complication rate related to pacemaker implantation

One of the two patients who was paced transesophageally for 20 days developed an esophageal stenosis and needed multiple esophageal dilations afterwards. We want to stress this complication as a warning. In the past, this procedure was used in our center in extremely preterm infants, but after a few days the electrodes showed electrolysis and infants developed caustic esophageal stenosis. Nowadays we use temporary epicardial pacing leads with an external pacemaker system.

Despite the early timing of pacemaker implantation, we found a surprisingly low complication rate: there was only one patient with a cardiac tamponade with the need for pericardiocentesis. More important there were no device infections, which is one of the most feared complications with a high morbidity. No fatal complications occurred.

Leads

All of our patients (17/17) received an epicardial pacing system at first. Taken into consideration the very early need for pacemaker and lead implantation, this is not an abnormal finding. Indeed, inserting a lead by the transvenous approach in a small sized vessel carries the inherent risk of stenosis or thrombosis.

A total of ten patients (59%) needed a lead replacement due to lead fracture (35%), lead failure due to high pacing thresholds (12%) or during an elective procedure (upgrade to dual chamber device) (12%). Reoperations are an inevitable problem associated with pediatric

pacemaker therapy and a very important predictor for lead problems is the age of the patients at implantation of the leads (12,13), which was very young in our population.

330 Compared to a study in 93 patients with congenital heart disease having epicardial leads (13), we found a higher percentage of lead failures, but the median time period before failure was comparable. In comparison to a retrospective study looking at longterm outcome of epicardial leads, 38% had a lead problem after five years, which is a lower percentage than in our findings (14). We have to mention that the cause of lead failure in 335 one patient was a twist in the pacemaker battery caused by a fall riding her bicycle. There could also be a sample size problem as our patient group was very small. In comparison to a retrospective study in Italy, where the mean age of implantation was significantly older, similar results were found: 53% of lead failure in pediatric patients with an epicardial system (15).

340 *Pacing mode*

345 Almost all of the studied patients were programmed in a VVI mode at first, but at latest follow up almost all of our patients were paced in the atrium and the ventricle. The contribution of atrial contraction to cardiac output has been the subject of extensive research. A small study published in 2011 found a noninvasive method to quantitatively measure the cardiac output in VVI versus DDD mode (with optimized atrio-ventricular delays) in patients with a congenital heart block. They found a significant increase of the cardiac output of 18% ($p < 0.001$) when patients were programmed from right ventricular pacing only to atrio-ventricular synchronous pacing (16). This supports the hemodynamic

350 advantage of atrio-ventricular synchronous pacing and therefore the implantation of a two
chamber pacing system with programming in DDD mode. One patient received an atrial lead
at implantation, but was initially programmed in VVI mode despite having both an atrial and
a ventricular lead. It is unclear to us in the patient file why this was done.

355 The majority of our patients had two ventricular leads, where the second ventricular lead
was used as a backup but not functional. This approach was useful as in 29% (2/7) patients
with a lead problem the second lead had to be used.

Two patients, who had no underlying escape rhythm, were paced in both ventricles (cardiac
resynchronization therapy), although they had a preserved ejection fraction before
implantation of the cardiac resynchronization therapy device. There is evidence that in
360 patients with bradycardia and need for pacing, there is superiority of biventricular pacing to
right ventricular apical pacing in the prevention of left ventricular adverse remodeling and
deterioration of systolic function, even in patients with preserved ejection fraction. Because
these patients had no escape rhythm and needed 100% pacing, a biventricular pacing device
was chosen to prevent deterioration of the left ventricular function (17).

365 **Left ventricular systolic function**

Gebauer and Tomek evaluated the systolic left ventricular function of 82 pediatric patients
with complete heart block who had been 100% paced on the right ventricle (18). The
incidence of left ventricular dilatation or dysfunction was 13% (11/84) and epicardial right
370 ventricular free wall pacing was the only independent risk factor. In our population all had a
normal left ventricular ejection fraction at latest follow up. Two patients had biventricular

375 pacing, not because a decreased left ventricular function, but because they had no
ventricular escape rhythm. For this reason pacing on two leads was chosen for safety. As we
described higher in the article, there is some evidence that biventricular pacing can prevent
adverse remodeling of the left ventricle, even in patients with preserved ejection fraction
(18). There was one patient with borderline left ventricular systolic function at latest follow
up, but this was the patient who had had an epicardial lead implantation, but no pacemaker
because of a sufficiently high escape rhythm.

380 A recent study confirmed that the site of ventricular pacing has a major impact on left
ventricular mechanical synchrony, efficiency, and pump function in children who require
lifelong pacing. Of the sites studied, left ventricle apex/left ventricle midlateral wall pacing
has the greatest potential to prevent pacing-induced reduction of cardiac pump function
(19). Nevertheless the majority of patients in our population were paced on the right
ventricle without complications.

385 **Survival**

390 The mortality in children with congenital heart block is estimated in studies at 8-16% (20)
and even higher up to 29% in children with associated cardiomyopathy. We found no
mortality in our group, which is a very favorable outcome. This supports the need for and
long-term efficacy of early pacemaker implantation in patients with congenital heart block –
especially because the natural course of congenital heart block is known to have a high
mortality.

LIMITATIONS

Our study is retrospective starting from the database of pediatric and congenital heart disease with a known risk for selection bias. Because this is a database of congenital cardiology, we are not aware of fetal losses and there might be a selection bias affecting our survival rate.

It is a relatively small study from a single center. We decided to use no comparison group of paced infants without auto-immune disease in the mother as the low numbers would have insufficient statistical power to run valuable comparative statistics. Also was our patient database inhomogeneous concerning patient age and time of follow up. Some patients were lost of follow up.

We had not enough relevant information concerning the immune status of the newborns as antiRho SSA en antiLa/SSB status was not taken.

Data from referral centers were difficult to obtain, as in the both patients who received temporary transesophageal pacing, detailed information about the technique used was missing.

CONCLUSION

410 This is a retrospective study with a cardiologic viewpoint looking at fetal outcome and the
need for pacemaker implantation in newborns with congenital heart block from Systemic
Lupus Erythematosus mothers.

A very early timing of pacemaker implantation after birth seems needed with very few
complications and an acceptable battery life. The largest problem remained frequent lead
415 problems with 47 percent of patients needing lead replacement because of lead fracture or
lead failure after 5 years.

Systolic left ventricular function was preserved at latest follow-up despite pacing. A lifelong
follow-up in these patients is indicated, not only because the need for electrical follow-up
after pacemaker implantation, but also because of the high prevalence of associated
420 structural heart disease.

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CONFLICTS OF INTEREST

None.

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TABLES

Table 1. Listing of the temporary pacing mode, number and location of leads and pacing mode at implantation and last follow-up for each patient in the cohort. LV: left ventricle, RV: right ventricle.

	<u>Temporary pacing</u>		<u>Leads at implantation</u>			<u>Pacing mode at implantation</u>	<u>Leads at latest follow up</u>			<u>Pacing mode at latest follow-up</u>
	Transoesophageal	Epicardial	Atrium	RV	LV		Atrium	RV	LV	
Patient 1	Yes	Yes	0	1	0	VVI	0	0	1	VVI-R
Patient 2	No	No	0	2	0	VVI-R	1	1	1	DDD
Patient 3	Yes	Yes	0	1	0	VVI	0	1	0	VVI-R
Patient 4	No	No	0	2	0	VVI	0	2	0	VVI
Patient 5	No	No	0	2	0	VVI	1	1	0	DDD
Patient 6	No	No	0	2	0	VVI	1	2	0	DDD-R
Patient 7	No	No	1	2	0	DDD	1	0	2	DDD
Patient 8	No	No	1	1	0	DDD	1	1	0	DDD
Patient 9	No	No	0	2	0	VVI	1	2	0	DDD
Patient 10	No	No	0	2	0	VVI	1	2	1	DDD
Patient 11	No	Yes	0	0	1	VVI	1	2	0	DDD
Patient 12	No	No	0	1	1	VVI	0	1	1	VVI
Patient 13	No	Yes	1	1	1	VVI	1	1	1	DDD
Patient 14	No	Yes	0	1	1	VVI	1	1	1	CRT
Patient 15	No	No	0	0	1	VVI	1	1	1	CRT
Patient 16	No	Yes	0	2	0	VVI	1	2	0	CRT
Patient	No	No	0	1	1	VVI	0	1	1	VVI

FIGURE LEGENDS

Figure 1: Timing of pacemaker implantation

The X-axis represents the number of months after birth. The Y-axis represents the percentage of patients that have received a pacemaker.

Figure 2: Kaplan Meier battery survival plot.

The X-axis represents the number of years after pacemaker implantation/battery replacement. The Y-axis represents event-free survival meaning time without battery replacement. The blue line represents the first battery, the green line represents the second battery, and the brown line represents the third battery.