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Atrioventricular Valve Regurgitation in the Fetus With Atrioventricular Canal Defect: Transition From Prenatal to Postnatal Life

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Abstract

Atrioventricular valve regurgitation (AVVR) is a clinically important element of the common atrioventricular canal defect. Cardiac preload and afterload increase from prenatal to postnatal life. These hemodynamic changes may increase the degree of regurgitation and affect management and prognosis. We sought to investigate the frequency of change in degree of AVVR from fetal to postnatal life in this patient population. Subjects who underwent both fetal and postnatal echocardiography within 4 weeks of life between January 2008 and September 2010 were included in the study. Degree of AVVR was assessed by color Doppler imaging and scored as 0 (no regurgitation), 1 (hemodynamically insignificant regurgitation), and 2 (hemodynamically important regurgitation). Forty-nine subjects were included. Mean gestational age at fetal echocardiogram was 34 ± 2.8 weeks; age at postnatal echocardiogram was a median of <24 h of age (range 0–24). After birth, 69 % subjects had no change, 8 % of subjects had a decrease, and 22 % subjects had an increase in AVVR grade. Five patients progressed from a fetal score 0 or 1 to postnatal score 2. Neither trisomy 21 nor heterotaxy syndrome were risk factors for progression of AVVR. In patients with AV canal defects, 90 % demonstrate no hemodynamically significant change in AVVR from fetal to postnatal life, whereas 10 % display a hemodynamically significant change. AVVR appreciated in utero is predictive of neonatal regurgitation in the majority of patients. These findings have implications for the counseling and management of the fetus with AV canal defect.

Keywords

Atrioventricular valve; Regurgitation; Canal; Fetus; Echocardiography; Congenital heart disease

Introduction

Hemodynamic loading conditions affecting the heart change significantly from prenatal to postnatal life. Preload increases as pulmonary circulation is augmented due to the decrease

in pulmonary vascular resistance, thus resulting in increased pulmonary venous return [17]. Afterload also increases as the placenta, a low-resistance circuit, is eliminated from the circulation [15]. Both of these phenomena may lead to an increase in atrioventricular valve regurgitation (AVVR) in congenital heart disease, in which the valve is predisposed to insufficiency. In patients with AV canal defects, the degree of AVVR may change in the setting of these dynamic alterations in loading conditions from fetal to postnatal life. The natural history of AVVR in patients with AV canal defects as they transition from fetal to postnatal life has not yet been reported.

Degree of AVVR contributes to clinical outcomes in patients with an AV canal defect [2]. Pansystolic, or severe regurgitation, is associated with fetal hydrops [5]. In addition, significant regurgitation is associated with early development of heart failure in postnatal life [3]. AV canal defects are one of the cardiac anomalies most commonly diagnosed by way of fetal imaging [10]. They are appreciated on the four-chamber view during routine prenatal ultrasound, prompting a high referral rate for fetal echocardiography (echo). With improvement in resolution and quality of imaging, degree of AVVR is now accurately assessed in utero and can be compared with postnatal findings. The capacity to predict the development of important AVVR after birth can greatly influence prenatal counseling and influence postnatal management strategies.

The goal of our study is to define longitudinal trends in the natural history of AVVR as loading conditions change from fetal to postnatal life in patients with AV canal defects and to determine whether associated factors, such as heterotaxy or Down syndrome, influence this trend.

Methods

This study involved collection of data derived from human subjects and was approved by the Internal Review Board at Children's Hospital of Philadelphia and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

We performed a retrospective evaluation of the natural trend of AV valve regurgitation in patients with AV canal defects before and after birth. Patients with incomplete (no ventricular septal defect [VSD]), transitional (restrictive VSD), and complete (large VSD) common AV canal anomalies who underwent prenatal evaluation with fetal echo at the Fetal Heart Program at Children's Hospital of Philadelphia were identified. Data were collected from the records of patients diagnosed between January 1, 2008, and September 30, 2010. If more than one fetal echocardiogram was performed, we recorded information from the fetal echocardiographic report closest to birth for analysis. We then examined postnatal echocardiographic reports of AV valve regurgitation after birth within the first 4 weeks of life. If more than one postnatal echocardiogram was performed within the first 4 weeks of life, we analyzed information from the first full postnatal echocardiographic study.

Incomplete records that did not contain either a complete prenatal or postnatal echocardiogram resulted in exclusion from the study. When available, we also analyzed

preoperative echocardiograms performed at 1 month of age. If more than one echocardiogram was available, the final echocardiogram before surgery was evaluated. Data analyzed included fetal and postnatal echo reports, gestational age and postnatal age at the time of echo, additional diagnoses of heterotaxy syndrome and/or trisomy 21, and overall outcomes. Descriptions of the cardiac anatomy—including the type of AV canal defect, Rastelli anatomical classification of complete common AV valves, and any additional anatomical descriptions—were noted.

In our imaging laboratories, fetal echocardiograms are performed on Siemens Acuson Sequoia ultrasound machines (Mountain View, CA), whereas postnatal echocardiograms are performed on Phillips iE33 ultrasound machines (Bothell, WA). The default setting for color scale on all echo machines is between 60 and 80 cm/s. Degree of AVVR can be graded by echo in multiple ways. General principles for AVVR grading in our imaging laboratories follow guidelines from the semiquantitative assessment of AVVR by Doppler color flow by assessing the ratio of the regurgitant jet area to the atrial area [7, 18]. A maximal regurgitant color jet area-to-atrial area of <30 % indicates mild, 30–50 % indicates moderate, and >50 % indicates severe AVVR.

To focus on grossly significant changes in AVVR and account for observer variability within the echo reports, we cohorted report descriptions into three groups as follows: grade 0 = no AV valve regurgitation; grade 1 = hemodynamically *insignificant* AV valve regurgitation; and grade 2 = hemodynamically *significant* AV valve regurgitation. Moderate to severe AVVR was considered hemodynamically significant and therefore includes patients who may potentially be at risk of heart failure, poor growth and development, and/or impaired recovery time postoperatively due to AVVR. If AV valve regurgitation was specified to the right and/or left, we included the highest degree of regurgitation recorded. Data were collected and presented in categorical form. Statistical analysis was performed using chi-square and Fisher's exact tests with significance set at $p < 0.05$.

Results

One hundred patients with AV canal defects underwent fetal echocardiography during the specified study time period, and 49 met criteria for entry into the study. Despite the high number of patients excluded, the distribution of degree of prenatal AVVR, prevalence of heterotaxy syndrome or trisomy 21, and type of canal defect in the excluded subjects were similar to the group of study subjects who met inclusion criteria. In the study group, 43 of 49 (88 %) of the patients had complete common AV canal defect, whereas 6 of 49 (12 %) had incomplete or transitional AV canal defects. Of the patients with complete common AV canal, 18 of 43 (42 %) had moderately to severely unbalanced defects at the ventricular level that were not amenable to a two-ventricle repair. Rastelli classification assigned to common AV valves describes the absence or presence and location of superior bridging leaflet attachments. In the group of 25 balanced complete common AV canal defects, 16 cases were Rastelli type A, 2 cases were Rastelli type B, and 7 cases were Rastelli type C morphology. Ten fetuses had associated pulmonary atresia, and 7 fetuses had aortic arch hypoplasia or coarctation that required surgical intervention. Moderate right-sided obstruction secondary

to right-ventricular muscle bundle, pulmonary valve stenosis, or branch pulmonary stenosis was present in 7 cases.

Average gestational age at the time of the fetal echocardiogram was 34 ± 2.8 weeks. Of these patients, 9 of 49 (18 %) had grade 0 AVVR, 31 of 49 (63 %) had grade 1 AVVR, and 9 of 49 (18 %) had grade 2 AVVR at prenatal study. Median postnatal age at the first pediatric echocardiogram after birth was <24 h of life (range 0 to 24). Of these patients, 2 of 49 (4 %) had grade 0 AV valve regurgitation, 36 of 49 (73 %) had grade 1 AV valve regurgitation, and 11 of 49 (22 %) had grade 2 AV valve regurgitation at postnatal study. There was a slight difference in distribution by grade in the prenatal group compared with the postnatal group, with more patients showing some degree of AVVR after birth; however, this did not reach statistical significance ($p = 0.13$). Overall, at transition from prenatal to postnatal life, 69 % of patients had no change, 8 % a decrease, and 22 % an increase in degree of AVVR.

The postnatal grade change of AVVR for each grade of fetal regurgitation is listed in Fig. 1. Overall, 90 % of patients showed no significant change in AVVR. Five patients (10 %) had clinically important progression of AVVR from fetal grade 0 or 1 to postnatal grade 2. Characteristics of the five patients who showed a clinically significant hemodynamic increase in AVVR to postnatal grade 2 are listed in Table 1. Four patients had regression of AVVR; 3 patients with fetal grade 2 improved to grade 1 after birth; and 1 patient with fetal grade 1 had no AVVR after birth.

When available, we analyzed postnatal echocardiograms performed at 1 month of age before surgical intervention when none of the patients were receiving prostaglandin E1 therapy. Twenty-two patients (median age 1 month [range 1–10]) had an echocardiogram available for analysis. Of these patients, 18 of 22 (82 %) showed no hemodynamically significant AVVR progression from fetal life to 1 month of life.

The overall mortality rate of our study was 12 of 49 (24 %). Patients with grade 2 regurgitation on postnatal echo had a mortality rate of 55 % compared with 16 % and 0 % for grades 1 and 0, respectively. The mortality rate for patients undergoing two-ventricular AV canal repair was 9.7 % (3/31), whereas the mortality rate for patients undergoing single-ventricle palliation was significantly higher at 50 % (9 of 18). Heterotaxy syndrome was present in 19 of 49 (39 %) and trisomy 21 in 20 of 49 (41 %) of patients in the study. A high percentage of patients with heterotaxy were candidates for single-ventricle palliation at 89 % (16 of 18). There was a high incidence of unbalanced ventricular arrangement as well as systemic and pulmonary venous abnormalities in this group. The distribution of AVVR grades within the trisomy 21, heterotaxy syndrome, and no syndrome groups was similar in both prenatal and postnatal life (chi-square $p = 0.28$ and 0.52 , respectively) (Fig. 2). Neither trisomy 21 nor heterotaxy syndrome were found to be statistically significant risk factors for progression of AVVR ($p = 0.22$); however, the number of patients without trisomy 21 or heterotaxy syndrome was small (Table 2).

Discussion

In this study, we found that for the fetus with an AV canal defect, no significant progression of AVVR is associated with birth in the majority of cases despite the dramatic hemodynamic changes that occur during the transition from fetal to postnatal circulation. Degree of AVVR is sensitive to hemodynamic loading conditions. Evidence for this influence is seen in patients with AV canal defects in the perioperative setting when preload and afterload are low compared with the immediate postoperative setting. Studies demonstrate that more than one third of patients have an acute increase in degree of AVVR in the setting of these hemodynamic changes [8, 9]. The results of our study suggests that the changes in preload and afterload associated with birth alone are not sufficient to significantly influence the severity of AVVR.

Progression of AVVR may be due to specific risk factors. Valve morphology can affect the development of AVVR. A deficient bridging leaflet is associated with significant AVVR and often presents early in life [14]. Repair of this type of valve is difficult, resulting in greater morbidity and mortality directly associated with the degree of regurgitation. Additional morphologic abnormalities, such as papillary muscle malformations, contribute to significant postoperative left AVVR or stenosis after two-patch repair [1]. Irrespective of valve morphology, 52 % of patients with complete AV canal defects and preoperative valve regurgitation continue to have regurgitation after surgery compared with 28 % of patients without preoperative regurgitation [16]. Postoperative AVVR is one of the most common long-term complications resulting in reoperation in this patient population [11]. Therefore, the degree of AVVR is dynamic and clinically important in patients with AV canal defects.

In our study, group, a subset of only 10 % of patients developed a hemodynamically significant change in AV valve regurgitation from fetal to postnatal life. Factors in addition to altered loading conditions may contribute to these observed changes in AVVR. Although the group with a hemodynamically significant change in AVVR was small, they did demonstrate a high mortality rate: Three of 5 patients died during infancy. In addition, 3 of 5 patients showed right- and/or left-sided outflow obstruction. However, there were many other patients within the study group who had evidence of right- and/or left-sided outflow obstruction, including 10 patients with pulmonary atresia. In the overall group of patients with significant AVVR in the postnatal period, 6 of 11 (55 %) had evidence of right-and/or left-sided outflow obstruction. This could represent a risk factor in the development of worsening of AVVR from fetal to postnatal life; however, the numbers in our study are too small to make any definitive conclusions.

The majority of postnatal echocardiograms analyzed were performed within 24 h of life because the primary aim of the study was to identify changes associated with the physiological consequences of birth alone. As a result, the pulmonary vascular resistance would still be relatively increased compared with levels seen later on in infancy. AVVR could change over time because pulmonary vascular resistance naturally continues to decrease and pulmonary venous return increases. A small group of patients analyzed in this study had echocardiograms available for evaluation before surgical intervention after the neonatal period had passed. Our analysis of this subgroup suggests that despite patient

growth with a continued decrease in pulmonary vascular resistance, the majority of patients with AV canal defects demonstrate no significant AVVR progression from fetal life to later infancy. However, hemodynamic changes may influence AVVR progression in approximately one fifth of the patients analyzed in this manner. A larger group of patients is needed to further explore this phenomenon.

There are several limitations to our retrospective study. Inherent referral and selection bias may exist because patients with more complex lesions or greater AV valve regurgitation are more likely to be referred to our tertiary care referral center. As a group, patients with AV canal defects have a high incidence of associated cardiac and extracardiac malformations in addition to syndromes that include trisomy 21 and heterotaxy syndrome [6, 12]. The characteristics of our study population are similar to those of other published reports [4]. The percentage of patients in our group without syndromes was small and thus limited our ability to determine a difference in AVVR between the syndromic and nonsyndromic groups. Although 100 patients were initially identified for study, only approximately half met the criteria for inclusion. However, sub-analysis of the excluded showed similar characteristics to the subjects included.

The overall complication and mortality rates for patients with complete AV canal defects continue to be a significant challenge to providers despite fetal diagnosis [13]. In our study, the majority of patients with AV canal defects did not demonstrate a hemodynamically significant change in AVVR from fetal to postnatal life. Therefore, fetal echocardiography appears to be a good predictor of neonatal AV valve regurgitation in the majority of patients in this population. This documented trend in the natural history of AVVR enables physicians diagnosing the fetus with an AV canal defect to provide more accurate counseling for families. Further examination of the characteristics of a larger cohort of patients in whom a significant change in AVVR is noted may help elucidate additional mechanisms causing a change in this select group. These data would also allow for better identification and monitoring of patients at risk as well as a more accurate prognosis on an individualized level. The fetal-to-neonatal natural history of AVVR in other types of congenital heart defects in which valvulopathy plays a significant role in patient outcomes is also worthy of further study.

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Fig. 1.

Comparison of the distribution of prenatal and postnatal AVVR for patients within the study group. The *X-axis* represents the number of patients with a specific fetal grade of regurgitation, and the *Y-axis* represents the postnatal grade of regurgitation

Fig. 2.
Distribution of grades of AVVR from fetal and postnatal life by trisomy 21, heterotaxy, and neither-syndrome status

Table 1

Characteristics of five patients who showed a hemodynamically significant change in AVVR from fetal to postnatal life

Patient	Broad analysis	Syndrome	Type of AV canal	Ventricular balance	Rastelli class	Additional cardiac anomalies	Surgical repair	Outcome
A	1 → 2	Trisomy 21	Complete common AV canal	Balanced	Rastelli A	Conoventricular VSD	AV canal repair with conoventricular VSD closure	Followed-up as an outpatient
B	1 → 2	Trisomy 21	Complete common AV canal	Balanced	Rastelli C	None	N/A	Died before surgical repair
C	1 → 2	None identified	Complete common AV canal	Unbalanced	N/A	Moderate aortic arch hypoplasia with long-segment coarctation of the aorta	Aortic arch augmentation and pulmonary artery band	Died 2 mo after initial surgery
D	0 → 2	Trisomy 21	Complete common AV canal	Balanced	Rastelli C	RV outflow tract muscle bundle, mild hypoplasia of the aortic arch	AV canal repair, right ventricular muscle bundle resection (no arch intervention)	Followed-up as an outpatient
E	0 → 2	Heterotaxy	Complete common AV canal	Unbalanced	N/A	RV to aorta with pulmonary atresia; supracardiac obstructed TAPVR	Blalock–Tausig shunt, pulmonary arterioplasty, atrial septectomy, TAPVR repair	Died during the perioperative period

TAPVR total anomalous pulmonary venous return

Table 2

Change in percentage of fetuses with AVVR for the trisomy 21, heterotaxy, and no-syndrome groups

Change in AVVR	Trisomy 21	Heterotaxy	No syndrome
No change (%)	12 (60)	13 (68)	9 (90)
Increase (%)	7 (35)	3 (16)	1 (10)
Decrease (%)	1 (5)	3 (16)	0 (0)