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Dilated Cardiomyopathy in Isolated Congenital Complete Atrioventricular Block: Early and Long-Term Risk in Children

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OBJECTIVES We sought to identify the risk factors predicting the development of dilated cardiomyopathy (DCM) in patients with isolated congenital complete atrioventricular block (CCAVB).

BACKGROUND Recently evidence has emerged that a subset of patients with CCAVB develop DCM.

METHODS This was a retrospective study of 149 patients with CCAVB who had heart size and left ventricular (LV) function assessed by echocardiography and chest radiography over a follow-up period of 10 ± 7 years.

RESULTS Nine patients developed DCM at the age of 6.5 ± 5 years. No definite cause could be identified. In these nine patients, CCAVB was diagnosed in eight at 23 ± 2.3 weeks gestation and in one at birth. Maternal SSA/SSB antibodies were confirmed in seven of the nine patients. Pacemakers were implanted in eight patients in the first month and in one patient at five years of age. The initial left ventricular end-diastolic dimension (LVEDD) was in the 96th ± 2.6 percentile and the cardiothoracic (CT) ratio was 64 ± 3.8% in the nine patients who developed DCM, and differed significantly in patients with CCAVB ($p < 0.005$) who did not develop DCM. The LVEDD and CT ratio did not decrease in the patients with CCAVB and DCM, but decreased significantly in the patients with CCAVB without DCM ($p < 0.001$) once pacing was initiated. Two patients with DCM died within two months of diagnosis; one patient is neurologically compromised; two patients received a heart transplant; and four patients are listed for heart transplantation.

CONCLUSIONS Isolated CCAVB is associated with a long-term risk for the development of DCM. Risk factors may be SSA/SSB antibodies, increased heart size at initial evaluation and the absence of pacemaker-associated improvement. (J Am Coll Cardiol 2001;37:1129–34) © 2001 by the American College of Cardiology

The prognosis for children with congenital complete atrioventricular block (CCAVB) has been considered relatively benign, with a normal life-expectancy, although the majority of patients eventually require pacemaker implantation (1). However, evidence has recently emerged that a subset of these patients develop dilated cardiomyopathy (DCM) despite early pacemaker implantation (2). Most reported patients were diagnosed in utero to have CCAVB associated with maternal autoantibodies directed against SSA/Ro and SSB/La ribonucleoproteins (3). The SSA/Ro and SSB/La antibody-induced injury to the fetal conducting system of the heart can cause isolated CCAVB. This manifestation is well-described (4), but associated DCM is less well studied (2).

The purposes of this retrospective study were to investigate the prognostic signs in isolated CCAVB and to identify risk factors that may predict the development of DCM in a subgroup of these patients. We studied all children diagnosed with isolated CCAVB in the participating medical centers since 1972, focusing on patients who received a pacemaker and patients who subsequently developed DCM in the follow-up period.

METHODS

Study group. The study group comprised all children with CCAVB in the absence of associated structural heart disease, diagnosed since 1972 at the Pediatric Heart Center of the Wilhelmina Children's Hospital/University Medical Center, Utrecht; University Medical Center St. Radboud, Nijmegen; the Amsterdam Medical Center, Amsterdam, the Netherlands; the Johns Hopkins Hospital, Baltimore; Yale New Haven Hospital, New Haven; and the Children's

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Abbreviations and Acronyms

ANT = adenine nucleotide translocator
AV = atrioventricular
CCAVB = congenital complete atrioventricular block
CT = cardiothoracic
DCM = dilated cardiomyopathy
LV = left ventricle, left ventricular
LVEDD = left ventricular end-diastolic dimension
LVESD = left ventricular end-systolic dimension
SF = shortening fraction

Hospital of Philadelphia. Echocardiograms during pregnancy and/or additional electrocardiographic recordings during infancy confirmed complete and permanent atrioventricular (AV) block. A total of 149 patients with isolated CCAVB were studied after echocardiographic confirmation of normal cardiac anatomy. Pacemakers were implanted in 111 patients during follow-up. To evaluate the effect of pacing in patients with CCAVB, the 38 patients with CCAVB who did not undergo pacing were excluded from the analysis. However, none of these 38 patients developed DCM over 7 ± 6 years.

Study patients were assigned to two groups according to whether they subsequently developed DCM (CCAVB/DCM group) or not (CCAVB group). The CCAVB/DCM group included nine patients who developed DCM after the diagnosis of isolated CCAVB was made. No patient was diagnosed with DCM at the time the CCAVB was first diagnosed. The CCAVB group consisted of the remaining 102 patients with isolated CCAVB and a pacemaker, but without signs or symptoms of cardiomyopathy.

Clinical data and definitions. Available demographic data of the study cohort, including gender, age at diagnosis of AV block, heart rate at initial cardiac evaluation and the presence or absence of maternal autoantibodies to 48-kd SSB/La, 52-kd SSA/Ro and 60-kd SSA/Ro ribonucleoproteins, were retrospectively reviewed. Information on the presence of fetal hydrops, mode of delivery, birth weight, gestational age at birth, heart rate and condition at birth was also reviewed. Heart rate and age at pacemaker implantation were documented. Abstracted data included pacemaker mode, pacemaker complications and pacemaker reimplantations.

All available echocardiograms performed in utero and during the neonatal period, infancy, childhood and adolescence were reviewed. Left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) were measured, and p values (percentile of heart size corrected for weight) were estimated for every LVEDD (5) before and after the cardiomyopathy was diagnosed. Shortening fraction (SF) was calculated as (LVEDD − LVESD)/LVEDD × 100% (6). Chest radiographs were reviewed for cardiac enlargement, pulmonary venous congestion, pulmonary edema, atelectasis and/or pleural effusions. Heart size was expressed as the cardiothoracic (CT) ratio and graded for each individual patient. A CT ratio >0.60 indicated cardiomegaly in infants ≤1 month of age. In children >1 month old, a CT ratio >0.50 indicated cardiomegaly and was categorized as mild (CT ratio 0.50 to 0.60), moderate (CT ratio of 0.60 to 0.65) or severe (CT ratio 0.65) (7). Dilated cardiomyopathy was defined as LVEDD in the >97th percentile with SF <25% (8). Other identifiable causes of ventricular dysfunction (i.e., myocarditis) were not encountered.

Analysis of data. Comparisons between the CCAVB/DCM group and the CCAVB group were performed by using the unpaired two-sample *t* test or Mann-Whitney *U* test for continuous data, and the chi-square test or Fisher exact test for binary variables. Data are presented as the mean value ± SD. The follow-up data on heart size and function (LVEDD, SF and CT ratio) were analyzed with linear regression. A p value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics of study cohort. There were significant demographic differences between the patients with isolated CCAVB (n = 102) and those with CCAVB who subsequently developed DCM (n = 9) (Table 1). The age at diagnosis of CCAVB differed significantly between the groups (CCAVB: 24 ± 45 months; CCAVB/DCM: 23 ± 1 weeks gestation; $p < 0.001$). The average heart rate measured at birth was significantly lower in the patients with CCAVB and DCM. The mean length of follow-up was similar between the two groups (CCAVB: 10.1 ± 6 years; CCAVB/DCM: 10 ± 6.1 years; $p > 0.10$). The SSA/Ro and SSB/La antibodies were identified in 40 (77%) of 52 patients with CCAVB who did not develop DCM. Laboratory studies were not performed in the remaining 50 patients with CCAVB.

Dilated cardiomyopathy was diagnosed in nine patients (8%) at 6.5 ± 5 years (median 5.7 years [range 0.4 to 16]) (Fig. 1, Table 2). Five of the nine patients with DCM were delivered by cesarean section. Hydrops was observed in one patient. Maternal laboratory studies confirmed SSA/Ro and SSB/La antibodies in seven (78%) of these nine patients. In one patient, no antibodies were identified, and in the one remaining patient, no tests were performed. No other features of the neonatal lupus syndrome were noted. Signs and symptoms at the time of diagnosis of DCM included congestive heart failure (n = 8), increasing fatigue with exertion (n = 5), chest pain (n = 2), dyspnea (n = 4) and/or poor feeding (n = 2). Physical examination findings revealed hepatomegaly (n = 3), hyperactive precordium (n = 3), crepitations (n = 2) and/or poor perfusion of the lower extremities (n = 2). No patient with DCM had a history suggestive of familial cardiomyopathy.

Echocardiograms at the time of diagnosis of DCM revealed LVEDD measurements in the >97th percentile, with SF of 11 ± 5%. Chest radiographs at the time of

Table 1. Study Characteristics of 111 Patients With Congenital Complete Atrioventricular Block

	Patients With Cardiomyopathy (Group A; n = 9)	Control Subjects (Group B; n = 102)	p Value
Gender (M/F)	7/2	45/57	NS
Age (months) at diagnosis*	3 ± 1†	24 ± 44†	< 0.001
Prenatal	8 (89%)	27 (26%)	< 0.001
At birth	1 (11%)	25 (25%)	—
Postnatal	0	50 (49%)	—
Heart rate at birth (beats/min)	43 ± 6	62 ± 14	< 0.001
Follow-up (months)	123 ± 73	121 ± 74	NS
Hydrops	1 (11%)	3 (3%)	—
Mode of delivery (n)	8	53	—
Normal	3 (37%)	22 (42%)	—
CS	5 (63%)	31 (58%)	—
Gestational age			
(n)	8	53	—
(weeks)	37 ± 3	37 ± 3	NS
Mortality	2 (22%)	1 (1%)	NS

*Age of congenital complete atrioventricular block diagnosis. †Months before delivery. Data are presented as the mean value ± SD or number (%) of patients.
CS = cesarean section; F = female; M = male; NS = not significant.

diagnosis were available in four of nine patients and revealed a mean CT ratio of 68 ± 3.8%. Pulmonary venous congestion was seen in three patients, with progression to frank pulmonary edema in one child. Medical management included digoxin and diuretic agents in all patients. No patient had been treated with digoxin or diuretic agents before the development of DCM.

Outcomes. All patients with DCM had serial echocardiograms and chest radiographs for 25 months of follow-up (range 2 to 144) after the initial diagnosis. Cardiac catheterization was performed in four of these nine patients at the time of diagnosis. The mean cardiac index was 2.5 liters/min per m^2 (range 2.3 to 2.7). The pulmonary artery systolic pressure was 27 mm Hg (range 21 to 32), and the LV end-diastolic pressure was 15 mm Hg (range 12 to 18).

Six of these nine patients did well initially on medical treatment, but the SF diminished with duration of follow-up (Fig. 2). The LVEDD measurements were ≥97th percentile during follow-up of the patients with DCM. Two patients died within two months of the diagnosis, secondary to multiorgan system failure. Two other patients received a heart transplant three months and 7.5 years after the initial diagnosis. Four patients with DCM are currently awaiting heart transplantation. One patient was resuscitated shortly after the diagnosis and is neurologically compromised.

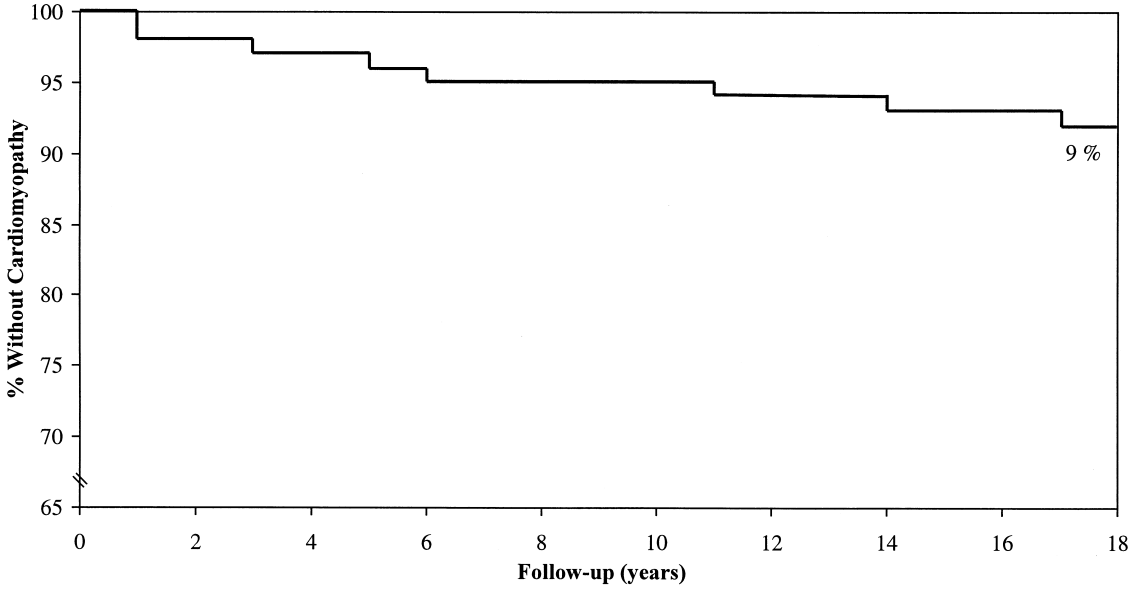

Figure 1. Kaplan-Meier curve presenting freedom from developing dilated cardiomyopathy in the years after the initial diagnosis of congenital complete atrioventricular block.

Table 2. Study Characteristics of Patients With Dilated Cardiomyopathy

Patient No.	Gender (M/F)	Age at Diagnosis of DCM	HR at Birth (beats/min)	Initial CT Ratio	Initial LVEDD (%ile)	Initial SF (%)	Indication PM Implantation
1	M	15 yrs, 9 mos	45	63	97	35	Progressive bradycardia (A)
2	M	5 mos	50	70	97	32	HR <50 beats/min (A)
3	F	14 yrs, 5 mos	30	71	—	—	HR <50 beats/min (A)
4	M	9 mos	42	61	97	45	CHF (D)
5	M	4 yrs 2 mos	46	61	97	31	CHF (D)
6	M	2 yrs 5 mos	45	63	—	—	HR <50 beats/min (A)
7	M	8 yrs	—	62	97	33	CHF (A)
8	M	9 yrs, 9 mos	—	65	90	29	HR <50 beats/min (A)
9	F	5 yrs, 8 mos	45	59	97	40	CHF (A)

A = alive; CHF = congestive heart failure; CT = cardiothoracic; D = dead; DCM = dilated cardiomyopathy; F = female; HR = heart rate; LVEDD = left ventricular end-diastolic dimension; M = male; PM = pacemaker; SF = shortening fracture.

Pathology and etiology. Endomyocardial biopsies were obtained in four patients with DCM (44%) and revealed no signs of myocarditis, infection or carnitine deficiency. There was no evidence of coronary artery abnormalities detected by echocardiography in these nine patients. Skeletal muscle biopsies obtained from one patient with DCM who was SSA/Ro and SSB/La antibody-positive revealed a deficiency of the adenine nucleotide translocator (ANT) (Sengers' syndrome) (9). This patient died at 10 months of age.

Pacemaker therapy. The median age at pacemaker implantation of the patients with CCAVB and DCM was significantly younger (7 days [range 1 day to 5 years]) than that of the 102 patients with CCAVB (4 years [range 1 day to 19 years]) ($p < 0.05$). The median heart rate at pacemaker implantation in the CCAVB/DCM group was 50 beats/min (range 42 to 124), and in the CCAVB group, 55 beats/min (range 37 to 104) ($p > 0.10$).

The indication for pacemaker implantation in the DCM group included: 1) heart rate <50 beats/min (n = 5, 56%); 2) progressive bradycardia noted on ambulatory monitoring (n = 1, 11%); and 3) congestive heart failure (n = 3, 33%). Isolated premature ventricular contractions were observed in six patients (67%). However, no patient in the CCAVB/DCM group had higher grade ectopy, including couplets or salvos of ventricular tachycardia. An endocardial device was implanted in two patients, and an epicardial system in seven patients.

Indication for pacing in the 102 patients with CCAVB included: 1) heart rate <50 beats/min (n = 48, 47%); 2) progressive bradycardia (n = 10, 10%); 3) syncope (n = 11, 11%); 4) pauses >3.5 s seen on ambulatory monitoring (n = 12, 11%); 5) exercise intolerance (n = 10, 10%); and 6) heart failure (n = 11, 11%). Isolated premature ventricular contractions were seen in 22 patients (21%), and ventricular couplets in six (6%). Ventricular tachycardia was not observed. Endocardial devices were initially implanted in 46 patients with CCAVB, and epicardial leads in 56 patients.

There was no significant difference in the type of pacing employed between the two study cohorts. Dual-chamber pacemakers were implanted in two patients with CCAVB and DCM (22%) and in 39 patients with CCAVB (38%). Single-ventricular chamber pacing was employed in the

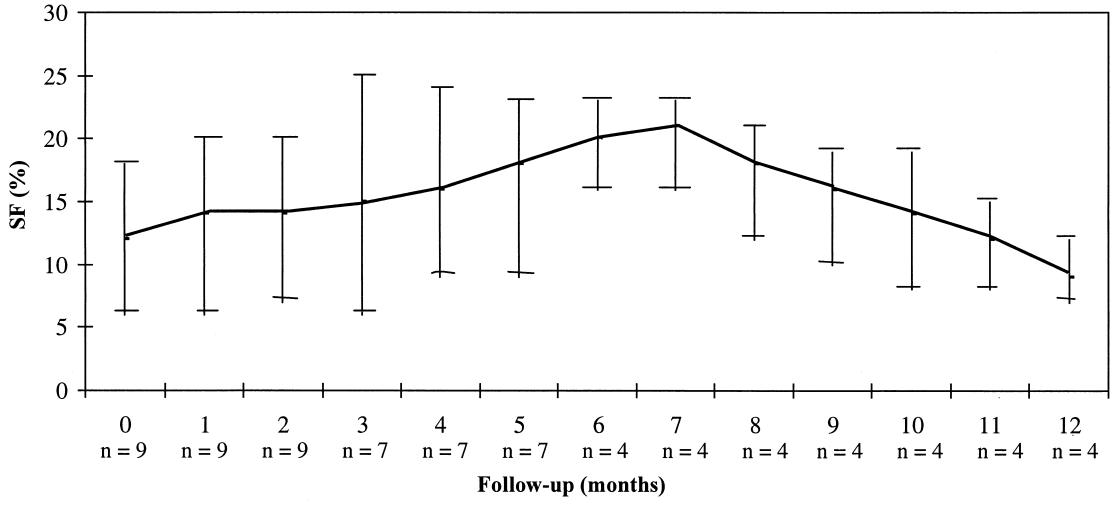

Figure 2. Shortening fraction (SF) of nine patients in the first 12 months after presenting with dilated cardiomyopathy. **Bold horizontal line** = average and range at given times.

Table 3 Initial Heart Size and Function in Patients With Cardiomyopathy and Control Subjects

	Patients With Cardiomyopathy (n = 9)	Control Subjects (n = 102)	p Value
Echocardiographic data (n)	7	87	
LVEDD (percentile)	95.8 ± 2.6	75.9 ± 24.3	<0.005
SF (%)	35.8 ± 5.1	40.1 ± 6.2	<0.5
Chest radiographic data (n)	9	76	
CT ratio (%)	64.0 ± 3.8	57.1 ± 7.2	<0.005
Normal	0	20 (26%)	—
Mild	4 (44%)	40 (53%)	—
Moderate	2 (22%)	11 (14%)	—
Severe	3 (34%)	5 (7%)	—

Data are presented as the mean value ± SD or number (%) of patients. Abbreviations as in Table 2.

remaining 7 patients with CCAVB and DCM (78%) and in 63 patients with CCAVB (62%). Re-implantations were indicated in six patients with CCAVB and DCM (67%) and in 80 patients with CCAVB (78%, $p > 0.10$) due to generator depletion or lead failure.

Echocardiographic measurements. Initial echocardiograms at the time of CCAVB diagnosis were obtained in 94 patients (85%) (CCAVB/DCM: n = 7; CCAVB: n = 87) (Table 3). The initial LVEDD (CCAVB/DCM: 96th percentile ± 2.6%; CCAVB: 76th percentile ± 24%; $p < 0.005$), without a significant difference in LV function (CCAVB/DCM: 36 ± 5.2%; CCAVB: 39 ± 7.9%; $p > 0.10$).

Mild mitral regurgitation was seen in four patients with DCM and persisted on serial echocardiograms during follow-up. Initial LVEDD values >97th percentile were measured in 22 patients with CCAVB (21%) and showed a decrease in LVEDD <97th percentile within 4 ± 3.5 years after pacemaker implantation. The initial SF in these patients was 38 ± 7.1%.

Over 6.5 ± 5 years, the nine patients with CCAVB who eventually developed DCM continued to have a LVEDD >97th percentile ± 1.8%, as well as a decrease in SF from 35.8 ± 5.1% to 11 ± 5%. This was significantly different from the CCAVB cohort (n = 102), which showed a significant decrease in LVEDD to the 65th percentile ± 20% ($p < 0.001$), without a change in LV function (36 ± 3.6%, $p < 0.01$) 7 ± 6 years after pacing. A decrease in heart size was initiated within two months (range 1 month to 1 year) after pacemaker implantation.

Radiographic features. Initial chest radiographs were available for all nine patients who eventually developed DCM (Table 3). There was no radiographic evidence of pulmonary venous congestion, edema or atelectasis. All nine patients had cardiomegaly, graded as mild (n = 4), moderate (n = 2) or severe (n = 3). An initial CT ratio of 64 ± 3.8% was measured in the CCAVB/DCM group and remained relatively constant over 6.5 ± 5 years at 63 ± 6.8%. Mild vascular congestion and perihilar edema were observed in two patients on the initial chest radiographs and at mid-term follow-up.

The CT ratio in the CCAVB group decreased significantly with initiation of pacing from 57 ± 7.2% to 49 ± 6.3% ($p < 0.01$) over 7.5 ± 4.6 years of follow-up. This decrease in the CT ratio was not seen in the CCAVB/DCM group during a similar follow-up period.

DISCUSSION

Dilated cardiomyopathy. Dilated cardiomyopathy is a heterogeneous group of myocardial diseases characterized by dilation and impaired systolic function of the heart (5,10). Although specific causes can be identified, such as myocarditis, familial cardiomyopathies, endocardial fibroelastosis and metabolic disorders, most cases are idiopathic (11–13). Similarly, no additional etiologic event could be identified in the nine patients with isolated CCAVB who eventually developed DCM.

SSA/Ro and SSB/La autoantibodies. The SSA/Ro and SSB/La antibodies have been suggested to be a major determinant (1,2) in the patients with CCAVB who eventually developed DCM. Evidence for a potential immunopathologic role of the SSA/Ro and SSB/La antibodies in CCAVB is described in several studies (3,4). Immunofluorescent studies have shown immunoglobulin G deposition throughout the myocardium on postmortem examination (14,15). Taylor et al. (16) demonstrated maternal antibodies directed against fetal cardiac tissue. Although these studies suggest a strong relationship between SSA/Ro and SSB/La antibodies and subsequent DCM (1,2,17), the actual mechanism of the disease process has not yet been documented. The SSA/Ro and SSB/La antibody-mediated AV block was confirmed in seven of the nine patients who developed DCM. However, 40 of 52 tested patients with CCAVB who did not develop DCM were also SSA/Ro- and SSB/La-positive. Thus, antibody positivity is not predictive in those patients with CCAVB who developed DCM.

Adenine nucleotide translocator deficiency. Although myocardial biopsies did not provide any specific information on DCM, skeletal muscle biopsies in one patient revealed a deficiency of ANT, which is associated with Sengers' syndrome (10). Sengers' syndrome consists of a triad of congenital cataracts, mitochondrial myopathy and hypertrophic cardiomyopathy and is not known to cause DCM (18). This observation may be described as a new clinical finding and warrants further investigation.

Pacemaker implantation. A previous study indicates that at least 10% of SSA/Ro and SSB/La antibody-associated patients with CCAVB do not respond favorably to pacemaker implantation, secondary to more diffuse cardiac involvement (2). This study observed a similar incidence (9 [8%] of 111 patients) whereby pacemaker implantation did not decrease the LVEDD. Although cardiomegaly is a common feature in the CCAVB population, severe dilation of the LV is rare (8). Some reports postulate that the increased heart size may be related to LV remodeling and reorganization of myofibers, secondary to an increase in

stroke volume and maintenance of a normal cardiac output in the face of chronic bradycardia (19,20).

Severe LV dilation may be associated with a less effective adaptation to this complex physiology. This study reported that patients with CCAVB with marked LV dilation at presentation who lack a reduction in heart size with pacemaker implantation are at risk of developing DCM. Pacemaker-induced DCM can be offered as a possible etiologic factor in these patients. However, this seems unlikely for the vast majority of the paced patients responding favorably to pacemaker support. In fact, 22 patients who did not develop DCM and whose initial LVEDD exceeded the 97th percentile had a reduction in LVEDD with pacing.

Etiology. In the absence of a clear etiology for the pathogenesis of DCM in the CCAVB population, we presume that DCM is associated with isolated CCAVB and may be a separate preexisting condition in some patients. This hypothesis is based on such common denominators as the presence of SSA/SSB antibodies, lower heart rate at birth, prenatal diagnosis of CCAVB, initial cardiac enlargement and diminished LV shortening despite early pacemaker implantation.

The availability of heart transplantation as a therapeutic option has increased the importance of early and accurate diagnosis. Two patients were successfully transplanted and are still alive, with no recurrence of DCM. Serial echocardiography for evaluating LV dimensions is therefore advisable and may allow for early medical management (i.e., upgrade to a DDD pacemaker system) and listing for potential heart transplantation.

Conclusions. Children with isolated CCAVB are at risk of developing DCM. Risk factors may include an early increased CT ratio and LV dilation, with little or no improvement in ventricular size with pacing, a prenatal diagnosis of CCAVB and a low heart rate at birth. The development of this cardiomyopathy seems to be independent of the age of pacemaker implantation. The relatively common occurrence of positive maternal autoantibodies in the CCAVB group (79%) and CCAVB/DCM group (87%) makes this an unlikely explanation for the development of DCM. Dilated cardiomyopathy can be considered as an associate of isolated CCAVB in some patients. These are major issues that should be discussed at the time of diagnosis.

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