Long-Term Outcome of Isolated Congenital Complete Atrioventricular Block Pacing Since Neonatal Period

— Experience at a Single Japanese Institution —

Ken-ichi Kurosaki, MD; Aya Miyazaki, MD; Ken Watanabe, MD; Shigeyuki Echigo, MD

Background Few investigators have examined the outcome of patients with isolated congenital complete atrioventricular block (CCAVB) paced from the neonatal period. The present study follows the clinical course and describes the outcome of patients who have been paced with CCAVB since they were neonates.

Methods and Results The medical records of 20 patients with CCAVB paced as neonates between 1981 and 2006 were retrospectively studied and reviewed; 18 were diagnosed in utero and 2 at birth. SS-A antibodies were detected in 9 of 14 (64%) mothers tested. The median age at follow-up was 5.6 years (range, 2 days to 21.9 years). Three (15%) of the early neonates died and 3 (15%) died later: 2 from dilated cardiomyopathy (DCM) and 1 from pneumonia. The total mortality rate was 30%. The cumulative probability of survival at 10 years was 73%. Of the 14 survivors, 4 developed DCM, representing a total morbidity of 30%. The cumulative probability of freedom from DCM at 10 years was 59%.

Conclusions Patients with CCAVB who undergo pacing as neonates have high mortality and high morbidity because of DCM. Left ventricular pacing or resynchronization can benefit patients who develop DCM and left ventricular epicardial pacing is recommended for neonates with CCAVB. (*Circ J* 2008; 72: 81–87)

Key Words: Atrioventricular block; Congenital; Dilated cardiomyopathy; Heart block; Pacemaker

Congenital complete atrioventricular block (CCAVB) without intracardiac structural abnormalities is a relatively rare disease, occurring at a rate of 1 per 20,000 live births.¹ The condition is associated with maternal autoimmune disorders such as systemic lupus erythematosus and Sjögren's syndrome, with autoantibodies against SS-A/Ro and/or SS-B/La antigens. Injury to the fetal cardiac conduction system induced by SS-A/Ro and SS-B/La antibody can cause CCAVB.^{1–3}

Improvements in pacing electrode design and pacemaker generator size have enabled satisfactory implantation of pacemakers during the neonatal period.^{4,5} The prognosis for children with CCAVB after pacemaker implantation has been considered benign, but some develop dilated cardiomyopathy (DCM) despite early pacemaker implantation.^{6,7} A recent report suggests that CCAVB detected in utero or at birth differs from that detected later in life in terms of early pacemaker requirement, poor childhood prognosis and increased risk of developing DCM.⁸

The prognosis of patients with CCAVB who develop DCM is poor, because most of them die from cardiac failure or require heart transplantation.⁶ However, recent advances in the management of patients with CCAVB who

develop DCM, such as using biventricular and left ventricular epicardial pacing, have improved their prognosis.^{9–12}

Because of the rarity of the disease, little is understood about the long-term outcome of patients with CCAVB who have been paced since the neonatal period. The present retrospective study examines the clinical presentation, course and long-term outcome of such patients. We also compared the clinical courses and outcomes of patients born before and after 1995 to determine the effects of advances in management.

Methods

This retrospective study at the National Cardiovascular Center, Osaka, Japan used a modification of the diagnostic criteria for CCAVB proposed by Brucato et al.¹³ We defined CCAVB as complete atrioventricular block diagnosed in utero or at birth in the absence of associated structural heart disease. The study group comprised consecutive patients between 1981 and 2006 with CCAVB who were paced since the neonatal period. Patent ductus arteriosus and small atrial septal defect were considered as the absence of structural heart disease.

The medical records were reviewed to assess gestational age at CAVB diagnosis, gestational age and weight at birth, mode of delivery, presence or absence of hydrops, congenital heart defect, presence or absence of maternal SS-A antibodies, age at pacing, indication for pacing, initial pacing site, mode and rate, change of pacing mode, clinical course and outcome especially with regard to DCM. Left ventricular end-diastolic dimension (LVDD) and left ventricular fractional shortening (LVFS) at the most recent echocar-

(Received April 19, 2007; revised manuscript received September 14, 2007; accepted September 21, 2007)

Department of Pediatrics, National Cardiovascular Center, Suita, Japan

Mailing address: Ken-ichi Kurosaki, MD, Department of Pediatrics, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita 565-8565, Japan

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Table 1 Patient Characteristics

Patient	Gender	Gestational age at diagnosis of CCAVB (weeks)	Gestational age at birth (weeks)	Birth weight (g)	Mode of delivery	Hydrops	Presence of CHD	Maternal SS-A antibody
1*	M	U (30)	36	2,485	C	–	Small ASD	Unknown
2*	M	B	34	2,690	N	–	None	Unknown
3*	M	U (17)	27	1,096	C	+	None	Unknown
4*	M	U (35)	37	3,070	N	–	None	–
5*,†	M	U (23)	36	2,874	C	–	None	–
6*,†	M	U (28)	37	2,828	N	–	Small ASD	+
7†	F	U (37)	38	2,620	N	–	None	–
8†	F	U (29)	37	2,382	N	–	None	+
9†	M	U (29)	38	3,024	N	–	PDA	–
10†	M	U (30)	38	3,232	N	–	None	+
11	F	B	38	2,576	C	–	None	Unknown
12	F	U (30)	38	2,808	N	–	PDA	Unknown
13	F	U (32)	32	1,999	C	+	None	+
14	M	U (24)	38	2,818	N	–	None	Unknown
15	M	U (23)	32	1,908	C	+	None	+
16	M	U (20)	38	2,752	N	–	None	+
17	F	U (27)	39	2,641	N	–	Small ASD	+
18	M	U (31)	38	2,700	N	–	None	+
19	F	U (28)	38	2,880	N	–	PDA	+
20	F	U (23)	37	2,075	C	–	PDA, small ASD	–

*Died; †developed dilated cardiomyopathy.

CCAVB, congenital complete atrioventricular block; CHD, congenital heart defect; U, diagnosed in utero; C, cesarean section; ASD, atrial septal defect; B, diagnosed at birth; N, normal delivery; PDA, patent ductus arteriosus.

Table 2 Pacing Since Neonatal Period

Patient	Age at pacing (days)	Indication for pacing	Initial pacing mode	Initial pacing site	Temporary system	Change of pacing mode
1*	3	VF, VT, HR <50	VVI	RV	+	PMI-VVI: 46 days, DDD: 6 years
2*	2	Symptomatic, HR <55	DDD	RA, RV	–	
3*	1	Symptomatic (hydrops)	VVI	RV	–	
4*	2	Symptomatic, VT, Long QT	VVI	RV	–	
5*,†	5	PVCmulti, HR <50	VVI	RV	–	DDD: 6 months
6*,†	2	Symptomatic, HR <55	VVI	RV	–	
7†	5	PVCs, HR <50, Long QT	VVI	RV	–	DDD (LV): 5 years
8†	10	HR <55	VVI	RV	–	DDD: 2 years, CRT: 4 years
9†	8	Symptomatic	VVI	RV	–	
10†	2	Long QT	VVI	RV	–	DDD (LV): 2 years
11	2	PVCmulti, HR <55	VVI	RV	–	DDD: 4 years
12	3	Symptomatic, HR <50	VVI	RV	–	DDD: 6 years, VDD: 12 years
13	2	Symptomatic (hydrops)	DOO	RA, RV	+	PMI-DDD: 65 days, VVI: 8 years
14	9	PVCs, HR <50, Long QT	VVI	RV	–	
15	1	Symptomatic (hydrops), HR <50	VVI	RV	+	PMI-VVI: 95 days, DDD(LV): 8 years
16	4	PVCmulti, Long QT	VVI	RV	–	
17	1	Low output (acidosis), HR <50	VVI	RV	–	
18	2	Symptomatic, HR <50	VVI	RV	+	PMI-VVI: 12 days
19	2	LV dysfunction, HR <55, Long QT	VVI	RV	–	
20	1	Symptomatic, HR <50	VVI	LV apex	–	

*Died; †developed dilated cardiomyopathy.

VF, ventricular fibrillation; VT, ventricular tachycardia; HR, heart rate; RV, right ventricle; PMI, pacemaker implantation; Symptomatic, symptomatic bradycardia; RA, right atrium; PVC, premature ventricular contraction; (LV), left ventricular epicardial pacing; CRT, cardiac resynchronization therapy; LV, left ventricle.

diography, cardiothoracic ratio (CTR) at the most recent chest radiography, and the most recent levels of serum atrial natriuretic peptide (ANP: normal value <43 pg/ml) and brain natriuretic peptide (BNP: normal value <20 pg/ml) were also reviewed to assess cardiac function. We express the LVDD as a ratio (%) of the normal predicted value of the body surface area (%LVDD).

We defined DCM as congestive heart failure associated with cardiomegaly on chest X-ray, reduced left ventricular function at cardiac catheterization or on echocardiography and pathological findings compatible with DCM at autopsy or myocardial biopsy.

We classified the patients with CCAVB according to date of birth and compared their clinical data: the Early and Late groups were born before and after September 1995, respectively.

The findings are described as frequencies, means $\pm$ standard deviation, and medians with range as appropriate. Data from the 2 groups were statistically compared using the unpaired 2-tailed t-test, the Mann-Whitney U test and Fisher's exact test. Kaplan-Meier product limit estimates were used to plot survival and freedom from DCM. Log-rank tests compared survival and freedom from DCM between the 2 groups. All p values below 0.05 were consid-

Table 3 Outcomes

Patient	Most recent echocardiography			Most recent chest radiography		Most recent natriuretic peptide			Outcome	Follow-up (years)
	Age (years)	%LVDD (%)	LVFS (%)	Age (years)	CTR (%)	Age (years)	ANP (pg/ml)	BNP (pg/ml)		
1	12.5	76	32	—	—	—	—	—	Died, 13 years, pneumonia	—
2	—	—	—	—	—	—	—	—	Died, 3 days, sudden cardiopulmonary arrest	—
3	—	—	—	—	—	—	—	—	Died, 2 days, multiple organ failure	—
4	0	112	45	0	63	—	—	—	Died, 3 days, endocardial fibroelastosis	—
5	0.6	217	6	0.6	70	—	—	—	Died, 7 months, DCM	—
6	4	152	6	4	66	4	700	2,920	Died, 4 years, DCM	—
7	9.3	103	38	7.6	54	10.3	26	17	Alive, DCM, onset 5 years	10.5
8	5.9	133	13	6.9	52	7	28	29	Alive, DCM, onset 1 years	7.1
9	6.6	106	43	6.1	56	6.5	41	10	Alive, DCM, onset 3 years	6.7
10	3.8	119	20	3.8	54	4	75	23	Alive, DCM, onset 2 years	4.3
11	21.1	110	36	17.1	52	20.9	45	16	Alive	21.9
12	21.2	86	32	17.9	40	20.8	20	29	Alive	21.4
13	11	94	27	11.5	49	10.9	—	21	Alive, West syndrome	13.9
14	5.5	100	39	5.5	50	4.3	34	8	Alive	11.3
15	10.5	83	31	10.1	55	10.7	56	56	Alive	11.2
16	7	96	35	4.1	55	7	43	13	Alive	7.6
17	3.7	77	28	2.2	47	3.8	160	27	Alive	4.4
18	4	85	30	4.2	52	3.8	59	17	Alive	4.3
19	2.6	99	28	2.8	48	3.3	84	21	Alive	3.5
20	1.4	70	35	1.4	50	1.2	49	23	Alive, West syndrome	1.5

—, data not available.

LVDD, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; CTR, cardiothoracic ratio; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy.

ered statistically significant.

Results

The study population of 20 patients comprised 8 females and 12 males (Table 1) among whom CCAVB was diagnosed in utero in 18 (90%). The mean gestational age of these 18 patients at CCAVB diagnosis was 27.6 ± 5.1 weeks (median 28.5 weeks, range 17–37 weeks). The other 2 patients were diagnosed immediately after birth. The study group did not contain any patients with familial conditions.

The mean gestational age at birth was 36.3 ± 2.9 weeks (median 37.5 weeks, range 27–39 weeks). The mean birth weight was $2,573 \pm 490$ g (median 2,695 g, range 1,096–3,232 g). Seven (35%) patients were delivered by cesarean section, and 3 of them had hydrops. Patent ductus arteriosus was identified in 4 (20%) patients, small atrial septal defects were found in 4 (20%) and SS-A antibodies were detected in 9 of 14 (64%) mothers tested.

All patients required ventricular pacing during the neonatal period (3.4 ± 2.7 days, median 2 days, range 1–10) (Table 2). All of the neonates were started on pacing before 10 days of age. Table 2 describes the indications for neonatal pacing. Ten patients had symptomatic bradycardia including the 3 with hydrops who required premature delivery by cesarean section and pacing at 1–2 days of age. Metabolic acidosis was caused by low output in 1 patient, and left ventricular dysfunction was revealed by echocardiography in another. Seven patients had premature ventricular contractions (2 had ventricular tachycardia). The ventricular rates were less than 50 beats/min in 9 patients and 6 had long QT intervals on electrocardiograms.

The starting mode of pacing was VVI in 18 patients and DDD and DOO in the other 2. Right ventricular epicardial pacing was used in 19 patients at the start of pacing, and the 1 was paced at a site near the apex of the left ventricular epicardium. Temporary leads and extracorporeal pacemakers

were used in 4 patients (Patients 1, 13, 15 and 18) who were later implanted with permanent leads and pacemakers (at 12–95 days). Patient 1 was the first to be paced as a neonate with CCAVB at our institution. Because the general physical condition of this patient had deteriorated because of ventricular fibrillation and ventricular tachycardia, less invasive procedures using a temporary system with extracorporeal pacemakers were performed in stages. Patients 13 and 15 weighed less than 2 kg, so pacemakers were implanted after they had gained sufficient weight. Because of the development of signs of infection, such as an elevated leukocyte count and positive C-reactive protein, patient 18 was implanted with artificial leads and a pacemaker after these values had normalized. The ductus was ligated at the same time as the pacing operation in the 4 patients with patent ductus arteriosus.

The median follow-up period was 5.6 years (range 2 days to 21.9 years) (Table 3). Patients 2, 3 and 4 died during the early neonatal period. Patient 2 was implanted with a dual-chamber pacemaker with DDD mode at 2 days of age because of symptomatic bradycardia, but died from sudden cardiopulmonary arrest at 3 days of age. The parents refused an autopsy. Patient 3 was diagnosed with CCAVB in utero at 17 weeks of gestational age. He also had fetal hydrops, required premature cesarean delivery at 27 weeks of gestational age and weighed 1,096 g at birth. An emergency pacemaker was implanted immediately after delivery, but the patient died on the following day from multiple organ failure. Patient 4 was implanted with a pacemaker at 2 days of age because of symptomatic bradycardia and incessant ventricular tachycardia, but died from cardiac failure at 3 days of age. The autopsy findings revealed endocardial fibroelastosis. None of the patients died during pacemaker implantation.

After the neonatal period, 2 patients died because of DCM (Patients 5 and 6). Patient 5 developed congestive heart failure with cardiomegaly at 5 months of age.

Fig 1. Kaplan-Meier survival curves of patients with congenital complete atrioventricular block paced since the neonatal period. Cumulative probability of survival at 10 years is 73% in all patients. The difference between the Early and Late groups was significant (log-rank test, $p=0.026$). Cumulative probability of survival at 10 years is 50% and 100% in Early and Late groups, respectively.

Fig 2. Kaplan-Meier freedom from dilated cardiomyopathy (DCM) of patients with congenital complete atrioventricular block paced since neonatal period. Cumulative probability of freedom from DCM at 10 years old is 59% in all patients. Cumulative probability of freedom from DCM in the Early and Late groups is 71% and 43%, respectively at 10 years (no significant difference; log-rank test, $p=0.50$).

Table 4 Comparison of Clinical Characteristics of the Early and Late Groups

Characteristic	Early group	Late group
<i>Patients</i>	<i>Patient 1–6, 11–14 (n=10)</i>	<i>Patient 7–10, 15–20 (n=10)</i>
Gender (F/M)	3/7	5/5
<i>Age at diagnosis</i>		
In utero/At birth	8/2	10/0
Gestational age (weeks)	29±6	28±5
Birth weight (g)	2,524±580	2,621±407
Gestational age at birth (weeks)	35±4	37±2
Mode of delivery (C-section/normal)	5/5	2/8
Hydrops	2	1
Patent ductus arteriosus	1	3
Small atrial septal defect	2	2
Maternal SS-A antibody (positive/tested)	2/4	7/10
Heart rate before pacing (beats/min)	50±8	52±9
<i>Indication for pacing as neonate</i>		
Symptomatic bradycardia, ventricular dysfunction, low output	6	6
Ventricular tachycardia, premature ventricular contraction	4	2
Heart rate <50 beats/min	4	4
<i>Initial pacing</i>		
Age (days)	3±2	4±3
Mode	VVI 8, DDD 1, DOO 1	VVI 10
Site	RV 10	RV 9, LV apex 1
Rate (per min)	116±16	117±14
Temporary system	2	2
Follow-up (years)	8.6±8.8	6.1±3.1
Dilated cardiomyopathy	2	4
West syndrome	1	1
Death/survival	4/6*	0/10*
<i>Survival without dilated cardiomyopathy</i>		
Most recent %LVDD (%)/LVFS (%)/age (years)	98±10/33±5/14.7±7.8	85±11/31±3/4.9±3.3
Most recent CTR (%)/age (years)	48±5/13.0±5.7	51±3/4.1±3.1
Most recent ANP (pg/ml)/BNP (pg/ml)/age (years)	33±13/18±9/14.2±8.1	75±44/26±16/5.0±3.4

Value are means±standard deviation; *significant difference ($p=0.04$).

Abbreviations see in Tables 2,3.

Although the pacing system was upgraded to dual-chamber pacing with DDD mode at 6 months of age, this patient died of congestive heart failure at 7 months. Patient 6 developed congestive heart failure with remarkable cardiomegaly at 3 years of age and died of heart failure at 4 years of age. The pathological findings of Patients 5 and 6 at autopsy were compatible with DCM. Another patient

(Patient 1) died of pneumonia at 13 years of age. The total mortality rate was 30%. The cumulative probability of survival at 10 years of age was 73% (Fig 1).

Of the 14 survivors, the median follow-up age was 7.4 years (range, 1.5–21.9 years), and 4 patients (Patients 7, 8, 9 and 10) developed DCM between 1 and 5 years of age. All of them had pathological findings compatible with

DCM at myocardial biopsy. Among the 4 survivors with DCM, left ventricular function improved in Patients 7 and 10 after changing the pacing site from the right ventricular epicardium to near the apex of the left ventricular epicardium, Patient 8 underwent cardiac resynchronization, and Patient 9 was administered with chronic medication including a β -blocker and an angiotensin-converting enzyme inhibitor. Of the survivors without DCM, 2 (Patients 13 and 20) who had been prematurely delivered by cesarean section had West syndrome.

Thus, 6 patients had DCM, indicating a total morbidity of 30%. The cumulative probability of freedom from DCM at 10 years of age was 59% (Fig 2). None of the patients developed DCM after 6 years of age.

The most recent echocardiography of the 10 survivors without DCM revealed a mean %LVDD of $90 \pm 12\%$ (median 90%, range 70–110%) and a mean LVFS of $32 \pm 4\%$ (median 32%, range 27–39%) at the mean age of 8.8 ± 7.2 years (median 6.3, range 1.4–21.2) (Table 3). The most recent chest radiography showed a mean CTR of $50 \pm 4\%$ (median 50%, range 40–55%) at 7.7 ± 6.1 years (median 4.9, range 1.4–17.9). The most recent serum ANP and BNP levels were 61 ± 41 pg/ml (median 49 pg/ml, range 20–160 pg/ml) and 23 ± 13 pg/ml (median 21 pg/ml, range 8–56 pg/ml), respectively, at 8.7 ± 7.1 years (median 5.7, range 1.2–20.9).

Table 4 summarizes the data obtained from the Early and Late groups ($n=10$ each) classified according to date of birth. The mortality rate in the Early group was 60%, which was significantly higher than that in the Late group, which was 0% (Fisher's exact test, $p < 0.05$). The following did not significantly differ between the groups: gender distribution, age at diagnosis, gestational age and weight at birth, mode of delivery, frequency of hydrops, patent ductus arteriosus and small atrial septal defect, positive ratio of maternal SS-A antibody, heart rate before pacing, indication for pacing, age, mode, site and rate of initial pacing, frequency of temporary pacing system, follow-up period, morbidity of DCM and West syndrome. Among the survivors without DCM, the most recent findings of %LVDD and LVFS by echocardiography, CTR by chest radiography, and ANP and BNP concentrations did not significantly differ between the groups.

Kaplan-Meier survival of CCAVB paced as neonates significantly differed between the Early and Late groups (log-rank test, $p=0.026$) (Fig 1). The cumulative probability of survival at 10 years was 50% in the Early group, but 100% in the Late group.

Respective Kaplan-Meier estimates of freedom from DCM in the Early and Late groups were 71% and 43% at 10 years of age (Fig 2). The difference was not significant (long-rank test, $p=0.50$).

Discussion

Technical improvements have enabled satisfactory pacing even immediately after birth.^{4,5} In fact, the prognosis of CCAVB without intracardiac structural abnormalities is thought to be quite good after successful pacing. However, recent reports have shown that some patients with CCAVB develop DCM despite pacing during the neonatal period.^{6,7}

Limited data have been published regarding the long-term outcome of patients with CCAVB paced since the neonatal period. Only one multi-institutional study¹⁴ in Japan has mentioned this condition, but not in detail. The

present report is the first from a single Japanese institution regarding the long-term outcome of CCAVB paced since the neonatal period.

The findings at birth in this series of 20 patients with CCAVB paced as newborns, such as gender distribution, age at diagnosis, gestational age and weight at birth, mode of delivery, frequency of hydrops, patent ductus arteriosus and small atrial septal defect, were comparable with previous findings.^{1–4,7,8,13–15} The positive ratio of maternal SS-A antibody (64%) was relatively lower than that of other recent studies.^{3,8,13,14} Villain et al showed that among 37 patients diagnosed with CCAVB in utero or during the neonatal period and implanted with pacemakers as neonates, 28 (76%) had maternal anti SS-A and/or anti SS-B antibodies.³ Jaeggi et al found anti-Ro and/or anti-La in 90–95% of patients diagnosed in utero or as neonates.⁸ Immunological studies using the most sensitive and advanced methods approached a positive ratio of 100%.¹³ The Japanese multicenter study conducted by Maeno et al investigated 19 patients with CCAVB who were implanted with pacemakers and identified maternal antibodies in 14 (74%) of them.¹⁴ As Burucato et al noted,¹³ the differences were probably related to laboratory methods at the time and the choice of tested institutions.

The indications for neonatal pacing, heart rate before pacing and age at pacing in the present study were similar to those of others.^{2–4,7,8,13–15} In the multicenter study of CCAVB by Eronen et al, 48 newborns required pacemakers and the indications were congestive heart failure (63%), low ventricular rate (23%), cardiomegaly (13%) and long QT (2%).¹⁵ The study of Buyon et al² that used the Research Registry for Neonatal Lupus found 35 children with CCAVB who required pacemakers within the first 9 days of life, and 15 within 1 year. The primary indications for pacemaker placement were congestive heart failure and a ventricular rate averaging less than 60 beats/min.² The indications for pacing in our series were (in order of frequency) symptomatic bradycardia, ventricular rate less than 50 beats/min and premature ventricular contraction.

Most of the patients in the present study received initial pacing using a right ventricular epicardial lead with VVI mode. However, the last patient was initially paced using the epicardial lead near the apex of the left ventricle. The reason for this is described later.

Eronen et al reported that 8 (17%) of 48 neonates who required pacemakers died within the first year of life because of DCM.¹⁵ In the report by Villain et al, 11 (30%) of 37 patients paced as neonates developed DCM and all 4 (11%) deaths were related to DCM.³ Buyon et al showed that 17% of 50 patients paced within the first year of life died of DCM within 1 year.² Jaeggi et al reported a 43% mortality rate among 29 patients with CCAVB diagnosed in utero, and 6% among 33 patients diagnosed as neonates. They concluded that a prenatal diagnosis of CCAVB is associated with high fetal and neonatal mortality.⁸ Moak et al studied 15 patients with CCAVB who had been paced within the first week of life and who developed late-onset DCM; 4 died, 5 required cardiac transplantation, 1 was awaiting transplantation and 4 survived.⁶ The single report in the Japanese literature showed that 2 (11%) of 19 patients with CCAVB who were implanted with pacemakers died after the neonatal period.¹⁴

In our series of 20 patients, 3 (15%) died during the early neonatal period and of them 2 were because of DCM. Among 14 survivors, 4 had DCM. The total mortality rate

was 30% and the total morbidity of DCM was 30%. The cumulative probability of survival at 10 years of age was 73% and that of freedom from DCM at the same age was 59%, which are compatible with the findings of other series^{2-4,6-8,13-15} Patients with CCAVB paced as newborns have a high mortality rate during the neonatal period, and after surviving this period, have high morbidity of DCM.

The most recent %LVDD and CTR values were within the normal range in all survivors without DCM, but the LVFS were slightly below the normal range in 3 (Patients 13, 17, and 19) who had been paced with right ventricular epicardial leads. The motion of the interventricular septum was paradoxical on echocardiograms from the patients with right ventricular pacing, and the accuracy of LVFS in the presence of a flattened septum or septal dyskinesis might be limited. The most recent ANP values were elevated in most survivors without DCM. Asynchronous atrial contraction, which occurs in VVI pacing, increases intra-atrial pressure and stimulates the release of ANP!⁶ The most recent BNP concentrations were slightly above the normal range in most survivors without DCM. These findings indicate subclinical cardiac dysfunction in apparently well patients with CCAVB after successful pacing.

Two patients in the present study had West syndrome. Low cardiac output in the prenatal and early neonatal periods might have contributed to injury of the central nervous system.

Genetic mutations have recently been identified in the SCN5A and NKX2.5 pathways, which might be implicated in progressive conduction defects!^{17,18} However, genetic factors were not analyzed in the present study.

Our secondary objective was to determine differences between the Early and Late groups at our institution. The mortality in the Early group was 60%, which was significantly higher than the 0% mortality in the Late group. Other findings in the 2 groups did not significantly differ. Three infants in the Early group died during the early neonatal period. We believe that progress in prenatal care and intensive care for severely ill neonates was partly responsible for reducing neonatal mortality in the Late group.

Two patients with DCM in the Early group died, whereas 4 (Patients 7, 8, 9 and 10) with DCM in the Late group are alive at the time of this report. Noting the poor outcomes of CCAVB with DCM in the Early group, we changed the pacing sites in 2 patients with DCM in the Late group (Patients 7 and 10) from the right ventricular epicardium to near the apex of the left ventricular epicardium. Left ventricular function improved in these 2 patients. Patient 9, who developed DCM, received chronic medication, and we are planning to insert a pacing wire into the left ventricular wall near the apex at the time of the next pacemaker exchange. Takasugi et al described the details of Patient 7. They thought that an artificial complete left bundle branch block induced interventricular asynchrony that contributed to left ventricular dysfunction!¹⁰ The recent report of Tissot et al describes a similar patient with CCAVB who was paced as a neonate and whose DCM improved after changing the pacing site from the right; that is, to the left ventricular wall towards the apex!¹² Patient 8 underwent cardiac resynchronization and ventricular function improved. In a recent report of DCM following right ventricular pacing for atrioventricular block in young patients, Moak et al suggest that early upgrading to biventricular pacing systems should be considered in the management of such patients before listing for cardiac

transplantation!¹¹ They also suggest that some neonatal lupus-induced cardiomyopathy results from pacing-induced dyssynchrony, rather than from inflammatory myocarditis. Karpawich et al have suggested that chronic right ventricular pacing contributes to left ventricular dysfunction!⁹⁻²¹ Currently, left ventricular or biventricular pacing has emerged as a suitable treatment for patients with DCM. These advances in the management of patients with CCAVB who develop DCM have improved the prognosis of patients with DCM in the Late group.

Although right ventricular epicardial pacing remains the dominant technique in neonates with CCAVB undergoing cardiac pacing, the morbidity of DCM was very high in this study of patients paced with right ventricular epicardial leads. Left ventricular function improved in the 2 patients with DCM (Patients 7 and 10) after changing the pacing site from the right to the left ventricular wall near the apex. The maternal SS-A antibody of Patient 10 was positive. We then postulated that some DCM could result from right ventricular epicardial pacing-induced dyssynchrony. Patient 20 was the first at our institution to be paced from the neonatal period at a site near the apex of the left ventricular epicardium. Long-term studies of left ventricular epicardial pacing on cardiac function in developing children have not been performed, so careful long-term follow-up is required.

The initial pacing modes in 10 survivors without DCM were VVI, except for 1 that was DOO, and the last pacing mode in 8 of these 10 survivors was VVI. On the other hand, the pacing mode of 2 patients (Patients 5 and 8) with DCM had been upgraded from VVI to DDD, but left ventricular function did not improve in either patient. Patient 5 died from cardiac failure and Patient 8 underwent cardiac resynchronization. We consider that the pacing mode was not related to DCM.

Based on the present findings, we conclude that patients with CCAVB who undergo pacing as neonates have high mortality and morbidity because of DCM. The mortality rate has recently decreased because of developments in perinatal care and in the management of DCM. After surviving the neonatal period, close long-term follow-up is required to monitor the development of DCM. If DCM develops, early left ventricular epicardial pacing near the apex or cardiac resynchronization therapy should be considered.

Conclusion

We have described the long-term outcome of patients with isolated complete atrioventricular block who have been paced since the neonatal period. The total mortality rate was 30%, and the cumulative probability of survival at 10 years old was 73%. The total morbidity of DCM was 30% and the cumulative probability of freedom from DCM at 10 years of age was 59%. Mortality rates were significantly lower in patients born after 1995, than in those born before (0% vs 60%, $p < 0.05$) and the cumulative probability of survival at 10 years was 100% and 50% in each group ($p = 0.026$). Patients with CCAVB who have undergone pacing since the neonatal period require careful long-term follow-up to monitor DCM. We recommend left ventricular epicardial VVI pacing towards the apex for neonates with CCAVB who require ventricular pacing. The long-term outcome of left ventricular epicardial pacing from the neonatal period requires further investigation.

References

1. Michaelsson M, Engle MA. Congenital complete heart block: An international study of the natural history story. *Clin Cardiol* 1972; **4**: 86–101.
2. Buyon JP, Hiebert R, Copel J, Craft J, Friedman D, Katholi M, et al. Autoimmune-associated congenital heart block: Demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* 1998; **31**: 1658–1666.
3. Villain E, Coatsdoat-Chalumeau N, Marijon E, Boudjemline Y, Piette JC, Bonnet D. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status. *J Am Coll Cardiol* 2006; **48**: 1682–1687.
4. Villain E, Martelli H, Bonnet D, Iserin L, Butera G, Kachaner J. Characteristics and results of epicardial pacing in neonates and infants. *Pacing Clin Electrophysiol* 2000; **23**: 2052–2056.
5. Cohen MI, Bush DM, Vetter VL, Vetter VL, Tanel RE, Wieand TS, et al. Permanent epicardial pacing in pediatric patients: Seventeen years of experience and 1200 outpatient visit. *Circulation* 2001; **103**: 2585–2590.
6. Moak JP, Barron KS, Hougen TJ, Wiles HB, Balaji S, Sreeram N, et al. Congenital heart block: Development of late-onset cardiomyopathy, a previously underappreciated sequela. *J Am Coll Cardiol* 2001; **37**: 238–242.
7. Udink ten Cate FE, Breur JM, Cohen MI, Boramanand N, Kapusta L, Crosson JE, et al. Dilated cardiomyopathy in isolated congenital complete atrioventricular block: Early and long-term risk in children. *J Am Coll Cardiol* 2001; **37**: 1129–1134.
8. Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block: A single institution's experience of 30 years. *J Am Coll Cardiol* 2002; **39**: 130–137.
9. Janousek J, Tomek V, Chaloupecky V, Gebauer RA. Dilated cardiomyopathy associated with dual-chamber pacing in infants: Improvement through either left ventricular cardiac resynchronization or programming the pacemaker off allowing intrinsic normal conduction. *J Cardiovasc Electrophysiol* 2004; **15**: 470–474.
10. Takasugi H, Watanabe K, Ono Y, Echigo S. Improvement of left ventricular function after changing the pacing site in a child with isolated congenital complete atrioventricular block and dilated cardiomyopathy. *Pediatr Cardiol* 2005; **26**: 87–89.
11. Moak JP, Hasbani K, Ramwell C, Freedenberg V, Berger JT, DiRusso G, et al. Dilated cardiomyopathy following right ventricular pacing for AV block in young patients: Resolution after upgrading to biventricular pacing systems. *J Cardiovasc Electrophysiol* 2006; **17**: 1068–1071.
12. Tissot C, Aggoun Y, Rimensberger PC, Sierra J, Kalangos A, Beghetti M, et al. Left ventricular epicardial VVI pacing for a congenital complete heart block with severe myocardial dysfunction: Shall epicardial pacing wires be positioned left? *Int J Cardiol* 2007; **116**: e7–e9.
13. Brucato A, Jonzon A, Friedman D, Allan LD, Vignati G, Gasparini M, et al. Proposal for a new definition of congenital complete atrioventricular block. *Lupus* 2003; **12**: 427–435.
14. Maeno Y, Himeno W, Saito A, Hiraishi S, Hirose O, Ikuma M, et al. Clinical course of fetal congenital atrioventricular block in the Japanese population: A multicentre experience. *Heart* 2005; **91**: 1075–1079.
15. Eronen M, Siren MK, Ekblad H, Tikanoja T, Julkunen H, Paavilainen T. Short- and long-term outcome of children with congenital complete heart block diagnosed in utero or as a newborn. *Pediatrics* 2000; **106**: 86–91.
16. Oldroyd KG, Rae AP, Carter R, Wingate C, Cobbe SM. Double blind crossover comparison of the effects of dual chamber pacing (DDD) and ventricular rate adaptive (VVIR) pacing on neuroendocrine variables, exercise performance, and symptoms in complete heart block. *Br Heart J* 1991; **65**: 188–193.
17. Pashmforoush M, Lu JT, Chen H, Amand TS, Kondo R, Pradervand S, et al. Nkx2–5 pathways and congenital heart disease; loss of ventricular myocyte lineage specification leads to progressive cardiomyopathy and complete heart block. *Cell* 2004; **117**: 373–386.
18. Probst V, Allouis M, Sacher F, Pattier S, Babuty D, Mabo P, et al. Progressive cardiac conduction defect is the prevailing phenotype in carriers of a Brugada syndrome SCN5A mutation. *J Cardiovasc Electrophysiol* 2006; **17**: 270–275.
19. Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. *Pacing Clin Electrophysiol* 1999; **22**: 1372–1377.
20. Tantengco MV, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. *J Am Coll Cardiol* 2001; **37**: 2093–2100.
21. Karpawich PP. Chronic right ventricular pacing and cardiac performance: The pediatric perspective. *Pacing Clin Electrophysiol* 2004; **27**: 844–849.