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Pediatric Cardiology

Outcome of Children With Fetal, Neonatal or Childhood Diagnosis of Isolated Congenital Atrioventricular Block

A Single Institution's Experience of 30 Years

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OBJECTIVES We reviewed our institution's experience with isolated (congenital) third-degree atrioventricular block (CAVB) to identify pre- and post-natal predictors of mortality and the requirement for pacemakers in infancy and childhood.

BACKGROUND Because of the relative rarity of the disease, there is a paucity of data concerning the outcome of fetuses and children with isolated CAVB.

METHODS The medical records of all cases of CAVB encountered at our institution from January 1965 to December 1998 were analyzed.

RESULTS Of 102 cases identified, 29 were diagnosed in utero (F) at 26.1 ± 5.6 weeks gestation, 33 as neonates (N; ≤28 days), and 40 as children (C) at 5.7 ± 4.8 years of age. Anti-Ro and/or anti-La were present in 95% of F and 90% of N, but only in 5% of C mothers tested ($p < 0.0001$). Patients with CAVB having F, N and C diagnosis had a mortality of 43%, 6% and 0%, respectively, in the first two decades of life. Increased mortality risk was associated with a fetal diagnosis of CAVB (13/15 deaths; $p < 0.05$), fetal hydrops (6/6 cases; $p < 0.0001$), endocardial fibroelastosis (5/5 cases; $p < 0.0001$) and delivery at ≤32 weeks (4/6 cases; $p < 0.05$). Timing of pacemaker implantation differed significantly among F versus N ($p < 0.05$) and N versus C ($p < 0.001$) cases. At 20 years of age only 11% and 12% of CAVB patients with N and C diagnosis, respectively, were not paced.

CONCLUSIONS Pre-natal diagnosis of CAVB is associated with high fetal and neonatal mortality. Among survivors, whether the diagnosis is made before or after birth, most undergo pacemaker implantation by adulthood, with earlier intervention and a significantly greater need for reintervention among those diagnosed in utero. (J Am Coll Cardiol 2002;39:130–7)

Isolated congenital third-degree atrioventricular block (CAVB) occurs in one in 14,000 to 20,000 live births (1) and has been recognized as a distinct clinical entity for almost 100 years (2). Neonatal lupus erythematosus accounts for 90% to 99% of all cases identified before six months and is associated with the transplacental passage of maternal anti-Ro and/or anti-La autoantibodies (3–6). These antibodies enter the fetal circulation beginning in the mid-second trimester (7) and may lead to permanent destruction of the atrioventricular (AV) conduction system (8).

With the advent of fetal echocardiography, which allows for accurate assessment of the fetal heart rate, rhythm and ventricular function, the majority of autoimmune-mediated CAVB may now be identified in utero before 30 weeks of gestation (9). However, as many as 50% of the total cases of isolated CAVB presenting during childhood are detected after six months of age (10). It has been suggested that children presenting late with CAVB may represent a different serological and clinical population, as maternal autoantibodies are frequently absent, the bradycardia is better tolerated, and the children are less likely to need early pacing (11).

The aim of our study was to outline the clinical presentation, management and course of fetuses and children diagnosed with CAVB at our institution. The second aim was to identify clinical, electrocardiographic and echocardiographic parameters that may predict long-term outcome and pacemaker requirement during infancy and childhood.

METHODS

We reviewed the diagnostic database of the Division of Cardiology at The Hospital for Sick Children for the years 1965 to 1998 and identified all patients with a diagnosis of CAVB. The diagnostic criteria of third-degree AV block proposed by Yater et al. (12) were applied and modified for this study. Isolated congenital third-degree atrioventricular block was defined as complete if there was no electrical (post-natal electrocardiogram) or mechanical (fetal M-mode echocardiogram) relation between atrial and ven-

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Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/American Heart Association
AV = atrioventricular
CAVB = isolated congenital atrioventricular block
CI = confidence interval
CR = cumulative risk
EFE = endocardial fibroelastosis
HF = heart failure

tricular contraction, and incomplete if this relation was present intermittently. The diagnosis of CAVB also required the absence of a history of any condition, including infections, myopathies, metabolic disorders or significant intracardiac structural malformation, that might result in or be associated with CAVB after birth. The time of detection of CAVB was taken as the earliest documentation of a patient's conduction abnormality, which usually occurred near the time of referral to our center.

The medical records of the affected patients were reviewed. Data collected included demographic information, patient age and status at presentation, pacemaker intervention procedures and patient age and status at follow-up. Data regarding signs and symptoms of maternal autoimmune disease, presence or absence of maternal autoimmune antibodies, medications taken during the pregnancy, gestational length of pregnancy, mode of delivery and presence or absence of malformations in the offspring were collected. After informed consent had been given, maternal sera were obtained, and anti-Ro and anti-La antibody status was determined using our previously described enzyme linked immunosorbent assay technique (13).

Videotaped recordings of fetal echocardiographic examinations were reviewed to determine the underlying rhythm and ventricular rates. Electrocardiographic tracings were reanalyzed for rhythm, atrial and ventricular rates, degree of AV block, QRS duration, and corrected QT (if QRS <0.1 s; normal: <0.45 s) or JT interval (if QRS >0.1 s; normal: <0.32 s) using Bazett's formula (14). Where available, Holter monitor data were examined for minimal, maximal and average ventricular rates, maximal duration of pauses and the presence or absence of significant ventricular arrhythmia. Our practice of pacemaker implantation was compared to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for pacemaker implantation in children and adolescents (15).

Statistical analysis. Data were expressed as frequencies, mean ± standard deviation and median and range, as appropriate. Differences in characteristics, management and outcome over time were determined by creating three patient groups depending on age of CAVB diagnosis: 1) fetal (F); 2) neonatal (≤28 days, N); or 3) childhood (>28 days to 18 years, C). Comparison of the three groups was initially performed with the χ^2 test for categorical variables and the Kruskal-Wallis nonparametric test for continuous variables. If the overall test was found significant, further comparison between the groups of interest was based on the Fisher exact test for frequencies and the Mann-Whitney *U* test for continuous variables. In order to account for multiple comparisons a conservative Bonferroni penalty was introduced by multiplying the p value by the number of tests performed. Kaplan-Meier product limit estimates were used to plot survival and freedom from pacemaker implantation. Log-rank tests were used to compare survival and freedom from pacemaker among the three groups. Further comparison between two groups of interest was done with the log-rank test and a Bonferroni correlation for the p value, as described above. In order to estimate a relative risk of pacemaker implantation between groups a Cox proportional hazards model was applied using the childhood group as a baseline. A p value <0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the clinical data of 102 cases of CAVB identified at our institution from 1965 to 1998. Figure 1

Table 1. Characteristics of 102 Pre- and Post-Natally Diagnosed Cases With Isolated CAVB

	Overall		Fetal Cases			Neonatal Cases		Childhood Cases		
	χ^2	p Value	Number or Median	Range or %	F vs. N p Value	Number or Median	Range or %	Number or Median	Range or %	N vs. C p Value
Case numbers			29			33		40		
Seropositive/tested mothers	48.4	0.0001	21/22	95%	NS	24/27	90%	1/20	5%	0.0001
Male/female	1.4	NS	14/11*	56% male		12/21	36% male	17/23	43% male	
Lower grade AVB at diagnosis	6.6	0.04	1/22	4.5%	NS	1/33	3%	9/40	23%	NS
Pacemaker†	0.1	NS	11/16	69%		24/33	73%	28/40	70%	
Age (yrs) at first pacemaker	31.7	0.0001	0.025	0.003–3.9	0.02	1.5y	0.005–25.3	10.2	0.23–18.7	0.001
Single/dual chamber pacer‡	13.8	0.001	14/1	93% single	NS	19/5	79% single	13/17	43% single	0.02
Mortality rate	29.8	0.0001	13/29	45%	0.002	2/33	6%	0/40	0%	NS
Age (yrs) at last follow-up	37.5	0.0001	0.7	0–11.6	<0.0001	9.9	0.8–27.7	14.2	1.1–27.1	0.02

*Gender unknown in four cases of intrauterine demise; †ratio of permanent pacemaker implantation in cases surviving the neonatal period; ‡ratio of patients with single-chamber/dual-chamber pacing mode at first pacemaker implantation.

Data are presented as median and range, or percentage (%). Statistical comparisons were initially done among the three groups, and if the overall test was found significant, further comparison using a Bonferroni penalty was made between cases with neonatal versus fetal and cases with neonatal versus childhood diagnosis of CAVB, respectively.

AVB = atrioventricular block; C = childhood; CAVB = congenital atrioventricular block; F = fetuses; N = neonatal period; NS = not significant.

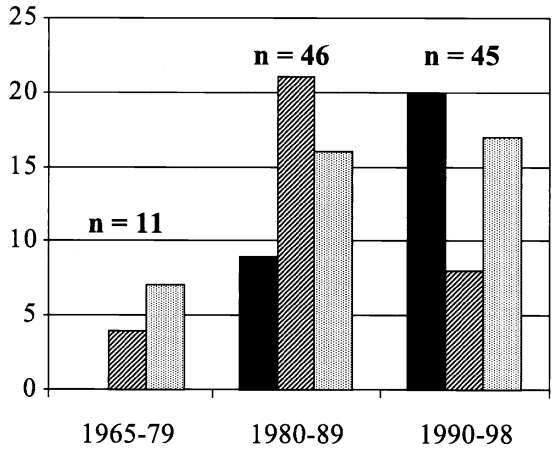

Figure 1. Number of new cases diagnosed with isolated complete heart block during different time periods.

shows the number of patients among the fetal, neonatal and childhood diagnosis groups identified during three different time periods.

Fetal group. Twenty-nine cases of CAVB were detected pre-natally, with the majority (19/29) diagnosed before 30 weeks of gestation (mean 26.1 ± 5.6 weeks, median 26 weeks, range 18 to 37 weeks). The primary indications for fetal echocardiography were for a diagnosis of fetal bradycardia (27/29) and hydrops fetalis (6/29). Anti-Ro antibodies were found in 20/22 tested mothers (15 Ro+/La+, 3 Ro+/La-, 2 Ro+/La not tested), and anti-La antibodies were found in isolation in one additional mother. Despite the presence of positive serology in 95% of tested mothers, only two had signs and symptoms of a connective tissue disease at the time of fetal CAVB diagnosis. One mother had a therapeutic abortion at 21 weeks for severe hydrops fetalis and endocardial fibroelastosis (EFE). Eleven mothers received dexamethasone, which was initiated at the time of diagnosis of fetal CAVB, with (n = 5) or without (n = 6) the presence of hydrops fetalis. In two mothers terbutaline therapy was initiated for a fetal ventricular rate of <55 beats/min (one with a 15% increase, one without change). Finally, one mother underwent fetal pericardiocentesis for a large pericardial effusion. Spontaneous intrauterine fetal death occurred in six cases: two with hydrops fetalis and EFE; one with ventricular rate <50 beats/min and two with rates ≥55 beats/min, all three without hydrops fetalis; and one after placental infarction. There were three intrauterine deaths despite maternal dexamethasone (n = 3) and terbutaline (n = 1) therapy.

Twenty-two (76%) of the fetal cases with CAVB were live-born at a mean gestational age of 35.1 ± 3.5 weeks (median 36 weeks, range 27 to 40 weeks). All had CAVB confirmed at birth with junctional (n = 21) or ventricular (n = 1) escape rhythms ranging from 40 to 90 beats/min (mean 53.5 ± 14.8). Transiently prolonged QTc intervals (range 0.48 to 0.51 s) were measured in five patients with junctional escape rhythms. One neonate had a prolonged QT syndrome with a ventricular broad QRS (100 ms) complex escape rhythm between 36 and 75 beats/min, severely prolonged JTc interval (0.43 s) and multiple episodes of torsade de pointes. The majority (15/22; 68%) of the neonates required some form of medical intervention shortly after birth, which consisted of isuprel (n = 9), corticosteroids (n = 3) and ventricular pacing (n = 12), including permanent epicardial pacing at ≥1,500 g. Six neonates died within one week of birth. The cause of death was related to at least one of the following: premature delivery (≤32 weeks gestation) in four patients; hydrops fetalis in three, EFE in one and long QT syndrome with ventricular fibrillation in one. No further deaths occurred after the neonatal period; however, one child with CAVB required cardiac transplantation because of progressive dilated EFE cardiomyopathy at 3.5 years of age. To date, a permanent pacemaker has been implanted in 11 of 16 infants who survived the neonatal period (69%).

Neonatal group. In 33 patients, although low heart rates were detected perinatally, isolated CAVB was diagnosed only after birth. As a consequence of late recognition of CAVB as the cause of fetal bradycardia, 14 of the 33 neonatal diagnosis group cases were delivered by emergency caesarian section between 28 and 42 weeks gestation for suspected fetal distress. Mean age at delivery was at 39.2 ± 2.5 weeks of gestation (median 39.5 weeks, range 28 to 42 weeks). Anti-Ro antibodies were present in 24 of 27 (89%) mothers tested (11 Ro+/La+, 7 Ro+/La-, 6 Ro+/La not tested). Neonatal electrocardiograms, available for reanalysis in 29 of 33 (88%) cases, showed permanent CAVB in all but one newborn. This latter patient had episodes of residual AV nodal conduction (first- to third-degree AV block). The ventricular rates ranged from 30 to 80 beats/min, with mean rates of 53.1 ± 13.7 beats/min. The escape rhythm was junctional in 26. One had additional atrial flutter and underwent D/C cardioversion. Three cases had broad QRS (90 to 140 ms) complex ventricular escape rhythms with left (n = 2) or right bundle branch block morphology, and one had prolonged JTc interval of 0.44 s without symptoms. Five neonates presented with signs of congestive heart failure (HF), but none had hydrops fetalis. Nine (27%) received isuprel (n = 2), and/or pacemaker (n = 8) treatment as newborns. There were no neonatal deaths, but two (6%) patients died at 0.9 and 1.5 years of age. One died of low output failure after an episode of severe bradycardia. The other developed poor ventricular function and EFE over the first year of life and died of therapy-refractory ventricular fibrillation during a diagnostic cardiac catheterization procedure. At a mean follow-up of 9.9 ± 6.4 years (median 9.9, range 0.78 to 27.7 years), 24/33 (73%) had required a permanent pacemaker.

Childhood group. Forty patients were first diagnosed with CAVB in childhood at a mean age of 5.7 ± 4.8 years (median 4.8 years, range 0.1 to 18 years). Of 20 mothers tested, only one was positive for anti-Ro antibodies (5%) and none were positive for anti-La antibodies. Six of the 40

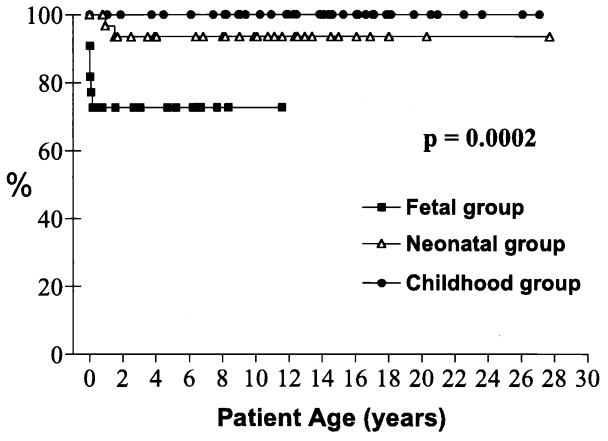

Figure 2. Kaplan-Meier survival of CAVB diagnosed during the fetal, neonatal and childhood periods differed significantly between the groups (log-rank; $\chi^2 = 17.2$, $p = 0.0002$). Further analyses using log-rank tests with Bonferroni corrections confirmed the reduced survival rate of the fetal cases (fetal vs. neonatal: $\chi^2 = 6.04$, $p = 0.03$; fetal vs. childhood: $\chi^2 = 12.3$, $p = 0.001$).

patients presented with bradycardia-related symptoms (four with syncope, two with reduced exercise tolerance) at diagnosis. The CAVB was complete at first presentation in 31 cases, with ventricular rates ranging from 32 to 65 beats/min. The CAVB was intermittent but predominated in eight patients, whereas one case had second-degree AV block with 2:1 AV conduction at diagnosis. Six of these latter nine patients progressed to complete CAVB during childhood. Thirty-eight patients had narrow QRS (junctional) and two patients had broad QRS (ventricular) complex escape rhythms on electrocardiogram. The QTc interval was normal in all but one. One five-year-old boy with a history of convulsions and episodes of torsade de pointes and ventricular tachycardia on 24-h Holter had a QTc interval of 0.62 s. At a mean follow-up of 7.8 ± 5.1 years (median 7.2, range 0.1 to 18.6 years) all patients with a childhood diagnosis of CAVB were alive and well, although 28 of 40 (70%) had undergone a permanent pacemaker implantation.

Mortality. Overall, there were 15 deaths, 13 of which occurred in patients diagnosed pre-natally. Kaplan-Meier survival analysis (Fig. 2) showed comparable survival rates of 94% (95% confidence interval [CI]: 77 to 98) for the neonatal and 100% for childhood cases (p = NS) in the first 20 years after birth. By contrast, only 73% (95% CI: 49 to 87) of the live born fetuses with CAVB reached 10 years of age (log-rank test $p < 0.001$). The majority of these deaths were in the neonatal period (F versus N: 6/22 versus 2/33, χ^2 $p < 0.05$). Results of risk factor analyses of death are shown in Table 2. Risk factors for death in addition to fetal diagnosis included hydrops fetalis, EFE, delivery at ≤32 weeks of gestation and a post-natal ejection fraction by echocardiography of ≤40%. Of note, of the four cases with pre-term delivery at <32 weeks, three had gross hydrops fetalis, which clearly contributed to their demise. Maternal autoantibodies, fetal heart rate of ≤55 beats/min, the presence of ventricular ectopy and the QRS duration were not significant risk factors for death.

Pacemaker implantation. The timing of pacemaker implantation differed significantly between the three groups (log rank, $\chi^2 = 28.4$, $p < 0.0001$). By 20 years of age only 11% of neonatal and 12% of childhood cases had not required pacemaker implantation. Kaplan-Meier estimates of freedom from pacemaker implantation (Fig. 3) of the fetal neonatal and childhood cases were 29% (95% CI: 12 to 51), 73% (95% CI: 54 to 85) and 98% (95% CI: 84 to 100) at six months. At 10 years estimates were 22% (95% CI: 8 to 40) and 64% (95% CI: 46 to 77) for the neonatal and childhood cases, respectively. Compared with the childhood group (baseline risk), the relative risk of pacemaker implantation was 6.2 (95% CI: 3 to 12.7) in the fetal group and 2.2 (95% CI: 1.2 to 3.8) in the neonatal group. The criteria for pacemaker implantation among the three patient groups, expressed in the standard ACC/AHA format (15), are listed in Table 3. Although some patients fulfilled several criteria, only one—the "most relevant" reason for pacemaker implantation—is indicated for each patient. Class I criteria was fulfilled in 14 of 15 fetal, 16 of 24 neonatal and 12 of 28

Table 2. Risk Factor Analyses of Mortality of CAVB Diagnosed In Utero, in the Newborn Period or During Childhood

	Patient Groups Analyzed (n)	Death Among Affected Cases	Death Among Nonaffected Cases	p Value (Risk for Death)
Maternal autoantibodies*	AB+(46) vs. AB−(23)	6/46	0/23	NS
Fetal diagnosis‡	F(22) vs. N+C(73)	6/22	2/73	0.02
Hydrops fetalis*	F(29), N(33)	6/6	9/56	<0.0001
Endocardial fibroelastosis*	F(29), N(33), C(40)	5/5	10/82	<0.0001
Fetal heart rate ≤55 beats/min*	F(29)	9/14	4/15	NS
Delivery ≤32 weeks‡	F(22), N(33)	4/6†	4/49	<0.03
Left ventricular ejection fraction ≤40% (echo)‡	F(13), N(26), C(36)§	6/7	0/68	<0.0001
VT/polymorphous PVC (Holter)‡	F(13), N(26), C(32)	1/6	1/65	NS
QRS duration ≥0.10 s (ECG)†	F(22), N(30), C(39)	1/7	4/84	NS

*Fetal and post-natal mortality; †three with demise also had gross hydrops fetalis; ‡mortality of live-born fetal and neonatal cases; §includes only patients with echocardiogram(s) after birth at The Hospital for Sick Children. In order to account for multiple comparison of the nine different risk factors a conservative Bonferroni penalty was introduced by multiplying the p values by 10.

AB+ or AB− = maternal autoantibody positive or negative cases; C = childhood diagnosis; CAVB = isolated congenital third-degree atrioventricular block; F = fetal diagnosis; N = neonatal diagnosis, NS = not significant; PVC = premature ventricular complexes; VT = ventricular tachycardia.

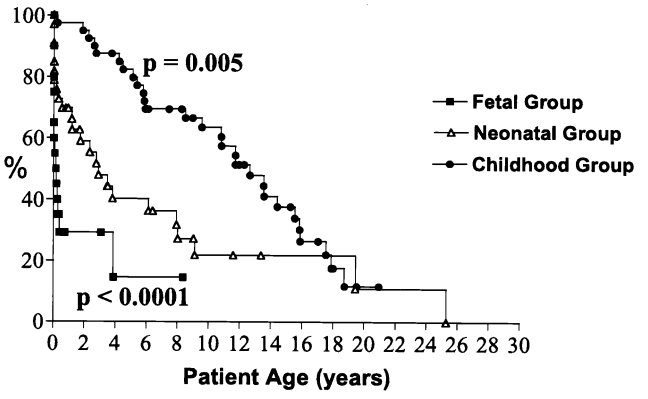

Figure 3. Kaplan-Meier freedom of pacemaker implantation comparing fetal, neonatal and childhood diagnosis of CAVB. Global differences between the groups (log-rank; $\chi^2 = 28.4$, $p < 0.001$) were further analyzed using log-rank tests and Bonferroni corrections. Time of implantation differed significantly between the childhood group and the neonatal group ($\chi^2 = 7.8$, $p = 0.02$) and between the childhood group and the fetal group ($\chi^2 = 33.9$, $p < 0.001$) but not between the neonatal and fetal groups ($\chi^2 = 4.4$, $p = 0.09$) after adjustment for multiple comparison.

childhood cases. Of symptomatic patients, congestive HF at birth was the main cause for early neonatal pacemaker placement. By contrast, syncopal episodes were experienced in three neonatal and 11 childhood cases at ages ranging from 0.5 to 25 years. Most of the cases diagnosed during childhood received a permanent pacemaker for class IIa indications, including low mean ventricular heart rates (< 40 beats/min: four cases; 40 to <50 beats/min: eight cases) and/or pauses of >3 s (four cases), before the appearance of major symptoms. Analysis of Holter findings, including average heart rate, minimal heart rate and the presence of >3 s pauses, and exercise test results, including maximum heart rate and endurance, revealed no significant difference between patients undergoing pacemaker implantation for syncope (Class I indications), Class II indications (prophylactic pacing) and unpaced patients (Table 4).

Pacemaker treatment had some important limitations and risks. Sixteen (25%; 3 F, 10 N, 3 C) of 63 patients who required pacemakers experienced at least one complication at the time of pacemaker implantation (three wound infections, one endocarditis, one cardiac perforation, one superior vena cava thrombosis) or within months of pacemaker implantation (10 ventricular lead fractures/loss of ventricular capture). The most common reasons for repeat interventions included pacemaker, lead and battery replacements, especially in young patients. All fetal cases underwent an average of 1.3 pacemaker interventions during a mean follow-up period of 3.1 ± 3 years after the first pacemaker surgery (cumulative risk [CR] of 4.2 pacemaker interventions/10 years). The neonatal cases required 2.2 interventions during a mean follow-up period of 7.6 ± 5.2 years (CR: 2.9 interventions/10 years), and childhood cases required 1.2 interventions during a mean follow-up period of 5 ± 3.2 years (CR: 2.4 interventions/10 years) after the first pacemaker intervention. In addition, six of the eight patients who died after birth had undergone pacemaker insertion before death.

DISCUSSION

Our retrospective study represents the largest reported single institution's experience with CAVB in fetuses, infants and children. In our review of 102 cases of CAVB, we have identified risk factors for mortality, which include a fetal diagnosis, fetal hydrops, ventricular EFE and delivery at ≤32 weeks of gestation. We have also demonstrated a significantly higher risk of early pacemaker insertion and repeat pacemaker-related interventions among patients with a pre-natal versus a post-natal diagnosis of CAVB. With

Table 3. ACC/AHA Criteria for Permanent Pacing of 67 of 102 Patients With Diagnosis of CAVB In Utero, as Newborn or During Childhood

Class	Third-Degree AVB With/In:	Fetal Cases (n = 15)	Neonatal Cases (n = 24)	Childhood Cases (n = 28)
I (1)	Symptomatic bradycardia, congestive heart failure, low output	6	9	10
I (4)	Wide QRS escape rhythm or ventricular dysfunction	0	1	0
I (5)	Infant with a ventricular rate <50 to 55 beats/min	7	5	1
I (6)	Sustained pause-dependent VT with and without prolonged QT	1	1	1
IIa (2)	CAVB beyond one year of age with a mean heart rate <50 beats/min or abrupt pauses in VR that are 2 to 3 times the basic cycle length	0	7	14
IIb (2)	Asymptomatic neonate, child or adolescent with an acceptable rate, narrow QRS complex and normal ventricular function	1	1	0
Others	No ACC/AHA criteria	0	0	2*

*One patient underwent pacemaker implantation for vasovagal syncope, one patient for poor heart rate response during exercise test.

ACC/AHA = American College of Cardiology/American Heart Association; CAVB = isolated congenital third-degree atrioventricular block; VR = ventricular rhythm; VT = ventricular tachycardia.

Table 4. Analysis of Heart Rate on 12-Lead ECG, Holter and Exercise Test of Class 1 and Class 2 N and C Patients and Unpaced Cases

	12-Lead ECG		Holter					ET				
Class	Age (yrs)	HR	Number	Age	HR	Min HR	Pauses >3 s	Number	Age	Max HR	Endurance	PM Age at First
Class 1	0.6	50.5	20/28	6.2	51	34	5/20	8/28	12.2	123	10.5	2.2
n = 28 (no females)	(0–17.5)	(35–76)	(71%)	(0–25)	(32–77)	(18–59)	(25%)	(29%)	(7.2–15.4)	(68–164)	(10–13)	(0.01–25)
No syncope	0.02	54.5	9/15	0.5	50	43	2/9	2/15	10.9	109	10.5	4.6
n = 15	(0–5.3)	(35–76)	(60%)	(0–17)	(35–77)	(27–59)	(22%)	(13%)	(8.9–12.9)	(82–136)	(10–11)	(0.01–18)
Syncope	8.9	47.5	11/13	7.6	52	28	3/11	7/13	12.2	123	11	8.5
n = 13	(0.5–17.5)	(38–62)	(85%)	(0.5–25)	(32–60)	(18–38)	(27%)	(54%)	(7.2–15.4)	(68–164)	(10–13)	(0.5–25)
Class 2	3.8	50	19/21	6.4	47	24	11/19	7/21	11.6	118	10	7.9
n = 21	(0.08–19.2)	(32–80)	(90%)	(2–19)	(37–80)	(17–41)	(58%)	(33%)	(10–19.2)	(70–135)	(7–12)	(1.9–19)
No PM	7.1	52	21/25	4.2	57	39	2/18	11/25	12	128	10	N/A
n = 25	(0.01–19.5)	(36–80)	(84%)	(0.01–17.4)	(43–79)	(32–77)	(11%)	(44%)	(5.5–17)	(111–140)	(7–12)	

Values are shown as median and range or ratio and percentage.
C = childhood; ECG = electrocardiogram; Endurance = ET duration in minutes; ET = exercise test; HR = heart rate; Min HR = minimal heart rate on Holter; N = neonatal period; PM = pacemaker.

advances in ultrasonographic technology and a growing experience in pre-natal assessment, CAVB has become reliably detectable in utero within the past two decades. The widespread use of pre-natal ultrasound screening provides explanation for the remarkable shift from neonatal towards a pre-natal diagnosis experienced in the most recent years (9).

Pre-natally diagnosed CAVB. As has been shown for structural cardiovascular abnormalities, our study suggests that CAVB detected in utero represents a more severe spectrum of the disease than encountered post-natally. Cases with hydrops fetalis, poor ventricular function and EFE are more likely to be detected during pregnancy. Although the pre-natal use of corticosteroids (16), plasmapheresis (17), sympathomimetics (18) and either pre-natal pacing (19) or early delivery with post-natal pacing (20) has been proposed, the true efficacy of therapy is not clear. Overall, the mortality of our fetal series was 43%, despite the frequent use of corticosteroids and inotropic agents pre- (38%) and post-natally (73%), and immediate ventricular pacing after delivery (55%). Furthermore, in contrast to a recent retrospective multicenter study (16), corticosteroid usage during pregnancy did not reverse hydrops fetalis or reduce the severity of AV block. A prospective multicenter study would clarify the real benefit of such a therapy, which may be more in the prevention of autoimmune-mediated pathology such as myocarditis and EFE.

Risk factor analysis indicated that the presence of hydrops fetalis was associated with a poor outcome, with a combined fetal and neonatal mortality of 100% in the present and 83% to 100% in published series (21). The emergence of hydrops fetalis in association with immune-mediated CAVB has been attributed to attenuated cardiac output due to bradycardia and electromechanical AV dissociation as well as myocarditis (17). In the present report, of the six cases with hydrops, three had EFE with ventricular dysfunction. Endocardial fibroelastosis has been previously described in the presence of CAVB (22,23), and we and others have shown deposition of maternal autoantibodies on the fetal myocardium (24,25). Although EFE was present in only a minority of our cases (5% overall, 14% of fetal cases), it accounted for more than one-third of the deaths. To our knowledge, this study is the first to demonstrate the incidence and important clinical impact of EFE among "isolated" CAVB patients.

Previous pre-natal reports have suggested a worse outcome for pre-natally diagnosed CAVB associated with negative maternal anti-Ro antibody status (21), and for fetuses (26) and neonates (27) with ventricular rates of <55 beats/min. In our series, all four patients with autoantibody-negative mothers and a fetal or neonatal diagnosis survived. However, 19% of those born to mothers with autoantibodies died, suggesting a worse outcome for autoantibody-associated CAVB. The majority of fetuses with ventricular rates of <55 beats/min did not survive the perinatal period in our experience, but this did not reach statistical significance. It is possible that the "natural history" of some of these fetuses had been altered by the use of pharmacological agents and aggressive perinatal management, including early, planned deliveries and immediate post-natal ventricular pacing. In contrast to the fetal diagnosis group, the outcome of CAVB detected after birth was excellent, with no severe HF observed among affected neonates and only a minority requiring therapy during the newborn period.

Based on our experience, our current approach to affected pregnancies is to initiate dexamethasone therapy at diagnosis of fetal AV block (4 mg/day) and to use maternal sympathomimetics for fetal ventricular rates of <55 beats/min. Weekly-biweekly fetal echocardiograms are used to follow the progress, and an elective delivery by caesarian section at 36 to 37 weeks is planned. If there is evidence of fetal compromise (e.g., pericardial effusion, ascites, increasing ventricular ectopy, reduced ventricular shortening fraction or AV valve regurgitation), we have elected for an earlier delivery with aggressive post-natal management, including placement of a permanent pacemaker as an early step. When there is oligohydramnios, maternal dexamethasone is tapered off; however, persistence of reduced amniotic fluid may prompt earlier delivery.

Pre-natal versus post-natal diagnosis of CAVB. Despite the comparable outcome of CAVB diagnosed neonatally or during childhood, our data continue to support the existence of two distinct clinical and serological entities. Although anti-Ro and/or anti-La antibodies are present in most mothers of offspring with CAVB diagnosed in the perinatal period, they are found in only a minority of those diagnosed after the newborn period. It is of note, however, that autoantibody screening was performed in only 50% of the mothers of children diagnosed beyond the newborn period, and as such it may not be fully representative of the positive mothers. There is evidence that once maternal anti-Ro/anti-La autoantibodies are present, they remain so lifelong (28), although the titers of the autoantibodies may change over time (29–31). Thus, the absence of maternal antibodies among patients presenting in childhood with isolated CAVB suggests a different pathogenic mechanism such as a degenerative process, when compared to isolated fetal and neonatal CAVB. It has been suggested that most CAVB diagnosed for the first time beyond infancy is congenital in origin and has escaped notice because of a higher ventricular rate and absence of symptoms (32). However, this statement was made in the early days of pre-natal ultrasound assessment. We suspect the majority of cases with a childhood diagnosis have preserved AV conduction at birth and acquire progressive AV nodal disease thereafter. This is supported by the fact that our numbers of referred childhood cases have been stable during the past two decades despite the introduction of fetal echocardiography and the wide availability of heart rate monitoring during pregnancy and labor. In addition, we have found CAVB to be absent or incompletely present in about 25% of affected children at their first clinical presentation (mean age 5.7 years). Although our data would suggest that CAVB diagnosed beyond the neonatal period is infrequently associated with maternal autoantibodies at presentation, we still recommend antibody screening of all mothers of affected children presenting with a significant conduction abnormality, particularly given the implications for future pregnancies and long-term maternal health (33,34).

Pacemaker implantation. Indications for permanent pacing in children with CAVB have evolved on the basis of natural history data and progress in pacemaker technology. Recent data indicate that pacemaker implantation may improve long-term survival and prevent syncopal events among asymptomatic patients with CAVB (35). Nevertheless, several criteria must be considered to justify prophylactic pacing in an asymptomatic patient with CAVB: the average heart rate, duration of pauses in the intrinsic rate, prolongation of the QT interval, wide QRS escape rhythm and impaired exercise tolerance (15,27). Our data confirm previous reports that most patients with CAVB will undergo pacemaker therapy by adulthood (10,18,36). However, there are striking differences in terms of patient age and indications for permanent pacing among our fetal, neonatal and childhood diagnosis groups. Most pre-natally diagnosed cases required a permanent pacemaker in early infancy, mainly because of congestive HF and/or mean ventricular rates of <55 beats/min. Nearly two-thirds of the cases diagnosed after birth were asymptomatic at the time of pacemaker implantation, and underwent pacemaker implantation prophylactically later in life, fulfilling the ACC/AHA criteria of ventricular rates <55 beats/min as infants or <50 beats/min after one year of age.

Unfortunately, pacemaker therapy was associated with a significant rate of complications, which may occur in up to 25% of cases. Lead fractures and lead insulation breaks, which occurred with loss of ventricular capture in 15% of the 67 paced patients in the present series, are complications that should be addressed with improved technology. In addition, most pediatric patients not only will receive their first pacemaker during childhood but also will eventually require further interventions for generator, lead and battery replacements.

Conclusions. Pre-natally diagnosed CAVB is associated with a high mortality. Risk factors for worse outcome include the coexistence of fetal hydrops and EFE, and delivery at ≤32 weeks gestation. Among survivors, most require pacemaker implantation during infancy, childhood or adolescence, with earlier intervention and a significantly greater need for re-intervention among those diagnosed before birth. Finally, although prophylactic pacing may reduce mortality, the use of pacemaker therapy is associated with significant morbidity, which includes pacemaker malfunction and the need for repeat interventions.

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