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Left Ventricular Remodeling and Function in Children with Biventricular Circulation after Fetal Aortic Valvuloplasty

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Abstract

Background: Fetal aortic valvuloplasty (FAV) has shown promise in averting the progression of fetal aortic stenosis to hypoplastic left heart syndrome. Altered loading conditions due to valvar disease, intrinsic endomyocardial abnormalities, and procedures that alter endomyocardial mechanics may place patients with biventricular circulation (BiV) after FAV at risk for abnormal LV remodeling and function.

Methods: Using the most recent echo data on BiV patients after technically successful FAV (n=34) we evaluated LV remodeling pattern, risk factors for pathologic LV remodeling, and the association between LV remodeling pattern and LV function.

Results: Median age at follow up was 4.7 years (range 1.0–12.5). Cardiac interventions were common. At latest follow-up, no patient had hypoplastic LV. Nineteen patients (55%) had dilated LV and 5 (16%) patients had severely dilated LV. LV remodeling patterns were: 12 (35%) normal ventricle, 11 (32%) mixed hypertrophy, 8 (24%) eccentric hypertrophy or remodeling, and 3 (9%) concentric hypertrophy. Univariate factors associated with pathologic LV remodeling were long-standing AR, ≥ 2 cardiac interventions, EFE resection, and aortic or mitral regurgitation moderate at most recent follow-up. In multivariate analysis only long-standing AR fraction remained associated with pathologic remodeling. Pathologic LV remodeling was associated with depressed ejection fraction, lower septal E₁' and higher E/E₁'.

Conclusion: Pathologic LV remodeling, primarily eccentric or mixed hypertrophy, is common in BiV patients after FAV and is related to LV loading conditions imposed by valvar disease. Pathologic remodeling is associated with both systolic and diastolic dysfunction in this population.

Keywords

Fetal cardiology; Aortic stenosis; Left ventricular remodeling; Diastolic dysfunction

Background:

Fetal aortic valvuloplasty (FAV) is an evolving technique that has shown promise in averting progression of in utero aortic stenosis to hypoplastic left heart syndrome (HLHS) with ~ 40–50% of patients achieving biventricular (BiV) circulation after technically successful FAV^{1–4}. Patients with BiV circulation frequently undergo multiple cardiac interventions and long-term outcomes remain uncertain³. Left-sided valvar disease can be effectively managed with surgery in most cases, but the long-term fate of the left ventricular (LV) myocardium is less certain^{3,5}. BiV patients are at risk for abnormal LV remodeling and mechanics due to altered loading conditions imposed by valvar disease, intrinsic endomyocardial abnormalities, and procedures that alter endomyocardial mechanics, primarily endocardial fibroelastosis (EFE) resection^{6–8}. Long-standing volume load on the LV due to valvar regurgitation has been well-described in both adults and children as a cause of LV remodeling characterized by LV dilatation and eccentric hypertrophy⁹. Pressure load on the LV causes concentric hypertrophy with increase in LV mass and mass:volume⁹. Patients with BiV circulation after technically successful FAV often have both pressure and volume load on the LV of variable severity and duration. BiV patients also have intrinsic endocardial and myocardial abnormalities and diastolic dysfunction^{6,10}. Additionally, many undergo EFE resection as part of LV recruitment strategy and this likely alters endomyocardial mechanics^{3,5,11}. To date, the frequency and severity of changes in LV architecture in this unique group of patients has not been described. Additionally, factors associated with pathologic LV remodeling and the relationship between pathologic LV remodeling and LV dysfunction in patients with BiV after technically successful FAV have not been evaluated. In this study we aim to describe LV remodeling pattern in patients with biventricular circulation after FAV and to identify risk factors for pathological remodeling. Additionally, we evaluate the association between pathological LV remodeling and LV systolic and diastolic function.

Methods:

Patients

Patients at our institution who underwent technically successful FAV for evolving HLHS with a BiV circulation at most recent follow-up and age ≥ 1 year were included. Technical aspects, selection criteria, and clinical outcomes after FAV have been previously published^{1–3, 12, 13}. The current investigation evaluates the same cohort of patients as a recent review of clinical outcomes after FAV³, but focuses exclusively on LV characteristics in this cohort. Patients < 12 months of age (n=5) and those who underwent FAV at this institution but have had all of their subsequent care at an outside institution and who do not have recent echocardiograms in our database were excluded (n=1). Demographic and clinical characteristics were collected from the medical record.

Echocardiograms

All available postnatal echocardiogram reports were reviewed for each patient through May 1st, 2014. The most recent complete echocardiogram was included in the analysis. Aortic stenosis (AS) gradient and aortic regurgitation (AR) grade were collected from reports

produced at the time of the study. We defined moderate AS as a Doppler gradient > 40 mm Hg using the higher value of the maximum instantaneous gradient from the apical imaging window or mean gradient from the suprasternal notch window^{14–15}. AS was considered long-standing if moderate AS was present for 1 year. In our echo lab, AR is qualitatively graded on a 4 point ordinal scale (0=none, 1=trivial, 2=mild, 3=moderate, 4=severe) by $\frac{1}{2}$ unit increments based on a combination of previously published schema^{15–17}. AR was considered long-standing if moderate AR was present for 1 year. The following LV parameters and their respective z-scores were recorded: end-diastolic volume (EDV), mass, mass:volume, and ejection fraction (EF). LV EDV was calculated using the $\frac{5}{6}$ th area-length formula and LV mass using volumetric 2D measurements. LV remodeling pattern was classified based on previously established criteria⁹ as: normal ventricle (normal mass, volume, and mass:volume), concentric remodeling/hypertrophy (normal LV volume, high LV mass, and/or mass:volume), eccentric remodeling (high volume, normal mass, and low mass:volume), eccentric hypertrophy (high volume, high mass, and low mass:volume), or mixed/physiologic hypertrophy (high mass, high volume with normal or high mass:volume). All remodeling patterns except for normal ventricle were considered pathologic in the analysis. Right ventricular (RV) pressure evaluation included tricuspid regurgitant jet velocity when sufficient tricuspid regurgitation was present and systolic septal configuration. RV pressure was considered elevated if tricuspid regurgitation jet velocity predicted RV pressure ≥ 40 mm Hg plus the right atrial v-wave or if systolic septal configuration indicated RV pressure $> \frac{1}{2}$ systemic pressure. Examinations were performed using commercially available ultrasound equipment (Philips iE33, Koninklijke Philips Electronics, N.V.).

Diastolic variables from most recent echocardiogram were retrospectively re-measured by a single echocardiographer from images obtained at the time of the study (KF). Standard mitral valve inflow pulsed-Doppler indices of diastolic function, including peak early (E) and late (A) diastolic transmitral velocities, E:A, and E-wave deceleration time were measured. Pulsed wave tissue Doppler velocities were obtained from the lateral mitral annulus and the interventricular septum from the apical 4-chamber view. Tissue Doppler measurements for each myocardial segment included 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 value was used. Peak early mitral inflow velocity/early mitral tissue Doppler velocity (E/E') was calculated. Z-scores for diastolic function variables derived from normative data at our institution.

Fetal Echocardiograms

All patients had a pre-FAV echocardiographic data collected from the clinical reports produced at the time of the study. The following fetal LV characteristics and the z-scores for each value were included: LV end-diastolic dimension (EDD), shortening fraction, and sphericity (calculated as the ratio of short-axis area to long-axis length). Mitral regurgitation (MR) velocity and aortic valve Doppler maximum instantaneous gradient were recorded. MR jet gradient > 2.2 m/s has emerged as a major criterion in our current selection process for FAV². Fetal LV pressure was categorized into 3 groups: 1= low pressure (MR jet velocity < 2 m/s), 2= moderate pressure (MR jet velocity 2–2.5 m/s), and 3= high pressure (MR jet velocity > 2.5 m/s). EFE was qualitatively graded for all FAV patients by a single observer

(KF) using a previously described 4-point scoring system¹¹ in half unit increments: 0, none; 1, mild (scattered echogenic spots within 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 system¹¹. 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).

Statistics

Median and range were used to describe continuous variables. Using the most recent echo data on BiV patients, we classified LV remodeling pattern. For patients with pathologic remodeling, the date of the first echocardiogram showing pathological remodeling was recorded and used to construct Kaplan-Meier curves to evaluate survival-free from pathologic LV remodeling. Logrank p test was used to evaluate for univariate factors associated with pathological remodeling. Cox multivariate models were created to evaluate for factors associated with pathological remodeling. Associations between left ventricular function and LV remodeling pattern were assessed using chi square test for binary variables and Wilcoxon rank-sum test for continuous variables. All statistical analyses were 2-sided and controlled at a level of 0.05. Analyses were performed using IBM SPSS Statistics version 20 for Windows (IBM, Armonk, NY).

Results:

In the cohort of 34 patients, median age at follow up was 4.7 years (range 1.0–12.5 yrs.). Prior cardiac interventions and current clinical status of this cohort have been recently described³. Cardiac interventions were common (Table 1).

LV characteristics and valvar function at most recent follow-up are shown in Table 2. At latest follow-up, no patient had a hypoplastic LV. Median LV end-diastolic volume z-score was 2.1 (range –1.3 to 7.8). Nineteen patients (55%) had dilated LV (EDV z-score > 2) and 5 (16%) patients had severely dilated LV (EDV z-score > 4). EF was normal (>55%) in 28 patients (83%) with median of 59% (range: 40–77%). RV hypertension was present in 13 (37%).

LV remodeling patterns were: 12 (35%) normal ventricle, 11 (32%) mixed hypertrophy, 8 (24%) eccentric remodeling (n=6) or hypertrophy (n=2), and 3 (9%) concentric hypertrophy. Of the 3 patients with concentric hypertrophy, 2 had undergone aortic valve replacement < 3 months prior and had mixed hypertrophy preoperatively with increased volume and mass. Post-operatively, with removal of AR and volume load, LV EDV decreased but LV mass remained elevated resulting in concentric hypertrophy in both patients. One patient with concentric hypertrophy was a 2 year-old with residual aortic stenosis with moderate to severe residual AS (maximum instantaneous gradient of 60 mm Hg).

Univariate factors associated with pathologic LV remodeling were long-standing AR, 2 cardiac interventions, EFE resection, and aortic or mitral regurgitation moderate at most recent follow-up (Table 3). No fetal or initial postnatal echo parameters, including LV size,

pressure and EFE grade on fetal echo, were associated with pathologic remodeling. Figure 1 shows Kaplan-Meier curves for survival-free from pathologic remodeling for the entire cohort (panel A) and based on individual risk factors (panels B-D). In multivariate analysis only long-standing AR (HR= 2.8 [1.2–8.1], p=0.026) remained independently associated with pathologic remodeling.

Pathologic remodeling was associated with worse LV systolic function (Table 4). Median EF in normal ventricle group was 65 % (range 55–77%) compared to 57 % (range 42–70%) in pathologic remodeling group (p= 0.011). All patients in normal ventricle group had EF ≥ 55% while 6 (24%) in the pathologic remodeling group had EF < 55% (p=0.022). Diastolic dysfunction was common (Table 4) and associated with pathologic remodeling. In the entire cohort, septal E' z-score was < -2 in 30 patients (88%), mitral annular E' z-score was < -2 in 22 patients (65%). In patients with pathologic remodeling, 100% had an abnormal septal E' (z-score < -2) compared to 6 patients (50%) with normal ventricles (p=0.009). E/Septal E' and E/septal E' z-score were higher in patients with pathologic remodeling than in those with normal ventricles.

Discussion:

Pathologic remodeling consisting primarily of LV dilation with or without increase in LV mass resulting in eccentric remodeling/hypertrophy or mixed hypertrophy is common in patients with BiV circulation after FAV. We found that LV volume load imposed by valvar disease is associated for pathologic LV remodeling. Pathologic LV remodeling in this patient population is associated with systolic and diastolic dysfunction.

Patients with BiV circulation after FAV have diffuse LV pathology including mitral and aortic valve disease and LV endocardial and myocardial abnormalities^{3,6,11,18,19}. Valve disease can often be managed with current surgical approaches^{3,5}, but the long-term fate of LV myocardium is less certain and needs to be a focus of both postnatal patient management and prenatal patient selection. Long-standing volume load due to AR contributes to pathologic LV remodeling and pathologic remodeling is associated with severity of LV systolic and diastolic function. This finding suggests that an aggressive approach to valve surgery and replacement, particularly in the presence of AR, may be a critical part of maintaining the integrity of myocardial structure and function and should be an important consideration in timing of surgical intervention in this patient population.

Patients with long-standing AR and pathologic LV remodeling were more likely to have systolic and diastolic dysfunction. While valvar disease appears to be primarily responsible for pathological remodeling the causes of LV dysfunction are likely multifactorial and are less clear. Diastolic dysfunction is likely associated with intrinsic LV endomyocardial characteristics such as EFE and myocardial fibrosis which are largely influenced by severity of in utero disease, but is also likely affected by postnatal LV volume and pressure load and postnatal interventions including EFE resection^{8,10,20}. Our results indicate that LV function and pathologic remodeling are interrelated and likely identify patients with worse disease including more severe valve disease, increased EFE burden, and therefore more cardiac interventions. The unique combination of in utero AS, followed by AR postnatally, which is

common in this cohort, may lead to distinct and deleterious effects on myocardial development, structure, and function.

Although, we were unable to identify prenatal factors associated with postnatal pathologic remodeling and diastolic dysfunction in this analysis, we hope in the future to identify fetal characteristics that are associated with postnatal LV dysfunction and incorporate these into FAV selection criteria. Recent work looking at diastolic dysfunction in fetal AS has shown worse fetal LV diastolic function is associated with other fetal LV characteristics that suggest the LV myocardium is less likely to recover after FAV, including low LV pressure, more EFE, more LV dilation, and increased sphericity¹⁰.

While eccentric and mixed remodeling/hypertrophy were common in this cohort, concentric remodeling was uncommon with only 1 patient having chronic concentric hypertrophy. This likely reflects current practice pattern for infants and children with aortic valve disease. LV pressure load due to AS is typically aggressive and effectively treated with balloon angioplasty, sometimes at the cost of volume load due to AR²¹. Volume load due to AR is harder to deal with, as surgical options are limited, particularly in young children, and all options (aortic valvuloplasty, Ross procedure or aortic valve replacement) have limitations. Reluctance to refer to surgery due to limited options as well as limited durability of surgical aortic valvuloplasty results in patients being more likely to be left with long-standing volume load rather than pressure load. This practice pattern is similar to the management trends in isolated congenital AS²¹. Adult criteria for valve replacement in isolated AR, recommend valve replacement when patients are symptomatic or the LV is severely dilated and has systolic dysfunction²². These criteria are not applicable to infants and children for several reasons including size and growth considerations and the frequency of mixed aortic valve disease and/or other left heart disease in younger patients. As such, optimal timing for aortic valve surgery/replacement in in this patient population as well as those with isolated congenital AS remains uncertain.

Further investigation is needed to determine the effect of EFE resection on LV remodeling and LV function. We found EFE resection to be associated with pathologic remodeling in univariate modeling but not in multivariate models. EFE resection was performed more frequently in patients with a heavier burden of disease including patients with more valvar disease, more cardiac interventions, and likely with worse intrinsic LV mechanics. In a previously reported small group of older patients with isolated congenital AS who developed diastolic dysfunction and had EFE, significant improvement in diastolic function was reported after EFE resection⁸. Improvement in diastolic function and increased capacity for LV growth in patients with borderline LV have been the rationale for EFE resection^{5,23}, but there are at least theoretical concerns that removal of EFE in the setting of volume load due to valve disease may allow LV dilation and pathologic remodeling due to removal of supporting endocardial tissue exposing a vulnerable myocardium.

This study is limited by the cross-sectional design and therefore variable follow-up duration, particularly in regards to LV remodeling which is dynamic and changes over time. Additionally, few patients have long-term follow-up due to this being a relatively new intervention. Management patterns in BiV patients have evolved over time towards a more

aggressive approach to valve pathology and this may result in an overestimate of prevalence of late pathological remodeling. The lack of identifiable prenatal risk factors for late pathologic remodeling, which may help refine patient selection in the future, may have been due to limited sample size. Lastly, for analysis purposes, EFE resection was a binary variable (i.e., performed or not performed) but, in reality, the degree of EFE resection varies greatly depending on patient size, surgeon's experience and other factors.

In conclusion, pathologic LV remodeling, primarily eccentric or mixed hypertrophy, is common in BiV patients after FAV and is related to LV loading conditions imposed by valvar disease. Pathologic remodeling is associated with both systolic and diastolic dysfunction in this population.

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Figure 1.

Kaplan- Meier Curves for Freedom for Pathologic Remodeling: A. Entire cohort B. Long-standing aortic regurgitation C. Moderate mitral and/or aortic regurgitation at most recent follow-up D. Endocardial fibroelastosis resection

Table 1.

Clinical Characteristics

	All patients n=34
Gestational age at FAV (weeks) (median, range)	23 (20–30)
Male	28 (82%)
Age at follow-up (years) (median, range)	4.7 (1.0–12.5)
Weight (kg) (median, range)	17.6 (7.3–53.5)
Number of cardiac interventions (n, range)	3 (0–10)
Balloon aortic valvuloplasty	29 (85%)
Balloon mitral valvuloplasty	6 (18%)
Surgical aortic valvuloplasty	18 (53%)
Aortic valve replacement or Ross	15 (44%)
Mitral valve surgery	19 (54%)
Mitral valve replacement	8 (24%)
Endocardial fibroelastosis resection	20 (59%)
# of EFE resection (n, range)	1 (0–3)
Biventricular conversion	6 (18%)
Long-standing aortic regurgitation ^a	11 (32%)
Long-standing mitral regurgitation ^a	6 (18%)
Long-standing aortic stenosis ^a	14 (41%)

FAV, fetal aortic valvuloplasty; EFE, endocardial fibroelastosis

All values are n, % unless otherwise specified

^aLong-standing valve disease defined as moderate valve disease for ≥ 1 year

Table 2.**Echocardiographic Characteristics**

Pre-FAV fetal echocardiogram	n=34
LV end-diastolic dimension z-score	2.9 (−0.8 to 16.10)
LV end-diastolic volume z-score	2.5 (−1.7 to 23.5)
Ejection fraction (%)	21 (10–55)
Mitral regurgitation jet velocity (mm Hg)	37 (10–93)
LV pressure category (1–3)	2 (1–3)
Endocardial fibroelastosis grade (0–3)	2 (1–3)
Most recent postnatal echocardiogram	n=34
LV end-diastolic dimension z-score	2.1 (0.1 to 7.0)
LV end-diastolic volume z-score	2.1 (−1.3 to 7.8)
LV mass z-score	1.5 (−1.4 to 7.9)
LV mass:volume	0.9 (0.5 to 1.5)
LV mass:volume z-score	−0.5 (−3.1 to 4.1)
Ejection fraction (%)	59 (40–77)
Ejection fraction < 55% (n,%)	6 (18%)
Aortic regurgitation (0–4)	1 (0–4)
Aortic regurgitation moderate (n,%)	7 (21%)
Aortic stenosis maximum instantaneous gradient (mm Hg)	17 (0–75)
Aortic stenosis moderate (n, %)	4 (12%)
Mitral regurgitation (0–4)	1 (0–3)
Mitral regurgitation moderate (n,%)	3 (9%)
Elevated left ventricular pressure (n,%)	13 (38%)

FAV, fetal aortic valvuloplasty; LV, left ventricle

All values are median, range unless otherwise specified.

Table 3.**Risk Factors for Pathologic LV Remodeling**

Univariate Analysis	Hazard Ratio [Confidence Interval]	p-value
Fetal Characteristics		
Gestational age at FAV >24 weeks	0.7 [0.3–1.9]	0.53
LV EDV z-score >2 on fetal echo	0.6 [0.18–1.5]	0.22
Moderate or greater EFE on fetal echo	1.4 [0.5–3.9]	0.50
Ejection fraction < 30% on fetal echo	1.6 [0.5–5.1]	0.42
High LV pressure on fetal echo ^a	0.6 [0.19–1.8]	0.33
Demographic and Clinical Factors		
Age ≤ 5 years	2.4 [0.8–7.5]	0.14
Number of cardiac interventions >2	3.1 [0.9 to 11.0]	0.05
Aortic valve surgery	3.4 [0.8 to 15.0]	0.104
Aortic valve replacement or Ross	1.2 [0.5–3.0]	0.72
Endocardial fibroelastosis resection	4.1 [1.0 to 17.8]	0.04
Mitral valve surgery	1.8 [0.7–4.9]	0.24
Biventricular conversion	1.6 [0.5–5.2]	0.44
Most recent echo characteristics		
Long-standing aortic stenosis ^b	1.1 [0.4–3.0]	0.92
Long-standing aortic regurgitation ^b	2.9 [1.1 to 7.6]	0.02
Ongoing aortic or mitral regurgitation ^c	2.8 [1.1 to 7.5]	0.005

FAV, fetal aortic valvuloplasty; LV, left ventricle; EDV, end-diastolic volume; EFE, endocardial fibroelastosis

^aHigh LV pressure on fetal echo defined as mitral regurgitation jet velocity > 2.5 m/s

^bLong-standing valve disease defined as moderate valve disease for ≥ 1 year

^cOngoing aortic or mitral regurgitation defined as moderate aortic or mitral regurgitation on most recent echo

Table 4.**LV Remodeling and LV Function Parameters**

	Entire cohort (n=34)	Normal Ventricle (n=12)	Pathologic Remodeling (n=24)	<i>p</i> value
Ejection Fraction (%)	62 (40–77)	65 (55–77)	57 (40–70)	0.011
Ejection fraction < 55% (n,%)	6 (18%)	0 (0%)	6 (24%)	0.022
Mitral E:A	1.63 (0.7–3.8)	1.4 (0.7 to 2.2)	2.1 (1.0–3.8)	0.12
Mitral E:A z-score	−0.6 (−1.8 to 2.6)	−1.1 (−1.5 to 0.4)	0.7 (−1.8 to 2.6)	0.072
Abnormal Mitral E:A (n, %)	5 (15%)	0 (0%)	5 (21%)	0.080
Mitral E deceleration time (msecs)	127 (61–306)	133 (79–268)	120 (61–306)	0.44
Mitral E deceleration time z-score	0.2(−2.4 to 5.6)	0.3 (−1.3 to 5.5)	1.0 (−2.4 −5.6)	0.24
Abnormal E deceleration time (n,%)	8 (24%)	1 (8%)	7 (29%)	0.19
Septal E'(cm/s)	6.9 (3.6–12.6)	8.8 (4.1–12.6)	6.1 (3.6–9.3)	0.016
Septal E' z-score	−2.8 (−5.7 to 0.5)	−1.9 (−5.4 to 0.5)	−3.4 (−5.7 to −2.0)	0.031
Mitral annular E' (cm/s)	9.1 (6.9 –19.0)	10.3 (6.9 to 17.0)	10.9 (6.9–19.0)	0.44
Mitral annular E' z-score	−2.3 (−4.0 to 1.4)	−2.3 (−4.0 to 0.4)	−1.9 (−3.8 to 1.4)	0.33
E/septal E'	21.2 (5.0–51.8)	16.6 (5.0 –43.8)	24.8 (11.1–51.8)	0.027
E/Mitral Annular E'	14.2 (4.1–24.8)	13.3 (4.1–24.8)	13.9 (5.9–22.0)	0.76

All values are median (range) unless otherwise specified.

E, early mitral Doppler inflow velocity, A, late mitral Doppler inflow velocity; cm, centimeter E', tissue Doppler early diastolic velocity.