Published in final edited form as:

Pediatr Cardiol. 2014 August ; 35(6): 906–913. doi:10.1007/s00246-014-0874-x.

Perinatal Outcome in Fetuses with Heterotaxy Syndrome and Atrioventricular Block or Bradycardia

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Abstract

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Congenital atrioventricular (AV) block is commonly associated with heterotaxy syndrome; together they have reportedly low survival rates (10–25 %). However, information about perinatal outcome and predictors of nonsurvival after prenatal diagnosis of this association is scarce. Therefore, we studied fetuses with heterotaxy syndrome and bradycardia or AV-block diagnosed between 1995 and 2011, and analyzed pre and post-natal variables. The primary outcome was death and the secondary outcome was pacemaker placement. Of the 154 fetuses with heterotaxy syndrome, 91 had polysplenia syndrome, 22/91 (24 %) with bradycardia or AV-block. Thirteen (59 %) patients had sinus bradycardia at diagnosis, 8 (36 %) complete AV block, and 1 (5 %) second-degree AV-block. Three patients elected for termination of pregnancy (3/22, 14 %), 4 had spontaneous fetal demise (4/22, 18 %), and 15 (15/22, 68 %) were live-born. Of the fetuses with bradycardia/AV-block, 30 % presented with hydrops, 20 % had ventricular rates <55 beats/min, and 10 % had cardiac dysfunction. Excluding termination of pregnancy, 15/19 fetuses (79 %) survived to birth. Among the 15 live-born patients, 4 had bradycardia and 11 had AV-block. A further 3 patients died in infancy, all with AV-block who required pacemakers in the neonatal period. Thus, the 1-year survival rate, excluding termination of pregnancy, was 63 % (12/19). Of the remaining 12 patients, 9 required pacemaker. Predictors of perinatal death included hydrops ($p < 0.0001$), ventricular dysfunction ($p = 0.002$), prematurity ($p = 0.04$), and low ventricular rates ($p = 0.04$). In conclusion, we found a higher survival rate (63 %) than previously published in patients with heterotaxy syndrome and AV block or bradycardia diagnosed prenatally. Hydrops, cardiac dysfunction, prematurity and low ventricular rates were predictors of death.

Keywords

Prenatal diagnosis; Heterotaxy syndrome; Atrioventricular block; Bradycardia

Introduction

Heterotaxy syndrome is an uncommon disease making up 0.4–2 % of structural heart disease and 1–2/10,000 live births [11, 17, 18]. Patients with polysplenia syndrome subtype (also known as isomerism of the left atrial appendages) [14] may also develop complete atrioventricular (AV) block with those diagnosed in utero reported to have a poor prognosis [16, 20, 26]. Despite early diagnosis and aggressive combined medical and surgical management, the overall mortality for these patients has been reported as high as 75–90 % [5, 20, 28].

Given the rarity of this disease, the literature on these patients is limited. Current data consist of isolated case reports and small patient series with mortality rates often confounded by the high rate of elective termination of pregnancy [1, 2, 9, 16, 21]. Data on fetuses with heterotaxy syndrome and sinus bradycardia are even more scarce [3, 19, 25]. Thus, the purpose of this study was to determine the mortality rate of patients with heterotaxy syndrome and bradycardia or complete AV block after prenatal diagnosis and to determine the risk factors associated with death.

Methods

This was a descriptive study designed primarily to determine the mortality rate of heterotaxy patients with bradycardia or AV block. Fetuses with heterotaxy syndrome and bradycardia and/or AV block were identified in the echocardiography database of Boston Children's Hospital from January 1995 to December 2011. Heterotaxy syndrome was diagnosed using the anatomical characteristics defined by Van Praagh et al. [29] and was classified as asplenia (isomerism of the right atrial appendages) or polysplenia phenotype based on previously defined patterns. Bradycardia was defined as heart rate of ≤ 100 beats/min (bpm) present for $>50\%$ of any fetal ultrasound. Fetal complete AV block was diagnosed when the atrial rate was greater than the ventricular rate with complete dissociation between the two. Fetuses with bradycardia were included in this study because, in our experience, patients with bradycardia have also been at risk for developing ventricular dysfunction and hydrops.

To evaluate a change in trend of prenatal and postnatal mortality over time, we performed a stratified analysis dividing our cohort in two periods depending on the year of diagnosis. One period was from 1995 to 2002, and the second period was from 2003 to 2010.

Fetal Variables

Variables assessed during pregnancy included gestational age at time of cardiac anatomic diagnosis and at bradyarrhythmia, atrial and ventricular rate at time of diagnosis, and presence or absence of hydrops at any time during pregnancy. For patients with AV block, the degree of heart block and ventricular rates were recorded as was the heart rate trend during the course of the pregnancy. Ventricular function was assessed qualitatively and defined as normal or abnormal. Ventricular dysfunction was defined as mild, moderate, or severe by the echocardiogram reader. For the purposes of the analysis, ventricular dysfunction was taken into account if at least mild qualitative dysfunction was present. Presence of AV valve regurgitation at each fetal echocardiogram was also recorded.

Postnatal Variables

Postnatal factors evaluated for those surviving to delivery included gestational age (prematurity defined as delivery before completion of 37 weeks), birth weight, need for inotropic support, and insertion of a pacemaker. Quantitative and qualitative assessment of ventricular function by echocardiography was recorded at birth and before and after pacemaker placement.

The primary outcome for this study was death before 1 year of life including termination of pregnancy, fetal death, or postnatal death. The secondary outcome was pacemaker placement after birth. Review of the medical records was approved by the Boston Children's Hospital Institutional Review Board.

Statistics

Patient characteristics and outcomes were summarized as number (%) for categorical variables and median (interquartile range) for continuous variables without normal distribution. Comparisons between survivors and nonsurvivors were performed using Fisher

exact test (for categorical variables) and Wilcoxon rank-sum test (for continuous variables). Values of $p < 0.05$ were considered statistically significant.

Results

Patient Characteristics

Of the 154 fetuses with heterotaxy syndrome, 91 had polysplenia phenotype with 22 of 91 (24 %) having bradycardia or AV block. Mean maternal age at diagnosis was 30 ± 5 years with a median gestational age of 23 weeks (range 19–27). The patient's fetal bradyarrhythmia was diagnosed concurrently with heterotaxy in 17 (77 %) patients with the remaining 5 cases diagnosed at a median of 4 weeks later (range 3.5–14). The most frequent structural heart disease found at echocardiography was AV canal defect ($n = 17$, 77 %), followed by double-outlet right ventricle ($n = 2$), single ventricle with l-loop transposition of the great arteries ($n = 1$), both atrial and ventricular septal defect ($n = 1$), and ventricular septal defect ($n = 1$) (Table 1).

Bradycardia and AV Block

Thirteen patients (59 %) had sinus bradycardia at diagnosis, and 8 patients (36 %) had complete AV block. One patient had second-degree AV block that progressed to complete AV block in 4 weeks (case no. 1). Median ventricular rate at diagnosis among those with sinus bradycardia was 90 bpm (range 77–100), which decreased to 80 bpm (range 62–98) before the end of the pregnancy. Of note, once a patient was found to be bradycardic, all subsequent ultrasounds showed continued bradycardia at or lower than the first recorded heart rate with no improvement in heart rate trend noted. Median ventricular rate among those with AV block was 60 bpm (range 55–60) at both diagnosis and before the end of the pregnancy with median atrial rates of 120 bpm (range 107–126) at both first and last fetal echocardiogram. Four (20 %) fetuses (3 with AV block and 1 with bradycardia) had ventricular rates < 55 bpm at the last fetal echocardiogram.

Cardiac Function

Of the 22 patients with bradycardia or AV block, 20 (91 %) had normal cardiac function at diagnosis. These patients maintained normal cardiac function throughout the pregnancy. Mild cardiac dysfunction was present at diagnosis in the 2 remaining patients (cases no. 5 and 9), both of whom had AV block with ventricular rates < 55 bpm. These patients subsequently developed hydrops 2 and 6 weeks later, respectively, and died in utero at 20 and 26 weeks of gestational age soon after the diagnosis of hydrops was made. Five patients with normal cardiac function throughout pregnancy developed hydrops (3 with bradycardia and 2 with AV block) with median ventricular rate of 60 bpm (range 57–70). Of these 5 patients with normal function and hydrops, 2 had severe AV valve regurgitation, and both died at 26 weeks of gestation. The other 3 patients were delivered prematurely at 30, 31, and 34 weeks of gestation. Of the 7 patients with hydrops, the median ventricular rate was 60 bpm (range 40–70).

Pregnancy Outcome

Fifteen patients (68 %) were live born, 4 (18 %) had fetal demise and 3 (14 %) families elected for termination of pregnancy. Excluding termination of pregnancy, survival to live birth for patients with heterotaxy syndrome and either bradycardia or AV block was 79 % (15 of 19). Survival to live birth for patients with AV block was 71 % (5 of 7) and for patients with bradycardia was 83 % (10 of 12). Of the 4 fetal deaths, 2 had sinus bradycardia with ventricular rates of 60 and 70 bpm and 2 had AV block; both had ventricular rates <55 bpm. The 3 mothers who underwent termination of pregnancy had fetuses with complete AV canal with normal cardiac function. Two had complete AV block, and 1 had sinus bradycardia. Of note, no treatment was given for fetal bradycardia or heart block with no beta-agonists used.

Postnatal Outcome

Among the 15 live-born patients, median gestational age at delivery was 37 weeks (range 35–38), and median birth weight was 3,100 g (range 2,315–3,700). Six of the patients who had sinus bradycardia in utero went on to develop complete AV block postnatally. Therefore, at birth, 4 patients had sinus bradycardia and 11 had AV block confirmed on electrocardiogram postnatally. Ventricular function was normal in all but 3 patients, all of whom had at least moderate dysfunction. Six infants were born prematurely. Two were born at 31 and 30 weeks of gestation and died at 1 and 3 days of life, respectively. Both had complete AV block with ventricular escape rates of approximately 40 bpm and severely decreased ventricular function. Both had temporary pacemakers placed during the first 6 h of life. The third premature infant was born at 34 weeks of gestation with complete AV block and ventricular escape rate of 50 bpm. This patient had a pacemaker placed at 6 days of life but died at 4 months of age from sepsis and multiorgan failure (case no. 15). The other 3 premature infants were born at 35 and 36 weeks of gestation and remained stable after pacemaker placement during the neonatal period.

With a median follow-up of 4 years (range 2–8), only 1 death occurred after the neonatal period at 4 months of age (case no. 15). There were no deaths after 1 year of life. Patients alive at the end of the study ($n = 12$) had good ventricular function on their last follow-up echocardiogram. The overall survival rate, starting with fetal diagnosis, among those continued pregnancies was 63 % (12 of 19). Excluding those with sinus bradycardia, patients who had complete AV block (either prenatally or had sinus bradycardia that progressed to AV block postnatally) had a survival rate of 73 % (8 of 11).

Treatment

Of the 15 live-born patients, 8 required inotropic treatment to maintain hemodynamic stability before pacemaker implantation. Of the 12 surviving patients, 9 required pacemaker placement: 8 for complete AV block [median ventricular rate of 60 bpm (range 30–70)] and 1 for sinus node dysfunction (ventricular rate of 60 bpm). All but 1 patient with AV block had pacemakers placed in the neonatal period at a median age of 5 days (range 1–8). The other patient (case no. 10), who progressed from sinus bradycardia at birth to AV block, had a pacemaker placed at 3 months of age.

Predictors of Fetal Death

Excluding termination of pregnancy, the only risk factors for fetal death were cardiac dysfunction ($p = 0.035$) and hydrops ($p = 0.009$). Complete AV block and ventricular rate <55 bpm were not predictors of fetal death (Table 2). All patients with cardiac dysfunction died in utero. There was no statistical difference in fetal death between the first and second half of the study (25 vs. 20 %, $p = 0.8$).

Predictors of Postnatal Death

When evaluating perinatal risk factors for postnatal death, hydrops ($p = 0.002$), prematurity ($p = 0.044$), low ventricular rates ($p = 0.044$), and cardiac dysfunction after birth ($p = 0.002$) were determined to be strong risk factors for nonsurvival. In contrast, patients who had low ventricular rates and cardiac dysfunction in utero, as well as those with complete AV block (in utero and/or after birth), were not at risk for postnatal death (Table 3).

All patients without cardiac dysfunction either prenatally or postnatally and those without hydrops survived at least until 1 year of life (Fig. 1). Postnatal mortality was not statistically different between the first and second half of the study (33 vs. 17 %, $p = 0.5$).

Discussion

This is the largest reported cohort of patients with heterotaxy syndrome and either sinus bradycardia or congenital AV block who survived the neonatal period. The survival rate in our cohort was greater than previously reported with 63 % surviving beyond 1 year of age. Previous studies have shown that congenital AV block associated with structural heart disease carries a poor prognosis, especially in those with the polysplenia phenotype in heterotaxy syndrome [24, 28]. In those studies, mortality rates ranged from 80 to 100 % [2, 16, 20]. However, the previously reported data come from studies limited to a small number of patients both due to the rarity of the disease and a high rate of elective termination of pregnancy [2, 16, 21, 26]. Similar to previous reports, predictors of mortality in our study included hydrops and ventricular dysfunction with mortality rates of hydropic patients >80 % [2, 7, 15, 16, 21, 22, 26]. Interestingly, low ventricular rates during pregnancy were not associated with increased fetal mortality in our study; however, as noted in other studies [8, 26], low ventricular rates after birth were associated with postnatal death. Therefore, the ventricular rate should not be the sole factor dictating patient management because patients with low escape rates can remain hemodynamically stable in utero. Consequently, allowing these patients to remain in utero with frequent monitoring may lead to better outcomes, especially given that premature delivery can be associated with worse outcome [4, 10, 15].

It should also be noted that patients with sinus bradycardia, not just patients with AV block, were also at risk for poor outcome, with the former comprising 50 % of fetal deaths. This stresses the importance of monitoring those with complete AV block and those with sinus bradycardia because both arrhythmias are at risk for developing cardiac dysfunction and/or hydrops. With the majority of the literature focused solely on AV block alone, it is vital that sinus bradycardia is recognized as a possible risk factor for poor outcomes given its

association with mortality and the possibility of progressing to AV block. Awareness of this will help in counseling families at the time of initial diagnosis.

No other heart rate parameters were noted to be associated with mortality. Both high (>160) and low (<120) atrial rates in the setting of AV block have been reportedly associated with poorer outcome [20, 23, 26], although no relationship was noted in this study, similar to a recent report [2]. Progression of heart block or slowing of the escape rate were also not shown to be correlated with mortality, which also conflicts with previous reports [26, 27].

Although the nature of the bradyarrhythmia is unique in patients with heterotaxy syndrome, the risk factors for death were similar to those found in patients with AV block from other etiologies, such as those with immune-mediated AV block [2, 4, 7, 22]. Patients with heterotaxy syndrome and polysplenia are inherently at risk for rhythm disturbances given their lack of right-sided heart structures. Sinus bradycardia may be due to the hypoplasia or absence of the sinus node, a structure related to the right atria [6, 13], whereas those with complete AV block may have a discontinuity between the AV node and His-Purkinje system [13] either due to an initial lack of fusion between AV nodal tissue and the His bundle or due to a secondary interruption of the AV conduction axis [12]. As such, it was not surprising that 6 of our patients with sinus bradycardia went on to develop complete AV block. Although not associated with death, 12 patients subsequently had pacemakers placed. Given the tenuous nature of the cardiac conduction in these polysplenia syndrome patients, expectant parents should be aware of the risk for AV block and counseled accordingly.

Similar to previous studies [2, 16, 20], the greatest attrition in the present series occurred prenatally and immediately postnatally. At a median follow-up of 4 years, only 1 patient died, at 4 months of age, from a cause not related to heart disease. The mortality rates in the present study were lower than those previously reported, although the reasons for this are not entirely clear. The strategy in our perinatal management is to monitor patients closely in the third trimester and let the pregnancy go to as close to full term as is possible. Timing of delivery to minimize fetal compromise and maximize maturity is critical as is the involvement of a multidisciplinary team consisting of obstetricians, neonatologists, cardiologists, and cardiac surgeons. Appropriate inotropic and chronotropic support after birth is imperative to optimize survival. Determining the exact mechanism for bradyarrhythmias in utero can be challenging, especially in patients with structural abnormalities. It is possible that patients diagnosed with significant sinus bradycardia during fetal life may have had complete AV block with isosynchronous atrial and ventricular contractions, which is evident only on postnatal electrocardiograms. A prospective multicenter study may allow for more accurate diagnoses while also better defining responsible for the improved patient survival noted in this study.

Despite the somewhat more encouraging results, this study is limited by the small patient cohort cared for at a single institution. However, it remains the largest cohort of surviving patients reported so far for those with heterotaxy syndrome and bradycardia/complete AV block. Because we did not follow a standardized protocol for the care of these patients, these results reflect a clinical practice in an experienced referral cardiac center taking care of the most severe end of the spectrum of heterotaxy syndrome patients.

In conclusion, the association of complete AV block and heterotaxy syndrome is an uncommon disease with previously reported high mortality rates. However, this study shows that survival of these patients beyond the neonatal period may not be as poor as previously reported. Fetuses with normal cardiac function and without hydrops can be delivered near term, and the survival rate can be expected to be high. Fetuses with heterotaxy syndrome and bradycardia, either sinus or due to AV block, should be closely followed-up during pregnancy to monitor the development of cardiac dysfunction and/or hydrops. The decision for delivery prematurely should not be made on ventricular rate alone.

Acknowledgments

Maria C. Escobar-Diaz is supported by a grant from La Caixa Foundation, Spain.

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Fig. 1.

Outcome of patients with bradycardia/AV block and heterotaxy syndrome

* With cardiac dysfunction in utero

† With cardiac dysfunction post-natally

Prenatal findings and postnatal outcome in fetuses with congenital AV block/bradycardia and heterotaxy syndrome

Table 1

Case	Year at diagnosis	GA at diagnosis	Cardiac defect	First A/V rate, bpm	Last A/V rate, bpm	Cardiac dysfunction in utero	Hydrops	Rhythm in utero	GA at end of pregnancy	Birth weight	VR at birth	Rhythm at birth	Postnatal Treatment	First pacemaker	Outcome
1	1995	23	CAVC, PS, AS	110/55	110/70	0	+	CAVB	31	1800	50	CAVB	Isoproterenol, dopamine, epinephrine	Temporary transvenous	Neonatal death
2	1995	19	CAVC, PS	120/60	120/60	0	0	CAVB	19						TOP
3	1996	31	Partial AVC	120/60	120/60	0	0	CAVB	37	2990	70	CAVB	Isoproterenol, dopamine, epinephrine	Epicardic single chamber	Alive
4	1997	20	CAVC, LVOT obstruction	105/55	88/47	0	0	CAVB	40	3200	40	CAVB	no	Temporary epicardic	Alive
5	1999	18	DORV, PS	140/50	120/40	+	+	CAVB	20						Fetal death
6	2001	20	CAVC	100/100	–	0	0	sinus brady	21						TOP
7	2002	19	CAVC	120/60	–	0	0	CAVB	20						TOP
8	2003	25	CAVC, LVOT obstruction	90/90	80/80	0	0	sinus brady	38	2900	40	CAVB	Isoproterenol, dopamine	Epicardic dual chamber	Alive
9	2003	20	CAVC, PA	120/55	120/40	+	+	CAVB	26						Fetal death
10	2004	19	CAVC	90/90	90/90	0	0	sinus brady	40	3800	60	sinus, 2nd AVB at 3 months	no	Epicardic dual chamber	Alive
11	2005	30	VSD, ASD	60/60	60/60	0	0	sinus brady	39	3400	60	CAVB	no	Epicardic dual chamber	Alive
12	2005	26	CAVC	70/70	70/70	0	+	sinus brady	26						Fetal death
13	2006	34	SV, PS, I-TGA	133/67	133/67	0	0	CAVB	38	3700	30	CAVB	Dopamine	Epicardic dual chamber	Alive
14	2006	26	Partial AVC, partial APVC	97/97	95/95	0	0	sinus brady	38	3300	132	sinus	no	no	Alive
15	2007	23	CAVC, PS, DORV	85/85	55/55	0	+	sinus brady	34	3100	50	CAVB	Dopamine	Epicardic dual chamber	Died at 4 months

Case	Year at diagnosis	GA at diagnosis	Cardiac defect	First A/V rate, bpm	Last A/V rate, bpm	Cardiac dysfunction in utero	Hydrops	Rhythm in utero	GA at end of pregnancy	Birth weight	VR at birth	Rhythm at birth	Postnatal Treatment	First pacemaker	Outcome
16	2007	38	VSD, partial APVC	100/100	100/100	0	0	sinus brady	38	4000	105	CAVB, good junctional rhythm	no	no	Alive
17	2008	33	DORV	100/100	100/100	0	0	sinus brady	37	3870	100	sinus	no	no	Alive
18	2008	23	CAVC, TOF	100/100	100/100	0	0	sinus brady	35	2100	70	CAVB	Dopamine	Epicardic dual chamber	Alive
19	2008	16	CAVC	95/95	75/75	0	0	sinus brady	36	2315	60	sinus node dysfunction	Isoproterenol	Temporary epicardic	Alive
20	2008	18	CAVC, DORV	60/60	60/60	0	+	sinus brady	26						Fetal death
21	2009	23	CAVC	105/60	100/60	0	+	CAVB	30	2000	30	CAVB	Dopamine	Temporary epicardic	Neonatal death
22	2009	26	CAVC	90/90	80/80	0	0	sinus brady	36	2600	60	CAVB	no	Epicardic dual chamber	Alive

APVC anomalous pulmonary vein connections, AS aortic stenosis, ASD atrial septal defect, AV atrial/ventricular, AVC atrioventricular canal, brady bradycardia, CAVB complete atrioventricular block, CAVC complete atrioventricular canal, DORV double-outlet right ventricle, GA gestational age, I-TGA l-transposition of the great arteries, LVOF left-ventricular outflow tract, PA pulmonary atresia, PS pulmonary stenosis, SV single ventricle, TOF tetralogy of fallot, TOP termination of pregnancy, VR ventricular rate, VSD ventricular septal defect, + present, 0 absent, – not performed

Table 2Risk factors for fetal death ($n = 19$)

Risk factors	Surviving patients ($n = 15$)	Non surviving patients ($n = 4$)	p
First ventricular rate <55 bpm (in utero)	2	1	0.530
Last ventricular rate <55 bpm (in utero)	2	2	0.178
Hydrops	3	4	0.009
Cardiac dysfunction in utero	0	2	0.035
AV block in utero	5	2	0.603

Data in bold represents statistically significant data ($p < 0.05$)

AV atrioventricular

Table 3Risk factors for postnatal death ($n = 15$)

Risk factors	Surviving patients ($n = 12$)	Non surviving patients ($n = 3$)	p
First ventricular rate <55 bpm (in utero)	1	1	0.371
Last ventricular rate <55 bpm (in utero)	1	1	0.371
Hydrops	0	3	0.002
Cardiac dysfunction in utero	0	0	NA
AV block in utero	3	2	0.242
Prematurity	3	3	0.044
Ventricular rate at birth <55 bpm	3	3	0.044
Cardiac dysfunction after birth	0	3	0.002
AV block at birth	8	3	0.516

Data in bold represents statistically significant data ($p < 0.05$)

AV atrioventricular