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Left Ventricular Diastolic Function and Characteristics in Fetal Aortic Stenosis

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Abstract

Fetal aortic valvuloplasty (FAV) has shown promise in averting progression of mid-gestation aortic stenosis (AS) to hypoplastic left heart syndrome in a subset of patients. Patients who achieve biventricular circulation after FAV frequently have left ventricular (LV) diastolic dysfunction (DD). This study evaluates DD in fetuses with AS by comparing echocardiographic indices of LV diastolic function in fetuses undergoing FAV (n=20) to controls (n=40) and evaluates for LV factors associated with DD in FAV patients. We also compared pre- and post-FAV DD variables (n=16). Median gestational age (24 weeks, range 18–29 weeks) and fetal heart rate were similar between FAV and controls. Compared to controls, FAV patients had universally abnormal LV diastolic parameters including fused mitral inflow E and A waves (p=0.008), higher E velocity (p<0.001), shorter mitral inflow time (p=0.001), lower LV lateral annulus E' (p<0.001), septal E' (p=0.003) and higher E/E' (p<0.001) than controls. FAV patients had abnormal right ventricular mechanics with higher tricuspid inflow E velocity (p<0.001), and shorter tricuspid inflow time (p=0.03). Worse LV diastolic function (lower LV E') was associated with higher endocardial fibroelastosis (EFE) grade (r=0.74, p<0.001), large LV volume (r=0.55, p=0.013) and sphericity (r=0.58, P=0.009) and with lower LV pressure by mitral regurgitation jet (r=-0.68, p<0.001). Post-FAV, fewer patients had fused mitral inflow E and A than pre-FAV (p=0.05) and septal E' was higher (=0.04). In conclusion, fetuses with mid-gestation AS have evidence of marked DD. Worse DD is associated with larger, more spherical LV, with more extensive EFE and lower LV pressure.

Keywords

Fetal cardiology; Aortic stenosis; Diastolic dysfunction

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Background

Fetal aortic balloon valvuloplasty (FAV) has shown promise in altering in utero progression of aortic stenosis (AS) to hypoplastic left heart syndrome^{1–4}. The postnatal course, including size of the left heart structures, left ventricular (LV) function, and surgical management, is variable in patients who have undergone FAV². Recent studies have reported promising results, with upwards of 35–40% of patients achieving a biventricular circulation^{2,4}. In children with other left heart obstructive lesions, including congenital AS and aortic coarctation, LV diastolic dysfunction (DD) is well described^{5–10}. Our previous work has shown DD in infants and children with biventricular circulation after FAV is common, more severe than isolated congenital AS and persists over medium term follow-up¹¹. DD in this patient population is a challenge as there are few management options and DD may limit some patient's ability to tolerate biventricular circulation. Timing of onset of DD, risk factors for DD and associations with other LV characteristics including LV size, geometry, pressure load and endocardial fibroelastosis (EFE), have not been well described. DD in patients with fetal AS has not been evaluated prenatally, but presumably occurs early in gestation and may be related to several factors including pressure-load on the LV leading to EFE and myocardial fibrosis, myocyte hyperplasia, decreased in utero flow through the LV resulting in altered myocardial compliance, and abnormal coronary blood flow^{12–18}. This study aims to evaluate DD in patients with fetal AS by comparing echocardiographic indices of LV diastolic function in fetuses with AS undergoing FAV to controls and to evaluate for LV factors associated with DD in FAV patients. Additionally, we compare pre-and post-FAV diastolic function variables to evaluate for acute change.

Methods

We retrospectively reviewed the records of the last 20 consecutive patients who underwent technically successful FAV between January 2010 and October 2013. Patient selection, technical performance and outcomes for FAV have been previously described^{1,2,4,19}. Echocardiograms from gestational age-matched control fetuses (n=40) with no structural or functional heart disease were used as controls. Reasons for fetal echocardiogram in the control group included: family history of heart disease (n= 28), increased nuchal thickness (n=3), suboptimal cardiac views on obstetrical screening (n=4), or other (n=5). Fetal echocardiograms were excluded in cases in which maternal or fetal systemic disease that could impact LV systolic or diastolic function was present (including maternal diabetes, lupus erythematosus, chromosomal anomalies). The Committee for Clinical Investigation at Children's Hospital Boston approved the use of patient medical records for this retrospective review.

All FAV patients had a pre-FAV echocardiogram on the day prior to FAV and a post-FAV echo (1–3 days post-FAV) included in the analysis. In the single case where 2 FAV were performed, only the second FAV was included in the analysis for both pre and post-FAV analysis. All fetal echocardiograms were performed using commercially available ultrasound equipment (Philips iE33, Koninklijke Philips Electronics, N.V) or Accuson Siemens Sequoia 512, Siemens Medical Solutions USA, Inc, Malvern PA).

Left-sided heart variables collected from reports produced at the time of the pre-FAV study included: end-diastolic volume (EDV), end-diastolic dimension, ejection fraction, aortic valve dimension, mitral valve dimension, and the z-scores for each of these variables. In our non-invasive imaging laboratory, LV EDV is calculated using the 5/6th area-length formula using 2D volumetric measurements. LV sphericity was calculated as the ratio of short-axis area to long-axis length. Mitral regurgitation (MR) jet gradient and aortic valve Doppler maximum instantaneous gradient were recorded. MR jet gradient > 20 mm Hg is a major criteria in our current selection process for FAV. EFE was qualitatively graded for all FAV patients by a single observer (KF) using a previously described 4-point scoring system in half unit increments: 0, none; 1, mild (scattered echogenic spots with the LV); 2, moderate (noncontiguous echogenic patches throughout the LV); and 3, severe (contiguous echogenic lining of the LV). Prior studies have shown moderate intra- and interobserver reproducibility using this scoring system²⁰.

Diastolic function assessment included pulsed-Doppler of the atrioventricular valve inflow and tissue Doppler imaging. All measurements of diastolic variables were retrospectively re-measured from images obtained at the time of the study. Conventional pulsed-Doppler indices of diastolic function, including peak early (E) and late (A) diastolic transmitral velocities, E:A ratio, and atrioventricular valve inflow duration were measured. To control for heart rate, mitral inflow was indexed as percentage of the cardiac cycle and as ratio of mitral to tricuspid inflow duration. Pulsed-wave tissue Doppler velocities were obtained from the lateral mitral annulus, the interventricular septum, and lateral tricuspid annulus from the apical 4-chamber view. Tissue Doppler tracings with an angle of interrogation 15 degrees from parallel were considered technically adequate. Tissue Doppler measurements for each myocardial segment included peak systolic velocity (S') peak early diastolic velocity (E') and peak late diastolic velocity (A'). Only tracings that demonstrated a clear E' were used. Each velocity was measured on 3 consecutive cardiac cycles and the average of these values was used for the analysis. E':A' and E/E' were calculated for all wall segments.

Median and range were used to express measures of central tendency and dispersion of data. Comparisons between FAV (pre-FAV echo) and control patients were evaluated using Mann-Whitney test. Comparisons between pre and post-FAV echo variables were performed using Wilcoxon signed rank test. Associations between LV characteristics and LV diastolic function parameters were evaluated. Associations between normally distributed continuous variables were assessed using Pearson correlation coefficients. Associations between ordinal variables (EFE grade) and continuous variables were assessed using Spearman correlation coefficients. Inter-observer agreement for two independent observers measurement of LV E' in 10 control fetuses, using Cronbach's alpha test showed good agreement (=0.862). All statistical analysis were 2-sided and type I error was controlled at a level of .05. Analyses were performed with SPSS (version 16.0, SPSS Inc, Chicago, Ill).

Results

Median gestational age at FAV was 22 weeks (range 19–29 weeks) and was similar to controls (23 weeks (18–28), $p=0.87$). One patient underwent FAV twice at 19 and 26 weeks. Pre-FAV left heart structural variables and z-scores are shown in Table 1. Systolic function

was severely depressed in 19 (95%) FAV patients and moderately depressed in one. All FAV patients had grade 1 or higher EFE with 15 (75%) having moderate or greater EFE. All patients had an estimate of LV pressure by MR jet (n=16) and/or aortic valve gradient (n=13). LV pressure-load was present in all patients with median MR jet gradient of 33 mm Hg and aortic valve gradient of 22 mm Hg with a wide range in degree of LV pressure elevation (MR jet range 20–70 mm Hg and aortic valve gradient range 10–58 mm Hg).

Compared to controls, FAV patients had universally abnormal mitral inflow and LV tissue Doppler diastolic function parameters (Table 2). FAV patients were more likely to have fused mitral inflow E and A waves (80% vs. 10 %, $p<0.001$), higher E velocity (0.49 vs. 0.27 m/sec, $p<0.001$) and shorter mitral inflow time (108 vs. 168 ms, $p=0.001$). FAV patients had lower LV lateral annulus E' (2.2 vs. 3.9 cm/sec, $p=0.001$) septal E' (2.4 vs. 3.2 cm/sec, $p=0.003$), and higher LV E/E' (19.1 vs. 7.8 cm/sec, $p<0.001$) than controls. FAV patients also had abnormal right ventricular mechanics with higher tricuspid E velocity (0.40 vs. 0.30 m/sec, $p<0.001$), shorter tricuspid inflow time (146 vs. 168 ms, $p=0.03$) and higher likelihood of tricuspid inflow E and A fusion (50% vs. 3%, $p<0.001$).

Higher EFE grade was associated with worse LV diastolic function (lower LV E' and higher E/E'). EFE grade had a strong inverse correlation with pre-FAV LV E' (Figure 1A) and positively correlated with E/E' ($r=0.56$, $p=0.012$). LVEDV z-score and LV sphericity were also significantly associated with LV E' and E/E'. Higher LV EDV z-score and more spherical LV correlated with lower LV E' (Figure 1B and 1C) and higher E/E' ($r=0.58$, $p=0.009$ and $r=0.59$, $p=0.009$, respectively). Higher pressure LV as measured by MR jet (Figure 1D) was associated with better LV diastolic function (higher LV E'). Higher LV pressure was also associated with less dilated and less spherical LV with the following inversely correlated to MR jet: LVEDV z-score (-0.74 , $p=0.001$) and LV sphericity (-0.65 , $p=0.005$). Figure 1, row A shows an example of fetus with normal LV size and sphericity, mild EFE, high MR jet velocity and high LV E'. Figure 1, row B is an example of a fetus with a dilated, spherical LV with high grade EFE and considerably lower MR jet velocity and LV E'.

Post-FAV, fewer patients had fused mitral inflow E and A than pre-FAV (80 vs. 47%, $p=0.05$) which was not attributable to change in heart rate (Table 3). Septal E' was higher post-FAV (2.8 vs. 2.3 cm/sec, $p=0.03$). There were no other acute changes in DD variables.

Discussion

In this study we show that fetal AS leads to significant alterations in diastolic function. DD occurs early in gestation and is present in mid-gestation fetuses undergoing FAV. Unlike DD in adults and children with AS, hypertrophy is not a contributing factor, as fetuses with severe AS universally have normal-sized or dilated LV with thin walls and normal or low mass:volume^{1,2,12,19,20}. Our results indicate that EFE is associated with DD and is may be a significant contributor to DD. In addition to EFE, myocardial fibrosis has been implicated as an etiology of diastolic dysfunction in other types of LV pressure-loading lesion and is likely a contributor to DD in this patient population^{16–18}. Other potential etiologies of DD in

fetuses with AS, include myocyte hyperplasia, intercellular changes within myocytes, and altered calcium handling^{12,13,21–23}.

Factors associated with worse diastolic function in fetuses with AS included higher LV volume and sphericity, more extensive EFE, and lower LV pressure. Previous work from our group has shown that LV pressure, specifically MR jet > 20 mm Hg, is an important predictor of postnatal biventricular outcome^{2,4}. This study informs both patient selection for FAV and pathophysiology of LV endomyocardial dysfunction in fetuses with AS. Although initially counterintuitive, we find that large LVs tend to be more spherical and have more EFE. In this study we show that these larger, more spherical and fibrosed LVs also generate lower pressure and have worse DD. The associations between worse DD, more EFE and a dilated, spherical, low-pressure LV may help to further define fetuses with AS who are unlikely to respond favorably to FAV. These associations also add to our understanding of the LV response to pressure load and suggest that timing of FAV is critical in order to alter the progression of fetal AS to a heavily fibrosed, low pressure, “burnt out” ventricle”. The pattern of increased LV dilation and sphericity, higher degree of EFE, lower pressure and worse diastolic dysfunction, as shown in Figure 2B, signals an LV that is less likely to be rehabilitated to support systemic circulation. On the opposite end of the spectrum, fetuses similar to the example in Figure 2A with AS and less EFE, higher LV E', higher LV pressure and less abnormal geometry may be more likely to respond well to FAV and may be more likely to achieve postnatal biventricular circulation.

In children with AS, relief of LV pressure load has been shown to improve diastolic function indices in most, but not all, patients^{8,10,14,24}. The degree to which relief of in utero pressure load alters diastolic mechanics is not clear. Immediately after FAV, there was improvement in septal E' and the percentage of patients with fused mitral inflow E and A decreased, both of which suggest an acute improvement in diastolic function. These post-FAV changes, along with data from adults and children showing improvement in DD after relief of LV pressure load, indicate that DD may be partially reversible^{8,10,14,17,18}. Different primary pathologic mechanisms in FAV patients (fibrosis) compared to children and adults with AS and other LV pressure-loading lesions (hypertrophy +/-fibrosis) may portend different responses to relief of pressure load. Follow-up data later in gestation, as well as comparison data from patients who underwent technically unsuccessful FAV, would be helpful in determining the effect of successful FAV on DD and potentially improving patient selection to target patients whose myocardium is more likely to respond favorably.

We have previously shown that DD is universal in FAV patients with biventricular circulation postnatally¹¹. DD is a significant clinical and management challenge. Despite normal LV size and reasonable LV systolic function postnatally, as well as effective valve surgery and ability to resect EFE when needed, many FAV patients struggle with clinical evidence of left atrial hypertension due to DD^{1,2,4}. Current patient selection for FAV relies on several factors including size of left heart structures, LV pressure, and EFE. A future approach incorporating DD parameters may improve patient selection and identify fetuses who are poor candidates due to concern for long-term DD.

Limitations of this study include the retrospective design and small cohort size. Lack of late gestation data on most patients and an insufficient number of true controls (technically unsuccessful FAV) limit our ability to assess the effect of FAV on DD. The small sample size also precludes ability to assess effect of fetal DD indices on postnatal ability to achieve biventricular circulation but we hope to evaluate this in future studies.

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Figure 1.

Scatterplots Evaluating LV Characteristics and Diastolic Function:

(A) Left Ventricle E' vs. Endocardial Fibroelastosis Grade (0–3)

(B) Left Ventricle E' vs. Left Ventricle End-Diastolic Volume z-score

(C) Left Ventricle E' vs. Left Ventricle Sphericity

(D) Left Ventricle E' vs. Mitral Regurgitation Jet Velocity

Figure 2.

Examples of Fetal Echocardiograms:

- A. Fetus with normal left ventricular end-diastolic volume and grade 1 EFE (panels 1,2), MR jet velocity ~ 4 m/s (panel 3), tissue Doppler left ventricular E' ~ 4 m/s (panel 4)
- B. Fetus with dilated, spherical left ventricle with grade 2–3 EFE (panels 1,2), MR jet velocity ~ 2 m/s (panel 3), left ventricle E' ~ 2.5 m/s (panel 4)

Table 1**Left Heart Variables in FAV Patients**

	FAV n=20
Aortic Valve (mm)	2.8 (2.4–4.0)
Aortic valve z-score	−2.8 (−3.9 to −1.2)
Mitral valve (mm)	6.3 (3.6–8.6)
Mitral valve z-score	−0.7(−2.8 to 3.5)
LV End-diastolic volume (ml)	2.5 (0.4 to 8.2)
LV End-diastolic volume z-score	1.9 (−1.9 to 5.1)
LV End-diastolic dimension (mm)	1.2 (0.5 to 2.0)
LV End-diastolic dimension z-score	1.2 (−2.6 to 6.2)
LV long axis dimension (mm)	1.8 (1.3 to 3.1)
LV long axis dimension z-score	0.5 (−1.7 to 4.8)
LV sphericity	0.69 (0.31–.81)
Ejection fraction (%)	24 (5–41)
Mitral regurgitation jet gradient (mm Hg)	33 (20–70)
Aortic valve gradient (mm Hg)	22 (10–58)
Aortic regurgitation grade (0–4)	0 (0–1)
Endocardial fibroelastosis grade (0–3)	2 (1–3)
Endocardial fibroelastosis moderate (n,%)	15 (75%)

FAV, fetal aortic valvuloplasty; LV, left ventricle

Table 2**Diastolic Function Parameters**

	FAV n=20	Controls n=40	p value
Fetal heart rate (beats/minute)	141 (120–156)	144 (120–157)	0.24
Mitral E (m/sec)	0.49 (.33–.78)	0.27 (0.17–0.48)	<0.001
Mitral A (m/sec)	0.46 (0.28–0.66)	0.42 (0.29–0.62)	0.21
Fused E:A (n, %)	16 (80%)	4 (10%)	0.008
E:A	0.8 (0.6–1.0)	0.6 (0.4–0.8)	0.12
Mitral inflow duration (ms)	108 (71–184)	168 (127–216)	0.001
Mitral inflow/cardiac cycle (%)	0.28 (0.17–0.42)	0.4 (0.28–0.50)	<0.001
Mitral inflow: tricuspid inflow	0.8 (0.6–1.0)	1.1 (0.9–1.2)	0.002
LV S' (cm/s)	3.6 (2.3–9.1)	4.0 (2.8–10.7)	0.19
LV E' (cm/s)	2.2 (1.8–6.6)	3.9 (2.9–6.4)	0.001
LV A' (cm/s)	3.5 (1.8–9.9)	5.8 (2.4–11.8)	<0.001
LV E/E'	16.9 (6.4–43.1)	7.5 (3.9–15.2)	<0.001
Septal S' (cm/s)	3.4 (2.0–7.1)	3.5 (2.3–7.1)	0.78
Septal E' (cm/s)	2.4 (1.6–5.6)	3.2 (1.8–7.0)	0.003
Septal A' (cm/s)	3.8 (2.0–8.6)	4.6 (3.2–9.1)	0.20
Septal E/E'	19.1 (6.4–36.6)	7.8 (3.4–15.3)	<0.001
Tricuspid E (cm/s)	0.40 (0.25–0.77)	0.30 (0.17–.56)	<0.001
Tricuspid A (cm/s)	0.52 (0.36–0.72)	0.44 (0.30–0.63)	0.005
Tricuspid inflow duration (ms)	146 (87–186)	168 (113–227)	0.03
RV S' (cm/s)	5.5 (3.2–11.0)	4.5 (2.2–7.3)	0.43
RV E' (cm/s)	4.3 (3.1–10.8)	4.5 (2.4–8.0)	0.63
RV A' (cm/s)	7.3 (4.9–11.3)	7.2 (3.1–11.9)	0.87
RV E/E'	8.5 (4.0–20.7)	7.1 (4.0–12.3)	0.41

FAV, fetal aortic valvuloplasty; E, mitral inflow early velocity; A, mitral inflow atrial velocity; LV, left ventricle; S', systolic tissue Doppler velocity; E' early diastolic tissue Doppler velocity; A' late diastolic tissue Doppler velocity; RV, right ventricle

Table 3

Pre and Post-FAV

	Pre-FAV n=20	Post-FAV n=20	p value
Fetal heart rate (beats/minute)	143 (120–156)	147 (135–170)	0.31
Mitral E (m/sec)	0.49 (.33–.78)	0.41 (0.29–0.69)	0.33
Mitral A (m/sec)	0.47 (0.28–0.66)	0.54 (0.35–0.82)	0.10
Fused E:A (n, %)	12 (80%)	7 (35%)	0.05
E:A	0.8 (0.6–1.0)	0.6 (0.6–0.9)	0.31
Mitral inflow duration (ms)	114 (77–184)	128 (82–176)	0.32
Mitral inflow/cardiac cycle (%)	0.28 (0.17–0.42)	0.35 (0.20–0.51)	0.16
Mitral inflow:tricuspid inflow	0.8 (0.6–1.0)	0.9 (0.7–1.3)	0.03
LV S' (cm/s)	3.4 (2.1–8.9)	3.3 (2.0–8.1)	0.98
LV E' (cm/s)	2.7 (2.1–6.6)	3.0 (2.2–7.2)	0.29
LV A' (cm/s)	3.6 (1.8–9.9)	3.1 (1.8–9.7)	<0.82
LV E/E'	16.3 (6.0–42.6)	12.0 (5.2–30.7)	0.13
Septal S' (cm/s)	3.3 (2.0–7.1)	3.1 (1.7–5.4)	0.99
Septal E' (cm/s)	2.3 (1.6–5.6)	2.8 (1.8–6.9)	0.04
Septal A' (cm/s)	3.5 (2.0–8.6)	3.3 (1.9–7.2)	.99
Septal E/E'	20.4 (6.4–36.6)	12.2 (7.1–31.6)	0.15
Tricuspid E (cm/s)	0.40 (0.25–0.77)	0.56 (0.31–.84)	0.18
Tricuspid A (cm/s)	0.52 (0.36–0.72)	0.50 (0.30–0.70)	0.83
Tricuspid inflow duration (ms)	146 (87–186)	133 (96–175)	0.23
RV S' (cm/s)	5.5 (3.2–11.0)	5.4 (3.1–10.8)	0.59
RV E' (cm/s)	4.3 (3.1–10.8)	4.8 (2.2–8.3)	0.54
RV A' (cm/s)	7.3 (4.9–11.3)	7.0 (3.0–14.1)	0.89
RV E/E'	8.5 (4.0–20.7)	8.2 (4.9–37.8)	0.84

FAV, fetal aortic valvuloplasty; E, mitral inflow early velocity; A, mitral inflow atrial velocity; LV, left ventricle; S', systolic tissue Doppler velocity; E' early diastolic tissue Doppler velocity; A' late diastolic tissue Doppler velocity; RV, right ventricle