Research Square

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Atrial distensibility predicts short-term prognosis in fetal single ventricle-type congenital heart disease with atrioventricular valve regurgitation

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Abstract

We aimed to determine whether the assessment of atrial distensibility helps predict perinatal outcomes in fetuses with a prenatal diagnosis of single ventricle-type congenital heart disease (SVCHD) with atrioventricular valve regurgitation (AVVR). We retrospectively identified 77 consecutive cases of fetuses with SVCHD examined between 2011 and 2023. Atrial distensibility and conventional echocardiographic parameters used to assess the severity of fetal heart failure were measured retrospectively. Fetuses with SVCHD were divided into two groups according to AVVR severity: no-mild or ≥moderate. The primary endpoint was the occurrence of composite adverse events (fetal demise, neonatal death of any cause, and early infantile valvuloplasty). The impact of atrial distensibility on prognosis was assessed using the receiver operating characteristic (ROC) curve analysis. Overall, 77 fetuses were diagnosed prenatally with SVCHD; 9 were terminated, and 8 were excluded due to chromosomal abnormalities. Of the 60 fetuses with SVCHD, 48 and 12 had no-mild and ≥moderate AVVR, respectively. Atrial distensibility was significantly lower in fetuses with SVCHD and ≥moderate AVVR than in those with no-mild AVVR ($p < 0.001$). Among fetuses with SVCHD and ≥moderate AVVR, atrial distensibility was impaired in fetuses with adverse events compared to those without adverse events ($p < 0.05$). ROC analysis indicated that atrial distensibility exhibited a significant predictive value for composite adverse outcomes in fetal SVCHD with ≥moderate AVVR (area under the curve 0.90; $p = 0.02$). Quantitative assessment of atrial distensibility may have clinical utility in predicting the perinatal outcomes of fetal SVCHD with significant AVVR.

Introduction

With improvements in perinatal management, the development of multistage palliation strategies, and surgery, outcomes in patients with single ventricle-type congenital heart disease (SVCHD) have improved dramatically in recent decades. However, high mortality is still observed in patients with SVCHD who have significant atrioventricular valve regurgitation (AVVR), and treating these patients remains challenging [1, 2]. Fetal SVCHD with AVVR is one of the highest-risk conditions, causing intrauterine heart failure (HF), fetal demise [3, 4], neonatal death [2], and neonatal HF requiring early atrioventricular valve repair [2]. As atrioventricular valve repair at first-stage palliation among patients with SVCHD is associated with high early mortality, some institutions consider this population suitable for heart transplantation or palliative care [2]. Given the significant impact of AVVR on clinical outcomes in fetuses with SVCHD, an accurate assessment of its impact on fetal circulation and predicting outcomes are crucial for providing appropriate counseling to families, determining the frequency of patient follow-up, delivery plan, post-birth strategy for AVVR, and overall prognostic assessment. However, early recognition of indicators of poor prognosis remains challenging.

Evidence for atrial function in modulating ventricular filling and ventricular performance has recently been growing. The left atrium (LA) plays a central role in the cardiac adaptive mechanism of mitral regurgitation (MR)-associated chronic HF in adults [5]. Atrial distensibility, reflecting LA reservoir function, also shows promise for evaluating ventricular filling pressure in patients with HF and for

predicting HF-related adverse outcomes [6–8]. Although published data have focused on some fetal ventricular functions as predictors of perinatal outcomes in fetuses with SVCHD, the efficacy of predicting perinatal outcomes remains conflicting [9, 10]. Evaluating atrial function may be important for determining the clinical outcomes of fetal SVCHD with AVVR. However, the role of atrial function in this population remains unclear.

In the present study, we aimed to determine whether there is an inherent difference in atrial function between fetal SVCHD with and without significant AVVR. Furthermore, we determined the association between perinatal outcomes and atrial distensibility in fetal SVCHD with AVVR. We hypothesized that impaired atrial function in fetal SVCHD with AVVR is associated with adverse perinatal outcomes.

Methods

Study design and population

This retrospective cohort study included 77 consecutive fetuses diagnosed with SVCHD during the fetal period between January 2013 and December 2023 at Nagano children's hospital, Nagano, Japan. SVCHD included both dominant right ventricular and dominant left ventricular lesions. Examples of dominant single RV (SRV) lesions include: hypoplastic left heart syndrome, unbalanced atrioventricular canal to the right ventricle. Examples of dominant single LV (SLV) lesions include: double-inlet LV, unbalanced atrioventricular canal to the left ventricle, tricuspid atresia, pulmonary atresia with intact ventricular septum. Fetuses with SVCHD and chromosomal abnormalities as well as terminated fetuses were excluded. Appropriately grown gestation-matched fetuses without structural or functional heart disease from normal pregnancies served as controls. This study was approved by the Research Ethics Committee of Nagano Children's Hospital (approval number: S-05-51).

Image acquisition and method of assessing atrial distensibility

Prenatal echocardiograms were obtained using the following ultrasound systems: GE Voluson E8, E10 ultrasound machine (GE Healthcare, Zipf, Austria) and Siemens Acuson S2000 ultrasound machine (Siemens Medical Solutions). In cases where multiple examinations of the same fetus were available, only the earliest serial studies with sufficient available images were analyzed. A single operator (Y.A.), blinded to the clinical data, performed all atrial area tracings of the patients. The apical four-chamber view was used for each patient. We traced the endocardial border of both atria as the entire common atrium. The 2D atrial area was measured immediately before AV valve opening (atrial area maximum, AA max) and immediately after AV valve closing (atrial area minimum, AA min), as shown in Fig. 1. The atrial distensibility was defined as (AA max- AA min) /AA min [6–8].

Other conventional echocardiographic parameters

Each selected echocardiographic study was retrospectively reviewed, and the following echocardiographic parameters were measured. AVVR was categorized as none, mild, with a narrow vena contracta (≤ 1/3 the valve annulus diameter), and ≥moderate with a wide color jet/vena contracta (> 1/3 the valve annulus diameter) [11]. To evaluate the diastolic component of the cardiac cycle, inflow velocities were assessed. Peak E and A wave velocities were measured and the E/A ratio was obtained [12]. Inflow time was corrected for cardiac cycle duration by dividing the measured inflow interval by the corresponding RR interval [13]. Ventricular systolic function was evaluated by ventricular fractional area change (FAC) [14]. Traditional echocardiographic parameters for assessing fetal HF, includingcardiothoracic area ratio (CTAR), presence of reversed end-diastolic velocity, presence of umbilical venous pulsations, and signs of fetal hydrops were assessed [15].

Clinical outcomes

Clinical outcomes in fetuses with SVCHD and significant AVVR were analyzed using predefined adverse clinical event criteria. An adverse clinical event was defined as any of the following: (1) fetal demise, (2) neonatal death, or (3) surgery for AVVR owing to HF within 2 months of birth. These events were analyzed as a composite outcome.

Statistical analysis

Demographic and echocardiographic measurements were compared using Student's *t* test or the Wilcoxon rank-sum test for continuous variables, depending on the distribution of the data. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values of atrial distensibility to predict outcomes as well as the area under the curve (AUC), sensitivity, and specificity. To evaluate the intraobserver agreement, the same observer (Y.A.) performed a second measurement after 3 months in 10 randomly selected fetuses. To evaluate the interobserver agreement, another observer (K.Y.) repeated the measurements. The intra- and inter-observer variabilities of atrial distensibility were evaluated using the intraclass correlation coefficient (ICC). Analyses were performed using GraphPad Prism 10.6.1 (GraphPad Software, La Jolla, CA) and SPSS statistics (version 31.0; IBM Corp., Armonk, NY). The significance level was set at $p < 0.05$.

Results

Clinical characteristics

A total of 77 consecutive fetuses with SVCHD were examined at our institution during the study period; of them, 9 were terminated, and 8 had fetal chromosomal abnormalities: 7 with 18 trisomy and 1 with 45 XO. Of the remaining 60 fetuses, 46 were diagnosed with dominant SRV lesions and 14 with dominant SLV lesions. The median gestational age at fetal diagnosis was 35.2 weeks (range: 21.4 to 39.3 weeks). Of these, three died in the fetal period, and five died in the neonatal period. The perinatal mortality rate

was 13.3%. Valvuloplasty for severe AVVR was performed in a fetal SVCHD with HF development within 2 months of age.

Among the 60 fetuses with SVCHD, ≥moderate AVVR was present in 12 (20%), mild AVVR was present in 10 (16.6%), and no AVVR was present in 38 (63%).

Of the 12 fetuses with ≥moderate AVVR (10 SRV and 2 SLV), 6 met the composite clinical outcome: 3 fetal demise, 2 neonatal death, and 1 valvuloplasty due to HF (Fig. 2).

Comparison of echo parameters between fetuses with SVCHD and controls

We evaluated whether echocardiographic parameters differed between fetuses with SVCHD and normal fetuses. Fetuses with SRV showed increased E, A wave velocities and decreased atrial distensibility compared to controls (Table 1). Both E and A waves velocities were significant higher in fetuses with SLV than in controls. There was no significant difference between SLV fetuses and controls for atrial distensibility Table 2. The E/A ratio, inflow duration and ventricular FAC values showed no significant differences between fetuses with SVCHD and controls (Table 1,2.

Table 1
Echocardiography parameters in normal fetuses and fetuses with prenatally diagnosed SRV

Parameter	**SRV (n = 46)**	**Normal right heart (n = 46)**	**p**
Gestational age at scanning (weeks)	34.3 ± 3.4	33.9 ± 3.1	0.33
Atrial distensibility	0.52 ± 0.24	0.62 ± 0.21	0.03
E (cm/s)	40.5 ± 11.5	35.2 ± 8.4	0.024
A (cm/s)	56.7 ± 16.2	49.3 ± 10.9	0.022
E/A	0.74 ± 0.24	0.72 ± 0.099	0.91
Inflow duration (normalized for RR interval)	0.41 ± 0.051	0.42 ± 0.059	0.63
Ventricular FAC	0.38 ± 0.087	0.37 ± 0.074	0.28
Data are presented as mean ± SD. SRV single right ventricle, FAC fractional area change			

Table 2
Echocardiography parameters in normal fetuses and fetuses with prenatally diagnosed SLV

Parameter	SLV (n = 14)	Normal left heart (n = 14)	p
Gestational age at scanning (weeks)	34.6 ± 5.1	34.6 ± 5.1	0.81
Atrial distensibility	0.57 ± 0.31	0.70 ± 0.19	0.19
E (cm/s)	40.6 ± 6.8	32.3 ± 10.9	0.0056
A (cm/s)	54.0 ± 12.5	41.8 ± 11.7	0.029
E/A	0.79 ± 0.27	0.79 ± 0.22	0.62
Inflow duration (normalized for RR interval)	0.48 ± 0.061	0.48 ± 0.041	0.58
Ventricular FAC	0.40 ± 0.10	0.42 ± 0.049	0.55
Data are presented as mean ± SD. SLV single left ventricle, FAC fractional area change			

Comparison of echo parameters between SVCHD with no-mild AVVR and SVCHD with ≥moderate

Findings in the 48 fetuses with SVCHD and no-mild AVVR were compared with those in 12 fetuses with SVCHD and ≥moderate AVVR. Gestational age at examination was lower for fetuses with ≥moderate AVVR than for those with no-mild AVVR (median 31.1 ± 5.2 vs 35.2 ± 3.0 weeks, p = 0.0061). Figure 3 shows the distribution of atrial distensibility for fetuses with SVCHD and no-mild AVVR and those with SVCHD and ≥moderate AVVR. Atrial distensibility of the SVCHD with ≥moderate group was significantly lower than that of the SVCHD with no-mild AVVR group (0.30 ± 0.17 vs 0.59 ± 0.24, p < 0.0001). We evaluated whether conventional metrics of ventricular systolic function, diastolic function, and the degree of fetal HF severity differed between the SVCHD with no-mild AVVR and SVCHD with ≥moderate AVVR groups (Table 3). Ventricular FAC was significantly lower in the SVCHD with ≥moderate AVVR group than in the SVCHD with no-mild AVVR group. Fetuses with SVCHD and ≥moderate AVVR had larger CTAR and higher frequency of both umbilical vein (UV) pulsation and fetal hydrops than fetuses with SVCHD and no-mild AVVR. Peak E, A wave velocities, E/A ratio and inflow duration did not differ between the groups. There was no significant difference in the number of umbilical artery reverse end-diastolic velocity between the two groups.

Table 3
Echocardiography parameters in fetuses with prenatally diagnosed SVCHD and no-mild AVVR versus ≥moderate AVVR

Parameter	AVVR no-mild (n = 48)	AVVR ≧ moderate (n = 12)	p
Gestational age at scanning (weeks)	35.2 ± 3.0	31.1 ± 5.2	0.0061
Atrial distensibility	0.59 ± 0.24	0.30 ± 0.17	< 0.0001
E (cm/s)	39.8 ± 10.2	43.7 ± 11.3	0.36
A (cm/s)	56.0 ± 13.7	56.2 ± 22.5	0.98
E/A	0.72 ± 0.11	0.92 ± 0.52	0.99
Inflow duration (normalized for RR interval)	0.43 ± 0.056	0.41 ± 0.077	0.55
Ventricular FAC	0.40 ± 0.09	0.33 ± 0.08	0.0088
CTAR (%)	31.2 ± 5.9	41.7 ± 8.1	0.0008
UA REDV	0/48	0/12	> 0.99
UV pulsations	1/48	3/12	0.023
Fetal hydrops	1/48	3/12	0.023

Data are presented as mean ± SD or as *n* (%). SVCHD single ventricle-type congenital heart disease, AVVR atrioventricular valve regurgitation, FAC fractional area change, CTAR cardiothoracic area ratio, UA REDV umbilical artery reverse end-diastolic velocity, UV umbilical vein

Association of atrial distensibility with clinical events among fetuses with SVCHD and ≥moderate AVVR

Among the included patients, 12 met the composite clinical outcome. Among fetuses with SVCHD and ≥moderate AVVR, the atrial distensibility was significantly reduced in SVCHD fetuses with composite outcomes than in those without (0.19 ± 0.07 vs 0.40 ± 0.17, p = 0.02, Fig. 4). There were no significant differences in the other echocardiographic parameters including peak E, A wave velocities, E/A ratio, inflow duration, ventricular FAC, CTAR, and UARI between the two groups. The frequency of UV pulsation and fetal hydrops were higher in fetuses with composite outcomes (Table 4). ROC curve analysis of atrial distensibility for predicting the composite endpoint is shown in Fig. 5. An atrial distensibility cutoff value of 0.24 had a high sensitivity (83.3%) and specificity (83.3%), with an AUC of 0.92 (95% confidence interval: 0.76 to 1.0) for predicting composite outcomes. Other echocardiographic parameters were not predictive of composite outcomes.

Table 4
Echocardiography parameters in fetuses with prenatally diagnosed SVCHD fetuses and ≥moderate AVVR according to the presence of clinical adverse events

Parameter	Event (-) (n = 6)	Event (+) (n = 6)	p
Gestational age at scanning (weeks)	32.9 ± 5.5	29.4 ± 4.7	0.26
Atrial distensibility	0.40 ± 0.17	0.19 ± 0.067	0.03
E (cm/s)	39.8 ± 11.8	48.6 ± 9.9	0.26
A (cm/s)	61.6 ± 11.6	49.4 ± 32.6	0.68
E/A	0.64 ± 0.10	1.28 ± 0.64	0.14
Inflow duration (normalized for RR interval)	0.41 ± 0.054	0.41 ± 0.11	0.97
Ventricular FAC	0.34 ± 0.072	0.32 ± 0.089	0.77
CTAR (%)	38.3 ± 6.8	45.0 ± 8.37	0.16
UA REDV	0/6	0/6	> 0.99
UV pulsations	0/6	3/6	0.18
Fetal hydrops	0/6	3/6	0.18

Data are given as mean ± SD or as *n* (%). SVCHD single ventricle-type congenital heart disease, AVVR atrioventricular valve regurgitation, FAC fractional area change, CTAR cardiothoracic area ratio, UA REDV umbilical artery reverse end-diastolic velocity, UV umbilical vein.

Intraclass correlation coefficients

The intraclass correlation coefficients for measuring atrial distensibility was evaluated in 10 randomly selected fetuses with SVCHD. The intraobserver agreement was 0.97 (95% CI 0.89 to 0.99), whereas the interobserver agreement was 0.89 (95% CI 0.63 to 0.97).

Discussion

To our knowledge, this study is the first to explore atrial function in fetuses with SVCHD. We demonstrated that fetuses with SVCHD and significant AVVR have impaired atrial distensibility compared with those without significant AVVR. Among fetuses with SVCHD and significant AVVR, those experiencing adverse clinical events had lower atrial distensibility than those without, and decreased atrial distensibility was prognostic for an increased risk of adverse clinical events in this population. Our study suggests that atrial distensibility is a useful biomarker associated with perinatal outcomes in fetal SVCHD with AVVR.

There is growing evidence on the contribution of atrial function to cardiac mechanics in various heart diseases. LA performance is associated with clinical outcomes in adult patients with MR. In patients

with MR, changes in LA volume during systole become minimal as the high LV filling pressure results in as much LA distension as possible during diastole [16]. Additionally, significant MR can accelerate LA remodeling, which leads to interstitial atrial wall fibrosis, causing progressively decreased LA compliance [17, 18]. Echocardiographic measurements like LA distensibility and LA reservoir strain have shown promise for evaluating LV filling pressure and reflecting LA compliance [7, 17, 19]. Although LA volume has been reported as a marker of adverse outcomes in chronic HF [20], LA reservoir strain could identify atrial dysfunction earlier, even before LA dilatation begins [21]. In this regard, LA reservoir function can be a sensitive marker for stratifying mortality risk and guiding the timing of cardiac surgery for MR [22, 23]. Similarly, the RA serves as a reservoir for systemic venous return and modulates the RV filling. Nishihara et al. demonstrated that right atrial (RA) reservoir strain is associated with adverse events due to HF in adults with significant tricuspid regurgitation (TR) [24]. Data on fetal atrial function in relation to AVVR are sparse. Howley et al. first reported that in fetuses with biventricular circulation, the RA reservoir function measured using velocity vector imaging in fetuses with severe TR was impaired and associated with fetal or neonatal demise [25]. However, to our knowledge, no studies have focused on atrial function in relation to AVVR in fetuses with SVCHD.

Although fetal ventricular functional measurements, including ventricular FAC, myocardial performance index, and ventricular strain, have been investigated in fetuses with SVCHD, whether impaired ventricular function has any prognostic effect on postnatal outcomes in this population remains controversial [9, 10]. In this study, FAC was decreased in fetuses with SVCHD and significant AVVR, but no association was observed between FAC and adverse perinatal outcomes in this population. To our knowledge, this is the first study to examine the association between atrial function and perinatal outcomes in fetal SVCHD with AVVR. While there are no studies on atrial function in fetuses with SVCHD, previous studies have reported the association between atrial function and clinical outcomes in patients with SVCHD with stage palliation status and post Fontan [26, 27]. Colquitt et al. demonstrated that reduced atrial reservoir strain was associated with death or heart transplantation in infants with a SRV before stage 2 palliation [26]. Among patients with SVCHD after the Fontan operation, increased atrial reservoir strain was associated with a higher cardiac index and inversely associated with composite clinical outcomes, including cardiac hospitalization, transplant and death [27].

In the circulation of fetuses with SVCHD, the atrium serves as a reservoir for both systemic and pulmonary returns to modulate single ventricular filling. Peak E and A wave inflow velocities were increased in fetuses with SVCHD compared to controls in our study. This is in line with the results of Axt-Fliedner et al. and Brooks et al. who found altered ventricular dysfunction with a strong reliance of ventricular filling on atrial function in both SRV and SLV fetuses [12, 13]. The hearts of fetuses with SVCHD have the inherent property of more altered ventricular relaxation and compliance than those of normal fetuses [28]. Due to this inherent lesser complaint of the ventricular myocardium, ventricular filling may be more dependent on atrial booster function [29]. Furthermore, significant AVVR results in volume overload on the atrium, eventually progressing to atrial remodeling with impaired atrial compliance, leading to reduced ventricular filling. In this study, we demonstrated that impaired atrial function is associated with adverse prognosis in this population. This observation suggests that the

atrium in fetuses with SVCHD may be important in buffering the regurgitant to keep low central venous pressure and adequate cardiac output. However, as the atrium becomes dysfunctional due to AVVR, it can no longer maintain its hemodynamics, leading to adverse clinical events.

Assessing the severity of fetal HF related to AVVR remains challenging. Our findings suggest that atrial function evaluation is useful for risk stratification with a high prognostic accuracy. Furthermore, assessing atrial function could guide counseling for parents and help decide early postnatal treatment strategy for high-risk fetuses. This parameter is readily measurable from clinical images using a standard echocardiography and has acceptable reproducibility. Additionally, the calculation of atrial distensibility requires neither special software nor specific training, providing an advantage over atrial strain measured using echocardiography for routine clinical use. Further prospective exploration of fetal atrial assessment as a prognostic tool for adverse outcomes in fetuses with SVCHD is warranted.

This study has some limitations. First, this was a small, retrospective, single-center study with inherent limitations. Future prospective multicenter studies with larger patient populations are warranted. Second, because fetal SVCHD with significant AVVR is relatively rare, our study included a limited sample size, which precluded an adequate multivariate regression analysis to assess the independence of our findings from other factors. Multivariate regression analysis is needed to determine whether atrial distensibility predicts perinatal outcomes in a future study. Third, mortality was ascertained by reviewing hospital records, and it was not possible to accurately separate cardiac and non-cardiac causes of death.

In conclusion, fetal SVCHD with significant AVVR impaired atrial distensibility, which was associated with perinatal adverse events. Quantitative assessment of atrial function may have clinical utility for risk stratification in this high-risk population.

Declarations

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Author Contributions YA and KT: contributed to the study design. YA: analyzed the data. YA: wrote the manuscript. YA and KY: collected the data. YS, RN, HO, and KT: gave critical comments and reviewed the manuscript. All authors read and approved the final version of the submitted manuscript.

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Data Availability The datasets generated and/or analyzed during the present study are not publicly available due to patient privacy concerns and institutional data use regulations but are available from the corresponding author on reasonable request and with permission from the institutional review board.

Conflict of interest The authors declare no competing interests.

Ethical Approval The Research Ethics Committee of the Nagano Children's Hospital approved this study (approval number: S-05-51).

Consent to Participate The requirement for informed consent was waived, and an opt-out approach was applied (patients were considered to have agreed to participate in this study unless they declined). Information regarding this study is available on the Nagano Children's Hospital website (https://nagano-child.jp/wordpress/wp-content/uploads/2016/08/S-05-51-.pdf)

Consent for Publication

The requirement for consent to publish was waived, and an opt-out approach was applied in accordance with the approval of the Research Ethics Committee of the Nagano Children's Hospital.

Informed Consent The requirement for informed consent was waived, and an opt-out approach was applied.

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Figures

Figure 1.

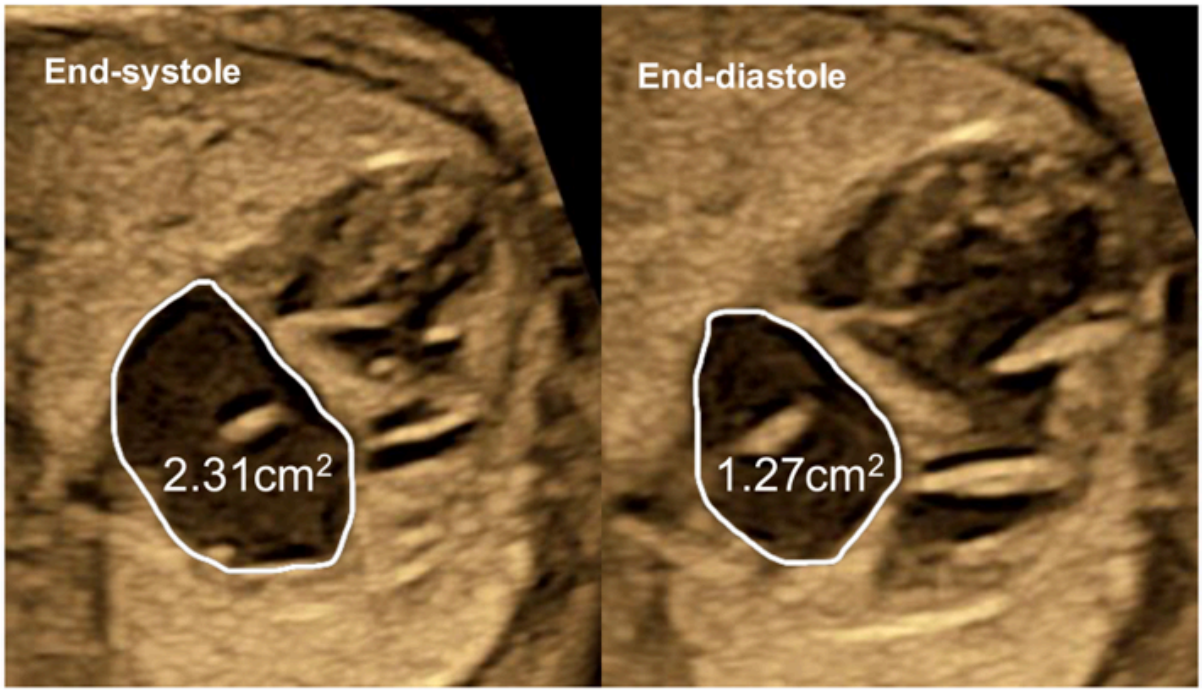


Figure 1

Prenatal echocardiography in a fetus with unbalanced atrioventricular canal to the right ventricle using Voluson E10. Using apical four-chamber view, maximum area of common atrium was 2.31cm^2 in end-systole and minimum area of common atrium was 1.27cm^2 in end-diastole. Atrial distensibility was calculated using the following formula: (2.31-1.27)/1.27=0.82.

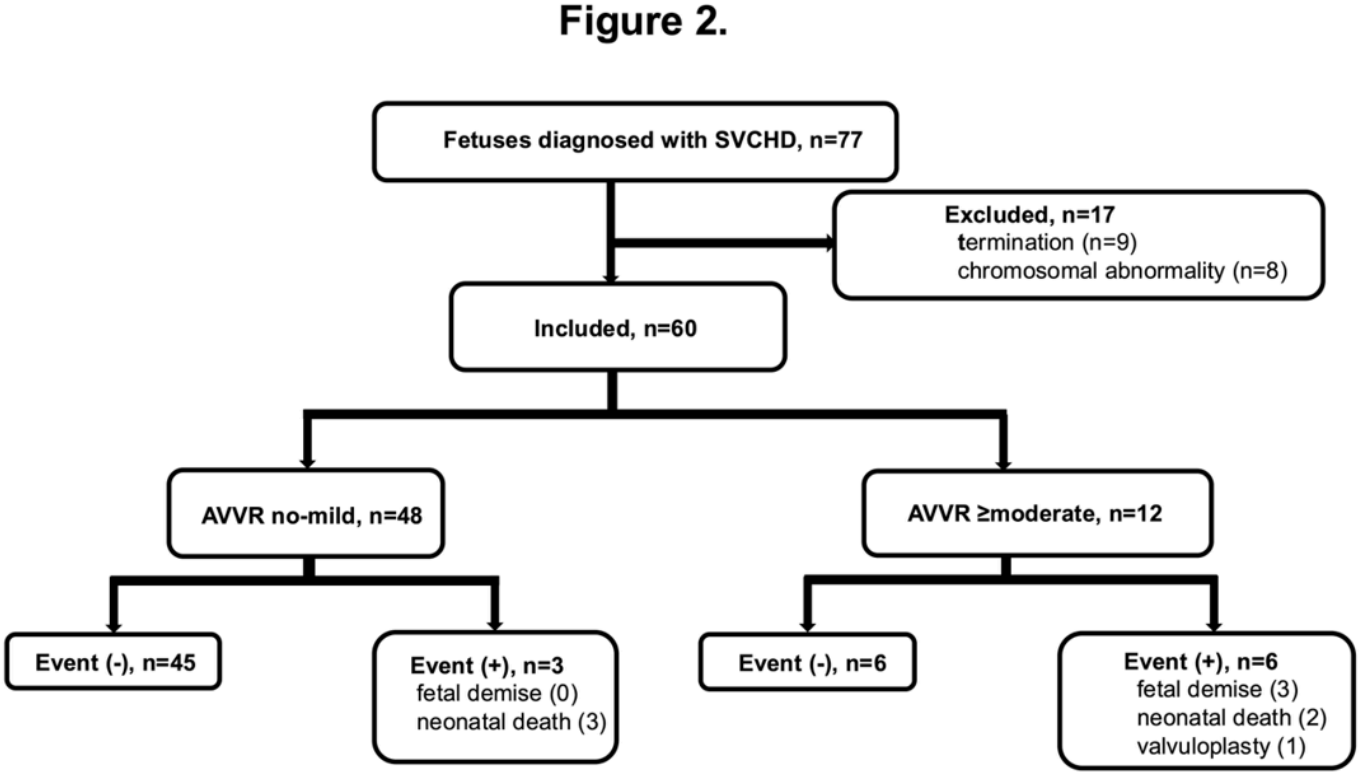


Figure 2

Flowchart summarizing the perinatal outcomes of fetuses diagnosed prenatally with single ventricle-type congenital heart disease (SVCHD) using fetal echocardiography.

SVCHD, single-ventricular type of congenital heart disease; AVVR, atrioventricular regurgitation

Figure 3.

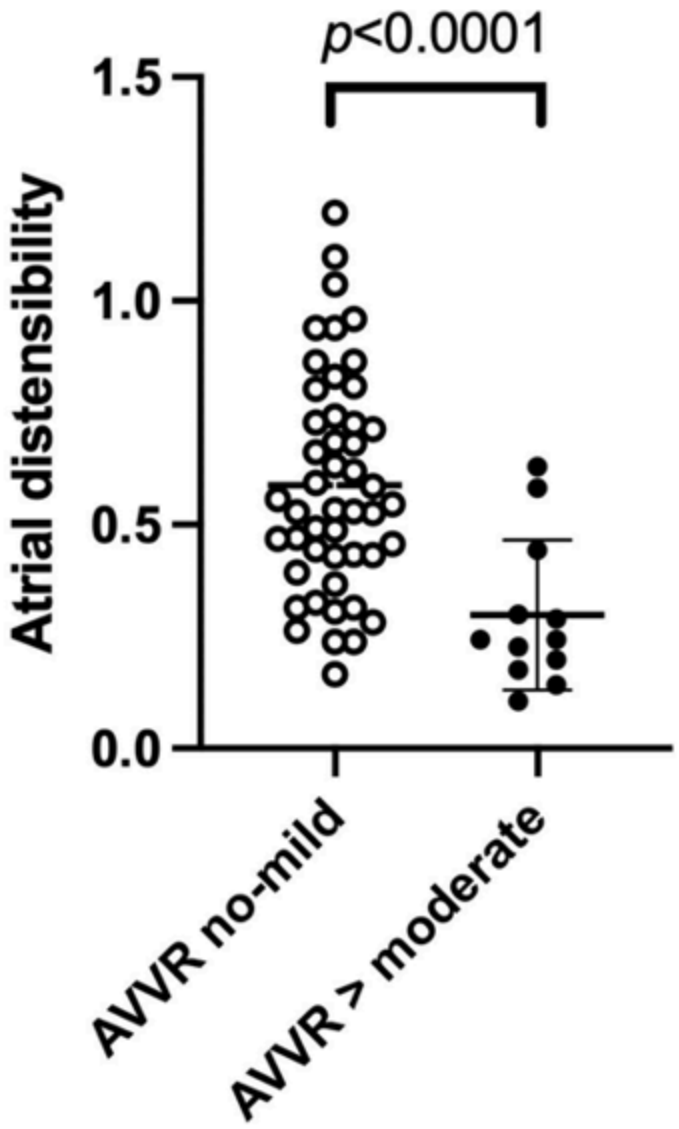


Figure 3

Atrial distensibility was lower in fetuses with single ventricle-type congenital heart disease (SVCHD) and ≥moderate atrioventricular regurgitation (AVVR) than in those with no-mild AVVR (p<0.0001).

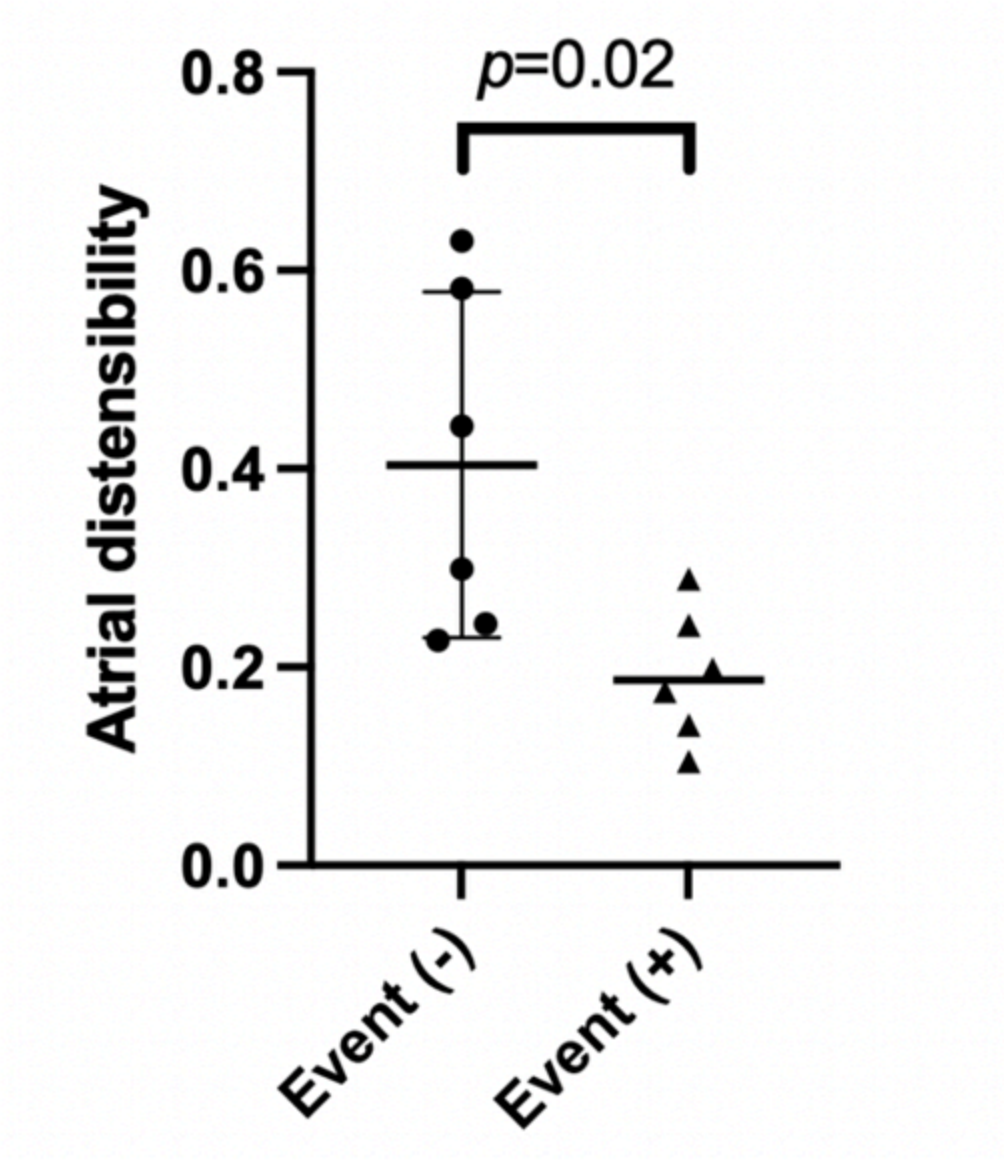


Figure 4

Atrial distensibility was lower in fetuses with single ventricular-type congenital heart disease (SVCHD) who experienced clinical adverse events than in those who did not (p=0.02).

Figure 5.

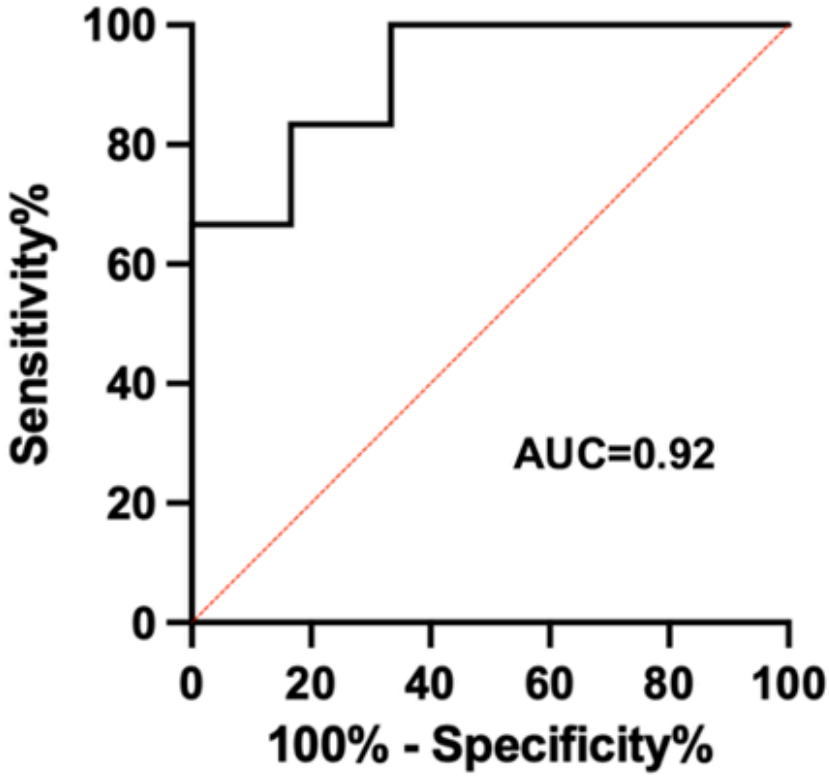


Figure 5

Among fetuses with single ventricle-type congenital heart disease (SVCHD) and atrioventricular regurgitation (AVVR), receiver operator characteristics analysis showed that atrial distensibility could distinguish fetuses with a clinical event from those without any event with a high degree of accuracy. Using the cutoff value of 0.24, sensitivity=83.3%, specificity=83.3% and AUC=0.92.