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Aortic Valve Disease in Turner Syndrome

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Objectives Our goal was to determine the prevalence and characteristics of aortic valve disease in girls and women with monosomy for the X chromosome, or Turner syndrome (TS).

Background Complications from congenital aortic valve disease are a major source of premature mortality in TS, but accurate data on the prevalence of aortic valve abnormalities and their association with aortic root dilation are not available.

Methods This prospective study characterized the aortic valve and proximal aorta in 253 individuals with TS age 7 to 67 years using transthoracic echocardiography as our primary screening tool, supplemented with magnetic resonance imaging.

Results Transthoracic echocardiography revealed a normal tricuspid aortic valve (TAV) in 172 and a bicuspid aortic valve (BAV) in 66 subjects. Transthoracic echocardiography could not visualize the aortic valve in 15 of 253 or 6%. Magnetic resonance imaging diagnosed 12 of 15 of these cases (8 BAV and 4 TAV), so that only 3 of 253 (1.2%) could not be visualized by either modality. The aortic valve was bicuspid in 74 of 250 (30%) adequately imaged subjects. The prevalence was equal in pediatric (<18 years, n = 89) and adult populations. Over 95% of abnormal aortic valves in TS resulted from fusion of the right and left coronary leaflets. Ascending aortic diameters were significantly greater at the annulus, sinuses, sinotubular junction, and ascending aorta in the BAV group, with aortic root dilation in 25% of subjects with BAV versus 5% of those with TAV.

Conclusions Girls and women with TS need focused screening of the aortic valve and root to identify the many asymptomatic individuals with abnormal valvular structure and/or aortic root dilation. (J Am Coll Cardiol 2008;51:1904–9)

Turner syndrome (TS) occurs in phenotypic female patients missing all or part of 1 sex chromosome in all or most somatic cells. It is the most common genetic disorder of female patients, affecting approximately 1 in 2,500 live female births (1,2). There is a broad phenotypic spectrum in this syndrome, but almost all have short stature and early ovarian failure (3,4).With current medical treatment including growth hormone and estrogen, girls may attain near-normal adult stature and feminization. The major source of premature mortality in TS is congenital cardiovascular disease, which is responsible for the demise of the great majority of TS fetuses by the second trimester (5,6). Clinically severe defects, mainly aortic coarctation and/or aortic valve disease, affect ~10% of live-born girls with TS. Transthoracic echocardiographic surveys of pediatric clinic TS patients in Europe suggest that congenital cardiovascular defects are found in 20% to 30% of young individuals, with bicuspid aortic valve (BAV) reported in 10% to 18% (7,8).

These studies did not focus on the aortic valve and did not provide morphologic detail of BAV structure or associated aortic diameters. Moreover, the actual prevalence of BAV in these studies remains uncertain because they did not report the number or percent of cases that could not be ascertained. Transthoracic echocardiography studies focused solely on defining aortic valve structure report inability to visualize or define aortic valve structure in 10% to 40% of subjects, with particular difficulty defining BAVs (9,10). Identifying a BAV in asymptomatic individuals is important because they are at increased risk for infective endocarditis, valve dysfunction, and for aortic aneurysm, which may

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require intervention to prevent dissection or rupture. This issue is a major concern in TS, since the risk of aortic dissection is greatly increased (11–14).

The present study aimed to define the structure of the aortic valve in a large group of girls and women with TS participating in a National Institutes of Health (NIH) natural history study. The primary examination was transthoracic echocardiography focused specifically on the aortic valve and ascending aorta. In cases where the valve was not adequately visualized by echocardiography, cardiac magnetic resonance imaging (MRI) studies were examined for aortic valve morphology.

Abbreviations and Acronyms

BAV = bicuspid aortic valve
BSA = body surface area
MRI = magnetic resonance imaging
NIH = National Institutes of Health
TAV = tricuspid aortic valve
TS = Turner syndrome

Methods

Study subjects. Study participants were part of an ongoing genotype-phenotype research study approved by the National Institute of Child Health Institutional Review Board. All adult participants and parents of minors gave written informed consent, and minors gave written informed assent. The study included bone mineral density, body composition, and metabolic function studies, as well as cardiovascular assessment. Study subjects were recruited through notices on the NIH web site and on the Turner Syndrome Society USA web site. There was no specific outreach to heart patients or providers. Inclusion criteria were phenotypic female subjects 7 years and older who had a 50-cell peripheral karyotype with ≥70% of cells demonstrating loss or partial loss of the second sex chromosome. One patient with a prosthetic aortic valve was excluded from the study. Two other patients had endovascular valvuloplasty, and these were included. Neck webbing (pterygium colli) was defined as redundant cervical skin folds arcing out from mastoid at ear lobe level to the acromium. The webbed neck has a trapezoidal shape and is always associated with a very low posterior hairline and usually with low set, mal-rotated ears, and down-sloping or hooded appearing eyes. All of these features are caused by the stretching of the developing fetal head and neck skin and scalp over the cystic hygromata.

Echocardiography. Transthoracic 2-dimensional and Doppler echocardiography were obtained on all subjects using commercially available echocardiography machines. The standard parasternal, apical, and subcostal views were obtained with the participants in the left lateral recumbent position. The images were stored digitally and on VHS videotape for analysis. Cardiac measurements were performed according to the American Society of Echocardiography guidelines (15). Two authors (V.S. and S.S.) reviewed all studies for evaluation of the aortic valve morphology and measurement of aortic diameters. Readers were blinded to prior clinical history and results of other imaging studies. The BAV was defined as partial or complete fusion of 2 cusps, with or without a central raphe, resulting in partial or complete absence of a functional commissure between the fused leaflets (16). Abnormal aortic valves were further classified as "right-left" (fusion of right coronary and non-coronary cusps) or "anterior-posterior" (fusion of right and left coronary cusps) according to previous studies (17). Supporting features of abnormal valves included doming, thickening, or redundancy of leaflets, eccentric closure, or the presence of significant aortic regurgitation. Aortic diameters were measured using a leading-edge to leading-edge technique at end diastole and were averaged for 3 beats at each site. Measurements were taken at the aortic annulus, sinuses of Valsalva, sinotubular junction, and 1 cm above the sinotubular junction. Some of the subjects in this study were reported in an earlier study investigating the association between fetal lymphedema and congenital heart defects in TS (18). However, all echocardiography studies were reread by expert echocardiographers (V.S. and S.S.) with additional measurements of aortic diameters for the present study.

MRI. Study subjects routinely had cardiac MRI as well as echocardiography. The thoracic vascular anomalies of the initial study cohort have previously been reported (19). Magnetic resonance imaging included cine MRI, black blood imaging, and velocity-encoded cine phase contrast pulse sequences. Magnetic resonance imaging studies were used as a secondary diagnostic modality when the echocardiography reading was uncertain or the aortic valve was not adequately visualized. Magnetic resonance interpretations were provided by Drs. Ho and Arai.

Statistical analysis. Data for continuous variables are shown as means ± standard error and are compared by analysis of variance or analysis of covariance adjusted for age and body surface area (BSA) followed by *t* test. Nominal data are presented as proportions and compared by chi-square tests. Linear regressions analyzed the correlation between ascending aortic diameter determined by MRI versus echocardiography. Statistical significance was a p value <0.05. Analyses were performed using Stat View for Windows, version 5.0.1 (SAS Institute Inc., Cary, North Carolina).

Results

The study included 253 consecutive study subjects that underwent transthoracic echocardiography. Participants ranged in age from 7 to 67 years, with 89 subjects <18 years old. Twenty-five study subjects had had surgical repair of aortic coarctation during childhood. Transthoracic echocardiography assigned aortic valve diagnoses as follows: 164 tricuspid aortic valve (TAV), 8 probable TAV, 63 BAV, 3 probable BAV, and 15 nonvisualized. One-third of these BAVs had no visible raphe, and two-thirds were functionally bicuspid with partial or complete fusion of 2 aortic valve

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leaflets along a raphe. Bicuspid valves had "anterior-posterior" configuration (fusion of right and left coronary cusps) in the great majority of patients (63 of 66). There was no significant difference in age, weight, or BSA that might explain the difficulty imaging the aortic valve in the group designated as nonvisualized by echocardiography.

For the 26 cases where aortic valves were not well visualized by echocardiography, MRI was used as a supplementary approach. Magnetic resonance imaging was able to determine valve structure in 12 of 15 cases not visualized on echocardiography; of these, 8 were BAV and 4 TAV. Moreover, MRI confirmed a TAV in all 8 "probable" cases and confirmed BAV in two-thirds of the probable cases. The third case was too poorly visualized on MRI to determine valve structure. Based on the high predictive value of the "probable" echocardiographic diagnosis in the other cases, we accepted the third case as BAV in subsequent calculations. Thus, in total, echocardiography supplemented with MRI identified 176 of 253 subjects (70%) with a normal TAV and 74 of 253 (29%) with BAV, and only 3 cases remained undetermined (1%).

Table 1 summarizes characteristics of the groups with BAV versus TAV. They were similar in age and body size. The prevalence of BAV in those <18 years of age was 28 of 89, or 31.5%, with 1 case undetermined. This indicates, on the one hand, that that there is no bias toward detecting BAV in small girls, and on the other hand, there does not seem to be any prominent increase in prevalence of abnormal valve structure over time in these patients.

As expected, peak flow through the aortic valve was greater in the BAV group, as were aortic diameters (Table 1). Aortic regurgitation was trivial or less in 55%, mild in ~30%, and moderate or severe in ~15%. Aortic stenosis was uncommon. Only 2 study subjects had a peak aortic flow velocity of 3 m/s or greater. One woman had a velocity of 3 m/s associated with a BAV and moderate-to-severe aortic regurgitation. She had undergone an endovascular valvuloplasty as a child. The second woman had a BAV with a peak velocity of 5.5 m/s, and had undergone valvuloplasty in recent years with little improvement. Aortic diameters were greater at all points in the BAV versus TAV group (Fig. 1A). Diameters at the sinuses of Valsalva and the sinotubular junction were plotted against BSA on Roman nomograms (20) to identify subjects with dilation of the aortic root. Measured at the sinuses, 25% of the BAV group and 5% of the TAV group had aortic dilation (Table 1). The results for measurements at the sinotubular junction were similar (data not shown).

Table 1 Features Associated With TAV Versus BAV in Girls and Women With TS

	TAV (n = 176)	BAV (n = 74)	p Value
Age (yrs)	28.8 ± 15.2	26.6 ± 14.0	0.22
Height (cm)	143.6 ± 11.1	143.3 ± 12.3	0.87
BSA kg/m^2	1.44 ± 0.3	1.42 ± 0.3	0.58
Sys BP (mm Hg)	115 ± 11	114 ± 12	0.9*
Dias BP	69 ± 9	70 ± 9	0.4*
HR (beats/min)	86 ± 11	88 ± 11	0.4*
Peak flow (m/s)	1.30 ± 0.21	1.62 ± 0.66	<0.0001*
Annulus (cm)	1.88 ± 0.35	2.07 ± 0.49	0.001*
Sinuses (cm)	2.61 ± 0.39	2.80 ± 0.49	0.003*
Sinotubular junction (cm)	2.11 ± 0.35	2.31 ± 0.46	0.001*
Ascending aorta (cm)	2.34 ± 0.38	2.62 ± 0.63	0.0005*
Dilated aorta†	9/169 (5.3%)	17/69 (25%)	0.002
Neck webbing	43/176 (24%)	33/74 (45%)	0.003
Aortic coarctation	9/176 (5%)	16/74 (22%)	0.002

Data for continuous variables are means ± standard error and are compared by analysis of variance or *analysis of covariance adjusted for age and body surface area (BSA) followed by *t* test. Nominal data are presented as proportions and compared by chi-square tests. †Measurements of aortic diameter at the sinuses were available for 246 subjects, 8 of whom were too small for the Roman nomograms.

BAV = bicuspid aortic valve; Dias BP = diastolic blood pressure; HR = heart rate; Sys BP = systolic blood pressure; TAV = tricuspid aortic valve; TS = Turner syndrome.

Correlation between echocardiographic and MRI measurement of ascending aortic diameter. Aortic diameter measurements were systematically acquired by MRI at the level of the right pulmonary artery origin, which is typically ~1.5 cm above the sinotubular junction measurement made by echocardiography. Simple regression showed a close correlation between the 2 measurements (Fig. 1B).

Phenotypic and genotypic correlations. There was a highly significant association between the presence of neck webbing and BAV, and similarly between aortic coarctation and BAV (Table 1). The table shows that a webbed neck is significantly more common in patients with BAV. To look at it another, more clinically relevant way, almost 50% of TS patients with neck webbing have congenital cardiovascular defects. Approximately 31% of our group of 250 study subjects had neck webbing; of these, 45% had BAV and/or aortic coarctation, whereas only 23% of the nonweb group had these defects. The majority (~63%) of study subjects had a pure TS karyotype of 45,X. The 46,XiXq group (IsoQ) have the second X chromosome missing the short arm (Xp) with 2 copies of the long arm fused together. Finally, there were small groups in which the second X chromosome was missing just the short arm (46,XdelXp; Pdel) or the long arm (46,XdelXq; Qdel). The prevalence of BAV in the different karyotype groups is shown in Table 2. Unfortunately, the most informative groups missing just a short or just a long arm are very small, and thus, statistical conclusions are limited. One may argue, however, that these data are more consistent with a locus on the short arm, Xp. This is because there is a significant increase in BAV in the groups lacking only the Xp, that is, the Pdel and IsoQ. Subjects in these karyotype groups are missing most or all of Xp but have retained the Xq (in the Pdel) or have an additional copy Xq (in the IsoQ group). Thus, they are monosomic for Xp only. Although the numbers are small, the BAV prevalence in these groups is still at least 10-fold higher than in the 46,XX population (21).

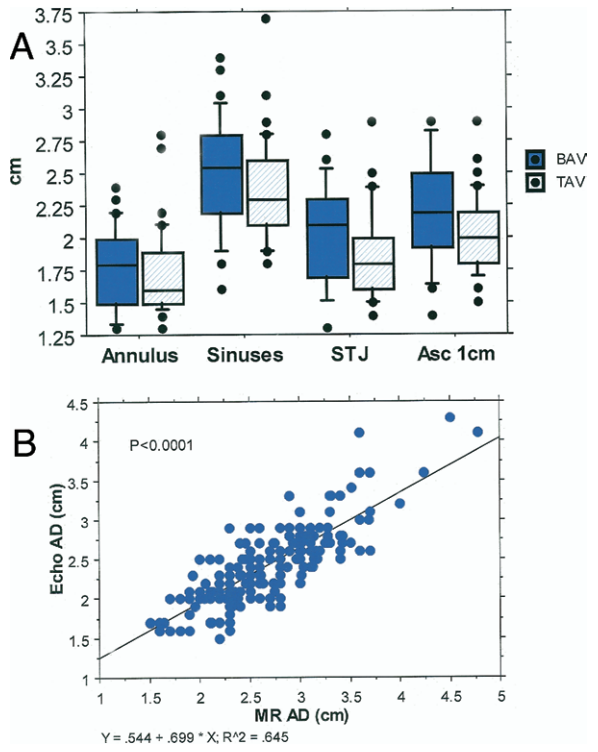

Figure 1 **Effect of AV Morphology on Ascending Aortic Diameters in Turner Syndrome**

(A) Measurements were at the annulus, midpoint of the sinuses of Valsalva, sinotubular junction (STJ), and ascending aorta (Asc) 1 cm above the STJ. The **box** includes the 25th to 75th percentiles and **whiskers** include the 10th to 90th percentiles. The **horizontal line in the box** indicates the median, and all observations less than the 10th and greater than the 90th percentiles are shown as **points**. **(B)** Correlation between Asc diameter measured by echocardiography (Echo AD) and magnetic resonance imaging (MR AD). The echocardiography measurement was 1 cm above the STJ, and the magnetic resonance imaging measurement was at the level of the right pulmonary artery. The distance between these 2 points is 5 to 10 mm. BAV = bicuspid aortic valve; TAV = tricuspid aortic valve.

Discussion

In the present study we have shown that ~30% of asymptomatic, unselected female subjects with TS have BAVs, almost all resulting from fusion of the right and left coronary leaflets. Previous echocardiographic screening studies have reported a prevalence of BAV in TS ranging from 10% to 18.5% (7,8,22–24). There are a few potential explanations for a lower discovery rate in the previous studies. The earlier studies were not particularly focused on the aortic valve and did not describe how many cases were not adequately visualized. Nor did they report on valve structure (i.e., leaflet fusion), function, or any association between abnormal aortic valve and aortic root dilation. Transthoracic echocardiography has difficulty in visualizing the aortic valve in 10% to 40% of subjects, especially those with BAVs (9,10). In the present, highly focused study, aortic valves were poorly visualized in ~5% and nonvisualized in 6% of subjects. However, with cardiac MRI evaluation of those not well seen on echocardiograms, we were able to determine aortic valve structure in almost 99% of study subjects. Interestingly, consistent with prior studies, we found the majority of aortic valves not captured by echocardiography to be abnormal. Thus, if early TS studies had a large proportion of inadequately imaged cases, there may have been a bias toward reporting normal valves. Another important difference is that in contrast to the NIH study, the previous studies included patients with high-grade mosaicism for normal cells. These patients are typically less expressive of most phenotypic features of the syndrome, so there may have been a true lower prevalence of BAV.

Selection bias is a potential concern in any prevalence study. Recruitment to this TS study reflects the current electronic age in that approximately one-half of the participants found the study by searching the web; the second largest group of individuals heard about the study by word of mouth from other participants or at TS support group meetings. Only about 10% came through medical referrals, and none of these were specifically related to cardiac concerns. Most of the adults received care from family practitioners or gynecologists, and about one-third had never had any previous cardiac evaluation (25). So it seems unlikely that we had any particular bias toward cardiac patients in this study. The prevalence of BAV determined in the present study pertains to TS individuals that have survived to age 7 years and older. The prevalence of aortic valve abnormalities and other congenital defects appears to be much higher in TS fetuses, with the great majority dying in utero due to circulatory failure (6,26,27). About 10% of newborns with TS have very serious cardiovascular defects, mainly hypoplastic left heart, and survival is poor (24). Hence, this and other studies evaluating the cardiovascular system in girls and adults with TS are seeing the survivors, in whom BAV is often an isolated defect that may not be clinically detected except by focused screening.

We have shown that the great majority (95.5%) of abnormal aortic valves in TS result from fusion of right and left coronary leaflets. This is somewhat different than in larger BAV populations, in which only 60% to 70% show fusion of coronary leaflets (28–30). This particular valve anatomy was highly associated with left-sided congenital defects (30). In a smaller previous study, we demonstrated a strong association between the presence

Table 2 **Genotype and BAV Prevalence**

	BAV	TAV	Totals
45,X	57 (36%)	101	158
IsoQ	5 (22%)	18	23
Pdel	1 (9%)	10	11
Qdel	0	4	4

For the sake of clarity, individuals with karyotypes including high-grade mosaicism (i.e., major contributions from 2 or more cell lines) were excluded from this comparison. See the Results section for further explanation of these karyotypes.

IsoQ = 46,XiXq; Pdel = 46,XdelXp; Qdel = 46,XdelXq; other abbreviations as in Table 1.

of neck webbing—the residua of central fetal lymphedema—and cardiovascular defects including BAV and aortic coarctation in TS (18). We have confirmed the association in the present much larger study. This association was first noted in spontaneously aborted fetuses with TS that had large cystic hygromas (31). The nuchal cystic hygromas are collections of lymph associated with blind-ended jugular lymphatics (26,27,31,32). In fetuses that survive, the lymphatics develop and hygromas resolve during the latter half of gestation, leaving redundant skin folds of the neck. Clark (31) suggested that centrally localized distended lymphatics compress the developing aortic root, resulting in specific left-sided defects, including hypoplastic left heart, BAV, and coarctation due to low flow, and specific right-sided defects such as persistent left superior vena cava, anomalous pulmonary venous return, and dilated right atrium, due to back pressure from obstruction to forward flow. The present study showing a pattern of anterior-posterior fusion of aortic leaflets seems consistent with predominantly left-sided outflow tract defects characteristic of TS.

An alternative explanation for the association between neck webbing and BAV in TS could be that haploinsufficiency for an X-chromosome gene causes central fetal lymphedema and aortic heart defects independent of each other. Haploinsufficiency for an autosomal gene (*FOXC2;* 16q) causes lymphedema and occasional cardiac defects in the Lymphedema-Distichiasis syndrome (33). However, targeted deletion of this gene in mice results in abnormal aortic arch development without lymphedema (34), suggesting that the heart defects and lymphedema may be independent effects of haploinsufficiency for *FOXC2*. Thus, it is possible that biallelic expression of 1 or more pseudoautosomal genes located on both X and Y chromosomes is essential for normal cardiovascular development in both genders. There are at least 20 such genes or putative genes that are expressed from both sex chromosomes and do not undergo inactivation on the supposedly inactive X. Thus far, we know the function of just 1 of these genes, *SHOX,* which is required in 2 copies for normal skeletal development and longitudinal bone growth (35). Haploinsufficiency for *SHOX* results in ~20 cm shortfall from the genetically predicted adult height, while an extra copy, as in Klinefelter syndrome (47,XXY), results in taller then expected stature. Most pseudoautosomal genes are located on Xp, consistent with our observations that the BAV phenotype is associated with mosomy for Xp specifically.

Bicuspid aortic valve is found in 1% to 2% of the general population, with a 2-fold higher prevalence in male versus female patients (21). Given the male predominance, one might expect an X-linked contribution to risk, and consistent with this view, mutations in the filamin A (*FLNA*) gene have been implicated in myxomatous cardiac valve disease (36). However, the cardiac phenotype in myxomatous valvular dystrophy (OMIM 314400) is very different than in TS. There are other X-linked genes that might be implicated in cardiovascular development (e.g., the genes encoding VEGF-D and the angiotensin type 2 receptor, both of which have roles in fetal development). However, if the increased prevalence of BAV in TS were due to exposure of a recessive mutation in *FLNA* or another X-linked gene, one would expect a frequency of a few percent, as seen in the male population, not 30%, as we have demonstrated among girls and women with TS.

We found that ascending aortic dilation, defined as aortic diameter greater than the 95th percentile for BSA, was present in 25% of BAV and 5% of TAV subjects with TS, at both the sinuses of Valsalva and sinotubular junction. Ascending aortic dilation has been reported in 10% to 40% of girls and women with TS (11,37–40), but these previous studies did not differentiate between those with BAV versus TAVs. The presence of a BAV is associated with aortic dilation in the general population, irrespective of valve functional status (41–43). For example, in the most recent study cited, the prevalence of aortic root dilation was 16% at the sinuses of Valsalva and 18% at the sinotubular junction for a group of adults with isolated BAV with a mean age of 44 years (43). The association between abnormal aortic valve anatomy and proximal aortic abnormalities including coarctation and dilation has shaped the view of a common underlying developmental defect involving the aortic valve and the wall of the ascending aorta. The present observations suggest this may be true in TS as well as in nonsyndromic BAV.

The diagnosis of BAV is predominantly determined by echocardiography, which is, according to our observations, quite sensitive (66 of 74 = 89%). Clinicians must insist on clear visualization of the aortic valve and root, and if not accomplished by echocardiography, then MRI should be the next approach. Expertise in cardiac MRI is not so widespread at present, and referral to a tertiary center may be necessary to obtain optimal visualization of the aortic valve (44). Transesophageal echocardiography is an alternative approach (10).

Conclusions

In summary, this study of a very large group of asymptomatic, unselected girls and women with TS has uncovered an extraordinarily high prevalence of BAV, which is clearly associated with aortic root dilation. Even though there is no effective treatment at present, close medical follow-up is essential to prevent complications such as endocarditis, aortic dilation and dissection, and to evaluate the severity of the valvular defects and determine when intervention is required. Given the high mortality rate of these complications (13), all patients with TS should undergo careful echocardiographic evaluation for early identification and follow-up of aortic valve and root abnormalities.

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