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Mixed Aortic Valve Disease in the Young: Initial Observations

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Abstract

Background—The short term surgical results for mixed aortic valve disease (MAVD) and long term effects on the left ventricle (LV) are unknown.

Methods—Retrospective review identified patients with at least both moderate aortic stenosis and aortic regurgitation prior to surgical intervention. A 1:1 comparison cohort of patients with MAVD, who were not sent for surgical intervention, was identified.

Results—Forty-five patients underwent surgical management for MAVD. A control group of 45 medically managed patients with MAVD was also identified. Both groups had elevated LV end diastolic volume (EDV), elevated LV mass, normal LV mass:volume ratio (MVR) and ejection fraction. Both groups had diastolic dysfunction by early diastolic pulsed-Doppler mitral inflow/early diastolic tissue Doppler velocity *z* score. LV end diastolic pressure (EDP) was correlated with age ($R = 0.4$, $p = 0.05$) and LV MVR ($R = 0.4$, $p = 0.05$), but not with aortic stenosis, aortic regurgitation, or a score combining gradient and LV size.

On 6–12 month postoperative echocardiograms, aortic valve gradients and aortic regurgitation significantly improved (gradient 65 ± 17 to 28 ± 18 mmHg, $p = 0.01$; median regurgitation grade moderate to mild, $p < 0.01$), LV EDV normalized, and LV mass significantly improved ($p < 0.01$). Diastolic dysfunction was unchanged. Symptoms did not correlate with any measured parameter; however preoperative symptoms resolved.

Conclusions—In conclusion, despite diastolic dysfunction, systolic function is invariably preserved and symptoms are not correlated with aortic valve function or LV EDP. Current surgical practice preserves LV mechanics and results in short term improvement in valve function and symptoms.

Keywords

CHD, valve; Aortic valve, repair; Ventricle, left; Pediatric

Introduction

Mixed aortic valve disease (MAVD), comprised of both aortic stenosis (AS) and regurgitation (AR), is a rare primary disorder. Some patients develop MAVD as a long term consequence of the catheterization and surgical management of critical AS or surgery for AR.[1–9] Given these procedures began in the 1980s, there is a growing, yet significantly understudied, population of patients with MAVD. The effects of MAVD on the left ventricle (LV) differ from pure AS or AR. Left ventricular end-diastolic dimension in MAVD patients is smaller than in pure AR and larger than in pure AS.[7,9] LV shortening fraction is lower in MAVD patients compared to pure AS patients.[8]

Although Zilberszac et al. shed light on the natural history of MAVD in adults, current management and timing of surgical aortic valve repair in children are idiosyncratic due to the lack of understanding of the unnatural history and consequences of MAVD on LV mechanics.[10] This study characterizes the effects of surgery on valve performance and LV function.

Methods

We retrospectively reviewed all patients who had an echocardiogram with MAVD from 1/2003 to 9/2011 and who had surgery for MAVD. MAVD was defined as at least moderate AS (either apical maximal instantaneous gradient or suprasternal notch mean gradient ≥ 36 mm Hg depending on which had a better angle of interrogation and/or better Doppler envelope) and moderate AR (vena contracta > 3.1 mm/body surface area (BSA)^{0.5} or a descending aortic Doppler profile with holodiastolic flow reversal).[11] Exclusion criteria were other significant structural heart disease (residual mitral stenosis, residual coarctation, or complex congenital heart disease).

A control group of the 45 most recent medically managed patients with MAVD was identified. These patients may have had prior surgery for isolated AS or AR but were not referred for surgery for MAVD. Echocardiograms from the preoperative, inpatient postoperative, and 6–12 month postoperative periods were included as were the most recent echocardiograms for medical patients. The following variables were recorded from each echocardiogram: age, BSA, indexed LV end-diastolic volume (EDV)/BSA, LV EDV *z* score, LV mass *z* score, ejection fraction (EF), fractional shortening, LV mass:volume ratio (MVR), LV MVR *z* score, AS grade, aortic valve gradient, AR grade. The aortic valve gradient was defined as the higher number between the maximal instantaneous gradient across the aortic valve from the apical view or the mean gradient from the suprasternal notch view.[12] LV volumes were calculated using the 5/6-area-length method.[13]

Diastolic function was assessed using pulsed-Doppler of the mitral peak early (E) and peak late (A) inflow velocities and tissue Doppler imaging (TDI). Pulsed-wave TDI velocities (peak early diastolic velocity [E'], and peak late diastolic velocity [A']) were measured from the lateral mitral annulus and the interventricular septum from the apical 4-chamber view. Conventional indices of diastolic function were calculated including mitral valve peak E and A velocities, E:A ratio, E wave deceleration time, and E/E' ratio. Echocardiographic

parameters were converted to z scores as recommended by the American Society of Echocardiography[13] using normative data developed at Boston Children's Hospital. [14,15]

Primary disease process(es), intervention history, gender, New York Heart Association (NYHA) functional or modified Ross heart failure (for preverbal children) classification, and transplant/death were recorded. NYHA functional classification or modified Ross heart failure classification II was considered symptomatic. Preoperative LV end-diastolic pressure (EDP) was recorded when available. The study was approved by the Department of Cardiology Scientific Review Committee and Boston Children's Hospital Committee on Clinical Investigation.

Statistical Analysis

Sample size was estimated to detect changes in LV EF and LV mass z score from preoperative to 6–12 months postoperative echocardiograms. Calculations assumed paired, two-sided tests of means conducted at 0.05 significance level and 90% power. Assuming a standard deviation for change in LV EF of 12%, [16,17] 24 patients would be required to detect an 8% difference. Assuming a standard deviation for change in LV mass z score of 2.1, [9] 47 patients would be needed to detect a mean difference of 1.0.

Continuous variables were reported as mean $\pm$ standard deviation for normally distributed variables and median (interquartile range) for not normally distributed data; categorical variables were reported as frequency (percent). Variables were compared with the paired t test for the pre and postoperative echocardiograms and the unpaired t test for the surgical vs medical patients. Baseline patient characteristics were compared for medical and preoperative surgical patients with Fisher's exact test or Wilcoxon rank sum test. Pearson correlation coefficients linked LV EDP, and echocardiographic data. Analyses were performed with SPSS 16.0 (SPSS, Inc., Chicago, Illinois) and STATA 11 (STATA Corporation, College Station, Texas).

Results

Patient Characteristics

From 1/2003 through 9/2011, 45 patients underwent surgery for at least moderate MAVD. Most (62%) underwent surgical valvuloplasty/repair, whereas fewer underwent aortic valve replacement or Ross procedure (27% and 11% respectively). Table 1 shows demographic and clinical data. Most patients in both groups had isolated aortic valve disease, had previous catheterization balloon dilations but had not had previous surgery. Eight surgical and 12 medical patients had no previous aortic valve interventions. Compared to medically managed patients, patients who went for surgery were younger ($p < 0.01$), had a history of more aortic valve surgeries ($p = 0.04$), and were more likely to be symptomatic with worsening NYHA functional or modified Ross heart failure classification ($p = 0.02$), as shown in Figure 1.

Echocardiographic Data

Echocardiographic variables are shown in Tables 2 and 3. LV EDV z scores were larger (3.5 ± 2.5 vs. 2.5 ± 1.6 , $p = 0.05$) and aortic valve gradients higher (65 ± 17 vs 55 ± 17 , $p = 0.01$) in surgical patients preoperatively than in medically managed patients. LV MVR z score was preserved in both groups (z scores 1.8 ± 4.6 and 1.1 ± 2.5 respectively). For surgical patients, 6–12 month postoperative echocardiograms showed significant improvement in indexed LV EDV, LV EDV z score, aortic valve gradients, and AR grade. The LV MVR z score remained normal after surgery. Although the decrease in LV EF was significant (68 ± 7 vs 62 ± 5 , $p < 0.01$), no patient had an LV EF $< 55\%$ on their 6–12 month postoperative echocardiogram.

Diastolic Function

Twenty-two (49%) of the 45 surgical patients had preoperative catheterizations while 8 (18%) of the medical patients had catheterizations. LV EDP was positively correlated with E/E' z score ($R = 0.51$, $p = 0.02$), age ($R = 0.37$, $p = 0.05$), and LV MVR z score ($R = 0.37$, $p = 0.05$) (Figure 2). LV EDP tended to be normal before age 14 and abnormal after age 16 years. LV EDP was correlated with E/E' z score ($R = 0.51$, $p = 0.02$, figure 2) and mitral inflow E-wave deceleration time z score ($R = -0.43$, $p = 0.04$) on echocardiographic diastolic assessment. Diastolic function, measured by E/E' z score, did not change postoperatively.

Symptoms

Of the intervention group, fourteen patients (31%) were symptomatic, with the majority of these patients classified as NYHA or modified Ross heart failure Class II. Only 3 patients (7%) were Class III. The medical group had only six (13%) symptomatic patients, all of whom were NYHA or modified Ross heart failure Class II. The age distribution of symptoms is shown in Figure 3. All symptomatic patients were over the age of eight years. Figure 4 depicts subanalyses of patients dichotomized by symptoms. Symptomatology did not correlate with LV EDP, E/E' z score, aortic valve gradient, or AR. Despite the lack of hemodynamic correlation, symptomatic patients were more likely to undergo surgery than asymptomatic patients ($p = 0.02$).

Discussion

MAVD in the young is rare in the absence of prior procedures to palliate that valve. However, the increased use of catheterization or surgery to improve (as opposed to replace) markedly abnormal aortic valves is causing this patient population to expand rapidly. [1,2,7,18] Although we and others have recognized this trend, a comprehensive description of the clinical and physiologic characteristics of these patients remains, to our knowledge, unreported.

The primary findings of this study are: (1) symptoms have no correlation with severity of aortic valve dysfunction or LV EDP. (2) LV systolic function is preserved in all patients, both with and without surgical management. (3) Diastolic dysfunction is common, increases with patient age, but seems to be unrelated to the severity of valve dysfunction, although our

measure of severity of valve dysfunction only captures one moment in time, as opposed to cumulative burden of disease. (4) Surgical management, generally valve repair, improves valve function, reduces LV volume and mass, and improves NYHA functional or modified Ross heart failure classification grade.

Symptoms

Adults with chronic AR tend to be asymptomatic for a long period of time.[19] Once symptoms begin, LV EF and survival decrease dramatically.[20,21] This has led to adult clinical practice guidelines including symptomatology as an indication for surgery.[22] Our data show that symptoms in children with MAVD tend to occur in later childhood and would be interesting to track with formal exercise testing. Our data indicated that symptoms do not correlate with severity of aortic valve dysfunction, systolic function, or diastolic dysfunction. Although this brings into question symptomatology as an indication for surgery in MAVD, symptoms resolve postoperatively and we lack longitudinal outcome data in patients who do not undergo surgery.

Systolic function

The adult experience with aortic valve replacement (AVR) has shed light on some predictors of LV systolic function recovery. Adults with chronic AR tend to have full recovery of systolic function by six months after AVR.[23] In those patients who do not have recovery by six months after AVR, the LV tends not to recover.[24] We also noted normalization of LV dilation and near normalization of LV mass by the 6–12 month follow-up time period. In adults, preoperative indexed LV size in systole and diastole were independent predictors of restored LV function.[23,25] Similarly, in adults with severe AS who have an AVR, a smaller preoperative LV EDV was a predictor of better postoperative LV functional recovery. [17,26,27]

In our surgical cohort, the preoperative LV EF was preserved and remained normal postoperatively in all of the patients. Although practitioners may have chosen surgical intervention prior to a significant decrease in LV EF, it is reasonable to assume that in the early stages of MAVD, LV EF is an insensitive marker of LV dilation, elevated filling pressures, or higher degree of valve dysfunction.

Diastolic function

Diastolic dysfunction as measured by E/E' z score was present in most patients in our study and correlated with LV EDP. There was no significant change in E/E' z score 6–12 months after surgery. We do not have invasive late postoperative assessments of LV EDP to correlate these findings. Other studies have shown that diastolic dysfunction is present in patients with congenital AS, and that it recovers after the outflow tract obstruction is relieved.[28–31] Some anecdotal data has also suggested that severe diastolic dysfunction is seen late after aortic valve balloon dilation in infancy.[32] Diastolic dysfunction is present in AS and MAVD patients more than pure AR patients and is associated with a higher LV mass z-score.[33] Our data suggest that in the MAVD population, diastolic dysfunction may take longer to recover than LV mass or volume as it persisted 6 – 12 months postoperatively. We

also found that LV EDP is unrelated to valve function, but is related to age: before age 14, LV EDP is generally normal; after age 16 years, LV EDP tends to be increased.

Surgical management

Referral to surgery in this patient population was idiosyncratic and not based on any set criteria as there were few, if any, data that might inform indications for surgery in children. However, referral was not totally random: patients undergoing operation had higher aortic valve gradients, higher degrees of AR and an increased prevalence of symptomatology. Our current idiosyncratic strategy for surgical intervention, resulted in short term valve function improvement and recovery of LV size and LV mass.

Our findings of LV recovery after surgical intervention for MAVD are similar to data from other studies with different types of aortic valve disease. Bacha et al. described outcomes for patients with a history of congenital AS status post balloon dilation who subsequently developed predominant AR. In this population, LV dilation and amount of AR both decreased after surgical repair and remained reduced over time.[18] In our population of MAVD patients, we found a similar recovery in LV EDV after surgical intervention. In another population of patients with predominantly AR, freedom from aortic valve replacement at 5 and 7.5 years was 72% and 54% and was shorter in MAVD patients than pure AR.[9] On the other hand, in patients who have had a Ross procedure, those with MAVD had a 10-year freedom from reoperation that was similar to pure AS (97% and 93% respectively) and higher than pure AR (69%).[34] The high freedom from reoperation rate is consistent with our finding of overall significant LV recovery after surgery for MAVD.

Limitations

Limitations of this study included its retrospective design, small number of patients and variability in patient characteristics. Not all patients had catheterizations. The lack of clinical guidelines for when to catheterize and refer for surgical intervention on the aortic valve made practice variation substantial between practitioners and over time. The contribution of placebo effect on improvement of symptoms postoperatively could not be assessed. Many patients were primarily followed at other institutions, thus the echocardiogram protocols differed and some data including duration of mixed aortic valve disease burden were unavailable. Longer term follow-up would clarify the course of diastolic dysfunction and patient outcomes, which then may shed light regarding the timing of surgical intervention for MAVD.

Conclusion

MAVD is surprisingly well tolerated at least for the first two decades of life. Postoperative recovery in terms of clinical status as well as LV volume, mass and valvar function is encouraging. Given current idiosyncratic management strategies, EF is preserved in MAVD patients and thus is not helpful in determining disease severity or optimal operative timing. Diastolic dysfunction progresses with age in MAVD patients, and does not recover in the immediate postoperative period. Further investigation of the outcomes in patients with diastolic dysfunction will aid in determining optimal surgical timing. Because MAVD is

infrequent, a standardized and systematic approach to preoperative assessment and surgical management with targeted prospective data collection and frequent analyses may speed the generation of persuasive data.[35]

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Abbreviations

LV	Left ventricle
EDP	End diastolic pressure
EDV	End diastolic volume
MAVD	Mixed aortic valve disease
AS	Aortic stenosis
AR	Aortic regurgitation
MVR	Mass:volume ratio
BSA	Body surface area
NYHA	New York Heart Association
EF	Ejection fraction

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Figure 1: Symptomatic Classification

Bar graph comparing New York Heart Association (NYHA) or modified Ross heart failure functional classification for medical, preoperative, and 6-12 month postoperative surgical patients. $p = 0.02$ comparing medical and preoperative classifications; $p < 0.01$ comparing preoperative and 6-12 month postoperative classifications

Figure 2: Left Ventricular End Diastolic Pressure Correlations

Scatter-plots showing correlations between a) left ventricular (LV) end diastolic pressure (EDP) vs early diastolic pulsed-Doppler mitral inflow (E)/early diastolic tissue Doppler velocity (E'); b) LV EDP vs age; c) LV EDP vs LV mass:volume (MVR) z score. Solid line represents the least squares regression line.

Figure 3: Age Distribution of Symptoms

Box plots showing patient age by NYHA or modified Ross heart failure classification. Boxes represent interquartile range, dark line represents median value, and whiskers represent range.

Figure 4: Comparisons of Asymptomatic vs Symptomatic Patients

Box plots showing a) left ventricular (LV) end diastolic pressure (EDP) vs symptoms; b) early diastolic pulsed-Doppler mitral inflow (E)/early diastolic tissue Doppler velocity (E') z score vs symptoms; and c) aortic valve gradient vs symptoms. Boxes represent interquartile range, dark line represents median value, and whiskers represent range. d) bar graph showing AR grade in asymptomatic and symptomatic patients.

Table 1.**Patient Characteristics**

	Surgical Patients (n=45)	Medical Patients (n=45)	p value
Age (years)	13.0 (0.0–27.6)	18.9 (0.6–54.8)	<0.01
Males	31 (69%)	38 (84%)	0.13
Associated congenital diagnoses			0.28
Isolated aortic valve disease	35 (78%)	40 (90%)	
Coarctation of the aorta	2 (4%)	2 (4%)	
Ventricular septal defect	1 (2%)	2 (4%)	
Mild mitral stenosis or regurgitation	3 (7%)	0 (0%)	
Coronary anomalies	3 (7%)	0 (0%)	
Patent ductus arteriosus	1 (2%)	1 (2%)	
Native aortic valve morphology			0.20
Unicuspid	13 (29%)	21 (47%)	
Bicuspid (left-right fusion)	16 (35%)	12 (27%)	
Bicuspid (right-non fusion)	13 (29%)	10 (22%)	
Bicuspid (left-non fusion)	0 (0%)	1 (2%)	
Tricuspid	3 (7%)	1 (2%)	
Previous aortic valve interventions			
Number of aortic valve surgeries			0.04
0	31 (69%)	39 (87%)	
1	12 (27%)	5 (11%)	
2	2 (4%)	1 (2%)	
Number of catheter balloon valvotomies			0.42
0	17 (38%)	15 (33%)	
1	17 (38%)	22 (49%)	
2	11 (24%)	8 (18%)	
Age at first intervention (years)	0.2 (prenatal-23.7)	3.2 (0.0–54.4)	0.32
New York Heart Association or modified Ross heart failure classification			0.02
Class I	25 (56%)	39 (87%)	
Class II	11 (24%)	6 (13%)	
Class III	3 (7%)	0 (0%)	
Functional classification not available	6 (13%)	0 (0%)	

Values expressed as n (%) or median (range).

Table 2.

Echocardiographic Parameters of Medical and Surgical Patients

	Medical Patients	Surgical Patients			<i>p</i> Value [†]	<i>p</i> Value [‡]
		Pre-Operative	At Discharge	Post-Operative *		
Indexed LV EDV (ml/m ²)	107 ± 26	117 ± 35	84 ± 31	91 ± 23	0.14	<0.01
LV EDV <i>z</i> score	2.5 ± 1.6	3.5 ± 2.5	1.0 ± 2.2	1.4 ± 1.7	0.05	<0.01
LV mass <i>z</i> score	3.4 ± 1.9	4.2 ± 2.1	4.1 ± 2.0	2.2 ± 1.5	0.07	<0.01
LV mass:volume ratio	1.0 ± 0.2	1.0 ± 0.3	1.4 ± 0.4	1.0 ± 0.2	0.78	0.57
LV mass:volume <i>z</i> score	1.8 ± 4.6	1.1 ± 2.5	4.1 ± 3.2	1.0 ± 1.7	0.40	0.69
LV ejection fraction (%)	67 ± 6	68 ± 7	60 ± 7	62 ± 6	0.64	<0.01
Aortic valve gradient (mm Hg)	55 ± 17	65 ± 17	28 ± 20	28 ± 18	0.01	<0.01
Aortic regurgitation grade [§]	2 [2, 3]	2 [2, 3]	1 [0, 2]	1 [0, 2]	1.00	<0.01

Values expressed as mean ± standard deviation or median [interquartile range];

* Echocardiographic evaluation 6–12 months after surgery;

† Comparison between medical and surgical preoperative echocardiograms;

‡ Comparison between surgical preoperative and 6–12 months postoperative echocardiograms;

§ AR grading system: 0=none/trivial, 1=mild, 2=moderate, 3=severe.

Abbreviations: EDV = end diastolic volume; LV = left ventricle; MAVD = mixed aortic valve disease.

Table 3.

Echocardiographic Diastolic Parameters of Medical and Surgical Parameters

	Medical Patients	Surgical Patients		<i>p</i> Value [†]	<i>p</i> Value [‡]
		Pre-Operative	Post-Operative [*]		
Mitral inflow E:A ratio	2.0 ± 0.6	2.1 ± 0.7	2.1 ± 0.8	0.55	0.73
Mitral inflow E:A ratio <i>z</i> score	-0.5 ± 1.1	0.1 ± 1.2	-0.2 ± 1.3	0.05	0.35
Mitral inflow E-wave decel time (msec)	156 ± 46	145 ± 62	146 ± 36	0.46	0.54
Mitral inflow E-wave decel time <i>z</i> score	-0.3 ± 1.3	-0.1 ± 1.7	-0.2 ± 1.0	0.62	0.91
Mitral annular E' (cm/s)	13.5 ± 3.3	12.9 ± 3.1	13.4 ± 3.3	0.46	0.65
Mitral annular E' <i>z</i> score	-1.8 ± 1.0	-1.7 ± 1.1	-1.7 ± 1.0	0.82	0.89
Septal E' (cm/s)	9.8 ± 2.4	9.5 ± 3.0	9.0 ± 2.0	0.72	0.78
Septal E' <i>z</i> score	-1.7 ± 0.8	-1.8 ± 1.4	-2.1 ± 1.0	0.82	0.68
E/E' ratio	11 ± 4.5	13.3 ± 7.2	12.3 ± 4.7	0.17	0.19
E/E' ratio <i>z</i> score	3.5 ± 4.2	3.9 ± 2.6	3.4 ± 1.6	0.08	0.61

Values expressed as mean ± standard deviation;

^{*} Echocardiographic evaluation 6–12 months after surgery;[†] Comparison between medical and surgical preoperative echocardiograms;[‡] Comparison between surgical preoperative and 6–12 months postoperative echocardiograms.**Abbreviations:** A = pulsed Doppler mitral inflow peak A wave velocity; decel = deceleration; E = pulsed Doppler mitral inflow peak E wave velocity; E' = tissue Doppler mitral inflow peak E wave velocity.