Aortic Dilatation and Dissection in Turner Syndrome

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Aortic Dilatation and Dissection in Turner Syndrome

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Background—The risk for aortic dissection is increased among relatively young women with Turner syndrome (TS). It is unknown whether aortic dilatation precedes acute aortic dissection in TS and, if so, what specific diameter predicts impending deterioration.

Methods and Results—Study subjects included 166 adult volunteers with TS (average age, 36.2 years) who were not selected for cardiovascular disease and 26 healthy female control subjects. Ascending and descending aortic diameters were measured by magnetic resonance imaging at the right pulmonary artery. TS women were on average 20 cm shorter, yet average aortic diameters were identical in the 2 groups. Ascending aortic diameters normalized to body surface area (aortic size index) were significantly greater in TS, and ≈32% of TS women had values greater than the 95th percentile of 2.0 cm/m^2. Ascending diameter/descending diameter ratios also were significantly greater in the TS group. During ≈3 years of follow-up, aortic dissections occurred in 3 women with TS, for an annualized rate of 618 cases/100 000 woman-years. These 3 subjects had ascending aortic diameters of 3.7 to 4.8 cm and aortic size indices >2.5 cm/m^2.

Conclusions—The risk for aortic dissection is greatly increased in young women with TS. Because of their small stature, ascending aortic diameters of <5 cm may represent significant dilatation; thus, the use of aortic size index is preferred. Individuals with a dilated ascending aorta defined as aortic size index >2.0 cm/m^2 require close cardiovascular surveillance. Those with aortic size index ≥2.5 cm/m^2 are at highest risk for aortic dissection. **(*Circulation*. 2007;116: 000-.)**

Key Words: aneurysm ■ aorta ■ magnetic resonance imaging ■ sex chromosomes

Turner syndrome (TS) is a relatively common chromosomal disorder affecting ≈1/2000 live-born girls.[1] It is caused by complete or partial loss of a second sex chromosome, with or without cell line mosaicism. Nearly all individuals have short stature, and ≈50% have congenital cardiovascular defects. Indeed, the loss of a sex chromosome affects ≈1/200 gestations, but most are lost as a result of major defects in cardiovascular development.[2–4] Despite the fact that this syndrome has been recognized for decades, there is still very little understanding of the genetic basis for the phenotype. A number of pseudoautosomal genes are present on the X and Y chromosomes that escape X inactivation and may be required in biallelic expression for normal development. The only established example of this genetic mechanism involved in the TS phenotype is short stature related to haploinsufficiency for the SHOX gene.[5,6] Mutations and microdeletions of this locus result in short stature and some skeletal anomalies as seen in TS but none of the other manifestations of the TS phenotype. So far, there are no candidate genes or even loci specifically implicated in the cardiovascular defects in TS.

Clinical Perspective p ●●●

For many years, the cardiovascular phenotype in TS was defined largely on clinical grounds, capturing mainly aortic valve abnormalities affecting ≈20% and aortic coarctation affecting ≈12%.[7,8] In recent years, however, investigations in asymptomatic individuals have revealed a far more complex and extensive cardiovascular phenotype. Magnetic resonance imaging has revealed that most women with TS have abnormal cardiovascular anatomy.[9–11] In nearly half of individuals with TS, magnet resonance angiography demonstrates elongation of the transverse aortic arch with prominent kinking in the juxta-ductus region of the inferior curvature of the aortic arch.[9] This distinctive aortic anatomy, sometimes called pseudocoarctation, is embryologically similar to coarctation and has been associated with dissection.[12] Additional vascular anomalies found by magnet resonance angiography include partial anomalous pulmonary connection and persistent left superior vena cava, each affecting ≈13%,[9] Almost 10% have anomalous origin of the right subclavian artery,[9] and 1% to 2% have septal defects or mitral valve prolapse.[13,14] A recent combined echocardiography and magnetic resonance imaging

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study found that ≈75% of adult women with TS had significant cardiovascular abnormalities.[11]

In recent years, there have been reports of a high rate of aortic dissections in TS, including patients without predisposing factors such as bicuspid aortic valve.[15–17] Possibly accounting for aortic complications, there seems to be a generalized dilatation of major vessels in women with TS, including the aorta, brachial, and carotid arteries.[18] Moreover, aortic compliance is reduced in TS,[19] as seen in Marfan syndrome. It remains unknown whether dilatation of the ascending aorta predicts aortic dissection in TS as in Marfan syndrome, and there are no current guidelines on what specific aortic diameter measurement should provoke concern in TS. This deficiency has resulted because there have been no systematic, longitudinal studies on aortic diameters and clinical outcomes in TS. Aortic dissections and ruptures in TS have been published as case reports or registry surveys in which the premorbid aortic parameters are not available. Because body size is a major determinant of normal aortic dimensions, it may not be appropriate to apply standards derived from adult men to small women with TS, many with an adult height of ≈140 cm and body surface area of nearly 1 m^2. Two major strategies have been proposed to circumvent the size problem.[11] The first is to use body surface area (BSA)– or height-normalized data compared with age-matched female control subjects. The second is to use ascending/descending aortic diameter (AD/DD) ratios to normalize the ascending aorta to each person's presumed body size–appropriate internal standard of the descending aorta.

It is clearly of great importance to establish parameters that can reliably identify girls and women at risk for acute aortic events in TS. This would allow caregivers to titrate frequency of follow-up and advice on risks of pregnancy or sports for at-risk individuals and to define specific points for prophylactic intervention. Thus, the present study aimed to investigate aortic diameters measured by magnetic resonance in a large group of women with TS to elucidate factors associated with variation in ascending aortic size and to compare methods to identify potentially ominous dilatation.

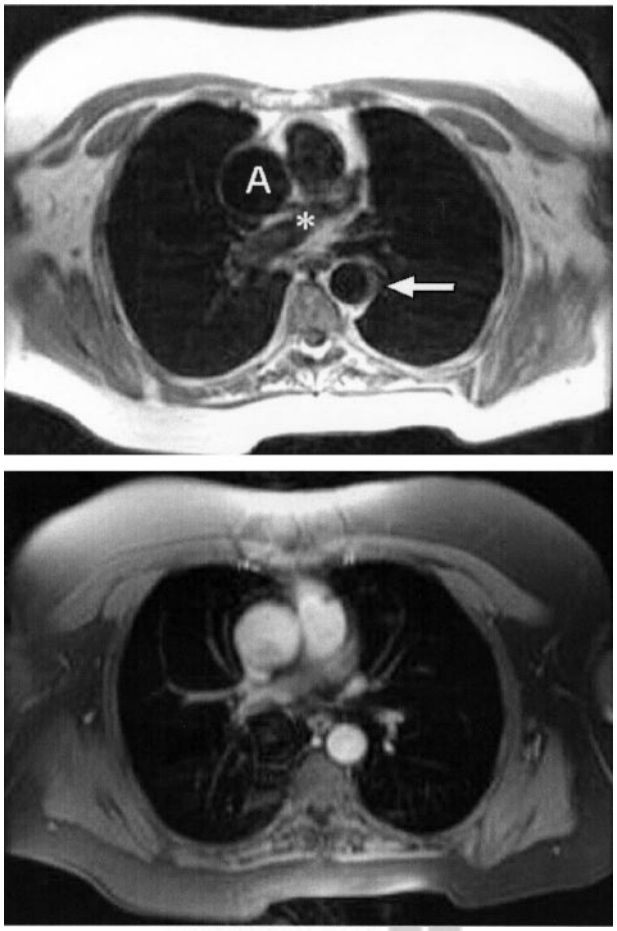

Figure 1. Magnetic resonance imaging of ascending and descending aorta. Top, Axial "black-blood" fast spin-echo demonstrates ascending aorta (A; diameter, 3.7 cm) and descending aorta (arrow, 2.2 cm) at the level of right pulmonary artery (*). Bottom, Axial "bright-blood" postgadolinium spoiled gradient-echo image obtained at the same level as above.

Methods

Study Subjects

Study participants were part of an ongoing intramural National Institutes of Health (NIH) TS genotype–phenotype protocol. This protocol was approved by the National Institute of Child Health Institutional Review Board. All adult TS participants and normal volunteers gave written informed consent. The protocol includes bone mineral density and metabolic function studies and cardiovascular assessment. Study subjects were recruited through notices on the NIH website, http://turners.nichd.nih.gov/. No specific outreach was made to heart patients or providers. Inclusion criteria were phenotypic females ≥7 years who had a 50-cell peripheral karyotype with >70% of cells that demonstrate loss or partial loss of the second sex chromosome.

One hundred sixty-six consecutive TS subjects and 26 normal volunteers ≥18 years of age who underwent chest magnetic resonance imaging were included. BSA and body mass index were calculated with the DuBois and DuBois formulas. Blood pressure measurements were performed over a 24-hour period (every 30 minutes during the day and every hour at night) with the Model P6 Pressureometer (Del Mar Reynolds, Hertford, UK). The total average systolic and diastolic blood pressures were included in the analysis. Height and weight for each participant were measured by the NIH Clinical Research Center nurses using a SRScale, model SR555, with a height rod.

Magnetic Resonance Imaging

All patients underwent imaging on a 1.5-Tesla magnetic resonance scanner (Signa, General Electric Medical Systems, Waukesha, Wis) using a phased-array coil and included axial and coronal T1-weighted fast spin echo. Magnet resonance angiography was conducted with a fast 3-dimensional spoiled gradient-echo pulse sequence and a 0.2-mmol/kg dose of gadolinium-chelate contrast media administered through an antecubital vein with a magnetic resonance–compatible injector (Spectris, Medrad, Indianola, Pa). Postgadolinium axial spoiled gradient-echo images also were performed. The diameters of the ascending and descending aorta were measured on axial T1-weighted images at the level of the right pulmonary artery, perpendicular to the long axis of the ascending aorta (Figure 1), in a blinded fashion.

Statistical Analysis

Data are displayed as means and SD. The group means were compared by ANOVA or ANCOVA with age as the covariate as indicated. Linear regressions analyzed the effects of age, body size, and blood pressure on aortic diameters. Statistical significance was

Table 1. Aortic Dimensions in Women With TS and Female Control Subjects

	TS (n=166)	NV (n=26)	NV 95th Percentile	*P*
Age, y	36.2/11.3	35.3/9.5	...	0.725
Height, cm	147.0/7.8	164.2/5.5	...	<0.0001
BSA, m^2	1.54/0.2	1.71/0.1	...	<0.0001
AD, cm	2.86/0.48	2.91/0.30	3.40	0.647
DD, cm	1.94/0.34	2.18/0.23	2.56	0.0007
AD/DD	1.49/0.25	1.34/0.10	1.50	0.002
AD/BSA (ASI), cm/m^2	1.89/0.34	1.70/0.16	1.96	0.008
DD/BSA, cm/m^2	1.28/0.26	1.27/0.11	1.45	0.855

NV indicates normal volunteer. Data are mean/SD. Mean values compared by ANOVA.

set at values of $P<0.05$. Analyses were performed with Stat View for Windows, version 5.0.1 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Aortic Diameters

Our study groups were similar in age, but the TS group was significantly smaller in both height and BSA (Table 1). AAs and DDs were measured at the level of the right pulmonary artery (Figure 1). Despite the smaller stature of the TS women, actual AD means were similar in the 2 groups (95% confidence interval for the difference in AD, −0.11 to 0.03 cm.). The AD corrected for BSA, or aortic size index (ASI), was significantly greater in the TS group, however (Table 1).

Average DD was significantly smaller in the TS group, appropriate to the smaller somatic size in women with TS (Table 1). After adjustment for variation in BSA, the difference between groups was abolished. The average AD/DD ratio was significantly greater in the TS group (Table 1).

Estimation of Aortic Dilatation

The distribution of ADs and AD/DD ratios in the 2 groups is illustrated by frequency histograms (Figure 2). This analysis demonstrates an essentially normal distribution of values in both groups and shows that the entire TS group is shifted to the right (ie, toward a larger ascending aorta). There did not appear to be distinct subpopulations in TS with regard to aortic dimension. Aortic dilatation could be defined as values greater than the 95th percentile for control populations for actual or absolute AD, BSA-normalized AD (ASI), and AD/DD ratio.

The 95th percentile for actual AD in our group of healthy controls was 3.4 cm, for the ASI was 2.0 cm/m^2 (rounding off

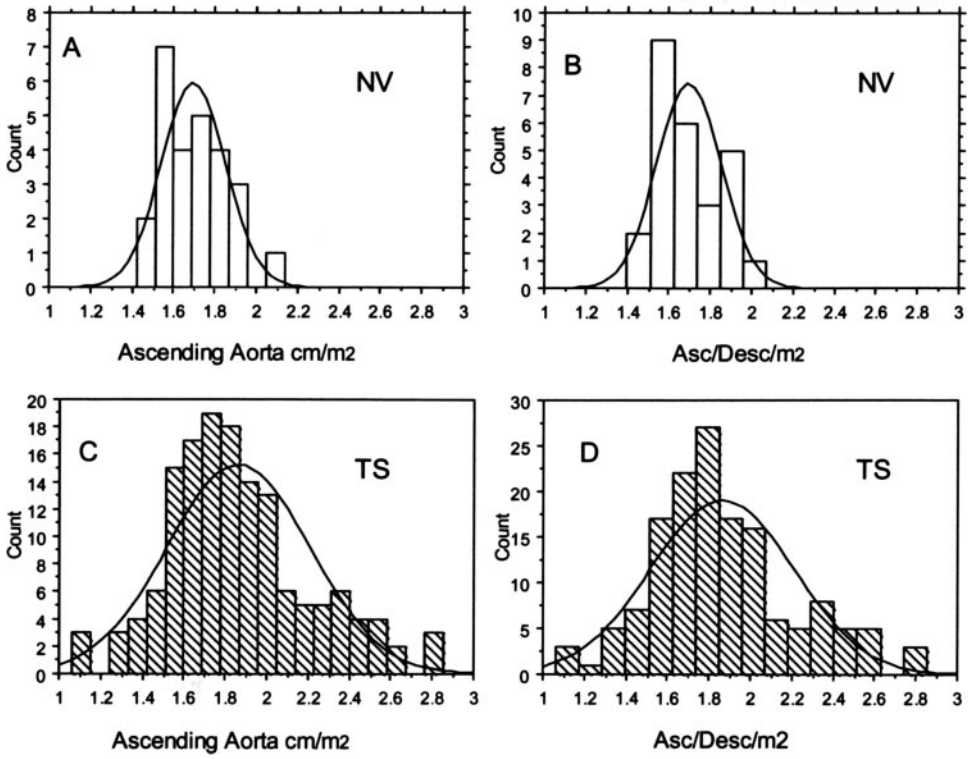

Figure 2. Frequency distribution of size-indexed ascending aorta diameters (A and C) and AD/DD ratios (B and D) in control women (A and B) and TS (C and D). Asc indicates ascending; Desc, descending; and NV, normal volunteer.

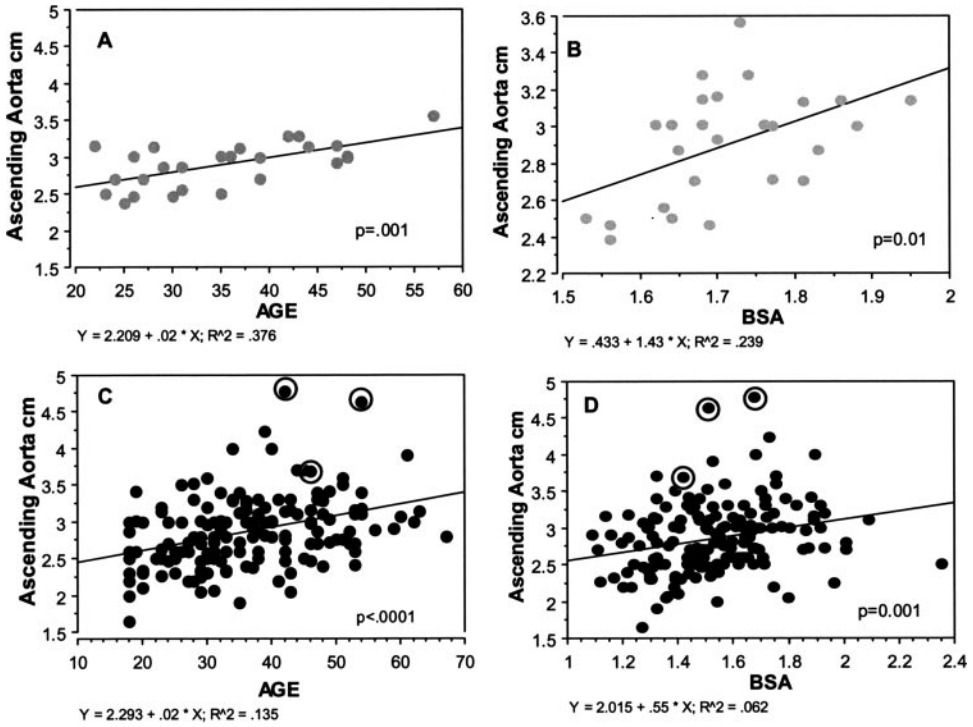

Figure 3. Relation between absolute ascending aorta size and age (A and C) and BSA (B and D) for women with TS (C and D) and age-matched control women (A and B). The encircled points represent individuals who experienced acute aortic dissection. Taken together in multiple regression, age and BSA each remain significantly related to aortic diameter at $P<0.0001$.

1.96 cm/m^2), and for AD/DD was 1.5 (Table 1). Only 9.5% of women with TS exceeded the 95th percentile for absolute AD; 24% exceeded the 95th percentile for ASI, and ≈45% exceeded the 95th percentile for AD/DD.

Factors Related to Aortic Diameter

We investigated a number of potential contributors to variation in aortic diameter in our study groups. Body size and age are the primary determinants of aortic diameter in TS and control subjects (Figure 3). Neither systolic nor diastolic blood pressure correlated with any of the aortic dimensions after controlling for age and body mass (not shown). The presence of a bicuspid aortic valve and/or elongation of the transverse aortic arch was associated with greater AD and AD/DD ratio (Table 2). Neither renal anomalies nor presence of neck webbing was associated with variation in aortic size.

To investigate which X-chromosome arm may be implicated in the aortic phenotype, we separated study subjects into specific karyotype groups (Table 3). The locus for the X-chromosome gene or genes implicated in aortic dilatation could theoretically be on the short (Xp) or long (Xq) arm. If on Xp, then the ASI should be greater than 46,XX and 46,XdelXq in groups monosomic for Xp despite retained Xq (46,XdelXp and 46,XiXq groups). If on Xq, however, then ASI should be higher in Xq deletion and normal or similar to 46,XX in the Xp deletion groups. Although the individual deletion groups are small, the differences in ASI seen in the different karyotype groups taken together are most consistent with an Xp site involved in aortic size determination (Table 3). Further observations, particularly in patients with Xp and Xq deletions, are needed to confirm this interpretation.

Table 2. Factors Associated With Aortic Dilatation in TS

	AD/M^2	*P*	DD/M^2	*P*	AD/DD	*P*
BAV (n=28/150)	2.0/0.4	...	1.2/0.2	...	1.7/0.3	...
TAV (n=122/150)	1.8/0.3	0.001	1.3/0.2	0.053	1.5/0.2	<0.0001
Web neck (n=49/152)	1.9/0.4	...	1.3/0.3	...	1.5/0.3	...
No web neck (n=103/152)	1.9/0.3	0.725	1.2/0.2	0.573	1.5/0.3	0.989
ETA (n=58/109)	1.9/0.4	...	1.3/0.3	...	1.5/0.2	...
No ETA (n=51/109)	1.8/0.3	0.017	1.2/0.2	0.016	1.5/0.2	0.814
X^M (n=81/113)	1.9/0.3	...	1.3/0.2	...	1.5/0.2	...
X^p (n=32/113)	1.9/0.4	0.835	1.2/0.2	0.469	1.5/0.3	0.292

BAV indicates bicuspid aortic valve; TAV, tricuspid aortic valve; and ETA, elongated transverse arch of the aorta. Data are from TS subjects. Mean values compared by ANOVA, with age as the covariate. Cardiac measurements are normalized to BSA.

Table 3. X-Chromosome Deletions and ASI

Karyotype (n)	ASI, cm/m^2
46,XX (26)	1.71/0.15
45X (116)	1.91/0.36
46,XiXq (15)	1.93/0.30
46,XdelXp (6)	1.90/0.10
46,XdelXq (4)	1.49/0.30

Data are mean/SD. The 46,XX subjects are our age-matched female volunteers. Age was not significantly different among the karyotype groups. The ANOVA for ASI differences between the 5 groups was significant at $P=0.009$. Fisher t tests were significant ($P<0.05$) for 46,XX smaller than 45,X and 46,iXq, and for 46,XdelXq smaller than 45,X, 46,XiXq, and 46,XdelXp.

Aortic Dissection

This study began as a cross-sectional, genotype-phenotype protocol. Study subjects with dilated ADs or other cardiovascular concerns were discharged for follow-up with cardiologists in their home area. During the past year, however, we were informed by referring physicians or family members of 3 cases of aortic dissection in our study population. In response to this information, we tried to contact all study subjects and eventually determined that at least 158 of the original 166 subjects were still in good health; 5 study subjects were lost to follow up. The average duration of follow-up was 2.9 years (range, 4 to 65 months). A total of 486 years of observation existed for the 158 patients we were able to track. Three cases of aortic dissection over 486 woman-years equals ≈618 cases per 100 000 woman-years.

The women who dissected were 44, 47, and 57 years of age. Two had a bicuspid aortic valve, and all 3 had elongated transverse arches. All had ADs >3.5 cm (3.69, 4.63, and 4.78 cm) and ASI >2.5 cm/m^2 (2.61, 2.85, and 3.06 cm/m^2). The AD/DD ratios were variable (1.42, 1.69, and 2.66). In summary, 25% of the women with absolute AD >3.5 cm and 33% of the women with ASI >2.5 cm/m^2 experienced aortic dissection within ≈3 years of follow-up. Only 3% of the women with an AD/DD ratio >1.5 experienced aortic dissection during the study follow-up.

Discussion

Thoracic aortic dissection is a relatively rare diagnosis, with ≈2000 new cases reported in the United States annually.[20] A very recent epidemiological study identified an incidence of ≈9 cases/100 000 woman-years.[21] The diagnosis is made twice as often in men as in women; men on average are in their mid-60s and women are usually in their mid-70s at diagnosis.[22] A recent Danish Registry study[15] provides the only available epidemiological information on aortic dissections in TS. This study reported a rate of 78 cases/100 000 years of patient observation for TS versus <1 case/100 000 for the 30- to 40-year-old female population in Denmark. The average age at dissection within the Danish cohort was 35 years, and 25% had no apparent risk factors for aortic dissection apart from the diagnosis of TS. Surveys of case reports on aortic dissection or rupture in TS support the young age of those affected and indicate that bicuspid aortic valve and/or hypertension were major risk factors for TS patients as for the general population, whereas 10% to 30% of patients had no apparent predisposing factor.[23,24] Unfortunately, aortic dimensions before the dissection/rupture are not available for these patients, so it is not known whether dilatation of the ascending aorta preceded the catastrophic events. Moreover, it is uncertain whether any of the aforementioned patients also had elongation of the transverse aortic arch, a more recently described feature of TS.

The present study recorded 3 cases of aortic dissection over 486 patient-years of observation, suggesting an incidence of ≈618 cases per 100 000 TS-years. This rate is almost 100-fold higher than that seen for women in general, who are usually affected in the eighth decade,[21,25] in contrast to younger TS patients. In support of the high dissection rate noted in our study, Karnis et al[17] found a 2% incidence of aortic dissection in pregnant TS women (or 2000 cases/100 000 pregnant TS-years). Gravholt et al[15] estimated a rate of 40/100 000 on the basis of the Danish Registry data; however, children at very low risk were included in the survey. Our study might have overestimated this complication if we had enrolled disproportionately high-risk patients. However, we made no effort to recruit cardiac patients and had no referrals from cardiology clinics. The prevalence of bicuspid aortic valve and aortic dilatation noted in our population is very similar to that reported in other studies.[10,11]

The origin of aortic defects in TS remains unknown. It is noteworthy that males have a higher rate of aortic abnormalities than 46,XX females, suggesting that X-linked genes in some way decrease susceptibility to aortic defects. For example, the absence of an X chromosome allows the expression of sex-linked recessive traits such as color blindness in TS similar to that found in males. Thinking along these lines, investigators in a recent study examined polymorphisms related to the X-linked gene AT2R that encodes the angiotensin II type 2 receptor. This receptor is highly expressed in the fetal vascular system and has been implicated in the Marfan aortopathy[26] and hence seemed a potential candidate for aortic defects in general. However, no association was present of AT2R polymorphisms with coarctation in nonsyndromic male cases or TS cases.[26] Such an explanation for the aortic defects in TS seems less likely when we consider that the frequency of bicuspid aortic valve in males is only ≈1/100, whereas in TS it is ≈25%. Moreover, aortic defects in TS are associated with lymphatic anomalies[27] not usually seen in males with bicuspid aortic valve. Hence, it seems more likely that haploinsufficiency for a pseudoautosomal gene is responsible for the linked cardiovascular and lymphatic defects in TS. In terms of identifying the genetic cause of the vasculopathy in TS, we have made a first step in that direction in the present study by tentatively localizing the aortic dilatation phenotype to short arm of the X chromosome that contains a large number of pseudoautosomal genes. Further longitudinal study is necessary to confirm our supposition that Xq deletion patients are not at risk for aortic complications.

The interesting constellation of developmental features recently described for the Loeys-Dietz syndrome is reminiscent of TS in its diversity and involvement of the vascular, skeletal, and neurological systems.[28] Genetic defects in this syndrome involve transforming growth factor-β receptors,

which are broadly involved in embryonic development and tissue homeostasis. Interestingly, the vascular pathology in Marfan syndrome also may be traced to the transforming growth factor-β system because fibrillin, in addition to its passive role in connective tissue, serves to bind and sequester transforming growth factor-β. These observations suggest that growth factor signaling also might be implicated in the diverse TS phenotype. As noted earlier, an altered compliance of the aorta exists in TS,[19,29] as well as enlargement of other large vessels, including brachial and carotid arteries,[18,29] suggesting a general vasculopathy. In a few cases for which pathology was available, cystic medial necrosis was reported,[23,24,30] similar to that found in Marfan syndrome.

In other patient groups at risk for dissection such as those with bicuspid aortic valve or Marfan syndrome, dilatation of the ascending aortic is used as a predictor of an acute aortic event. Thresholds of 5.5 cm for the general population and 5 cm for those with Marfan syndrome are used to guide "prophylactic" intervention to replace or stabilize the aneurysmal segment. Under this "one size fits all" prescription, however, women have a higher likelihood of dissection/rupture,[31,32] and it has been suggested that intervention at a smaller diameter such as 4.5 cm would save more women's lives.[32] In addition, it recently has been suggested that we should intervene sooner (eg, at 4-cm maximal aortic diameter) in the Loeys-Dietz syndrome[28] because patients tend to dissect at a younger age and at lesser aortic dilatation and because they seem to do well with aortic surgery. In the past, it was unknown whether specific parameters of aortic dilatation may predict which TS patients are at greatest risk and thus identify candidates for closer follow-up and potential prophylactic intervention.

The present study has evaluated aortic diameters and incidence of aortic dissection in 166 women with TS and contemporaneous, age-matched female control subjects in the only prospective study to date. We assessed 3 different indexes for aortic dilatation: actual AD, AD indexed for BSA (ASI), and the AD/DD ratio. Approximately 10% of women with TS had AD greater than the 95% percentile for healthy 46,XX women of 3.4 cm. Although 3.4 cm is just at the upper limit of normal for control women, it represents significant aortic dilatation for small TS individuals. In our small series, the 3 subjects who dissected had ADs between 3.7 and 4.8 cm.

Approximately 24% of women with TS had an ASI greater than the 95th percentile of 2 cm/m^2 for healthy female control subjects. This group included all those with absolute diameter $>$3.4 cm and those whose aortic diameter was disproportionately large for their small body size while still not above the upper limit for control women. We propose that this measure (ASI, 2 cm/m^2) be used to define the presence of significant aortic dilatation in TS and to identify individuals who deserve close cardiological surveillance of the type associated with Marfan syndrome. An ASI $\geq$2.5 cm/m^2 (99th percentile) represents extreme dilation and in our study was associated with very high risk for an acute aortic event. Thus, we suggest that this measure, in addition to the absolute diameter of 3.5 cm, should prompt evaluation for prophylactic intervention. Of note, the use of BSA-indexed aortic diameters appears to predict most accurately the risk for dissection or rupture in the population at large.[33]

The AD/DD ratio was not very helpful in this analysis. Nearly 50% of women had a ratio $>$1.5, and this classification missed several patients with absolute aortic diameters $>$3.4 cm or ASI $>$2.5 cm/m^2 and missed 1 of the dissecting patients. The reason may be that the descending aorta is not "normal" in many individuals with TS, who may have dilatation associated with aortic coarctation or a diffuse vasculopathy. Thus, for screening purposes, we suggest using the ASI 95th percentile of 2 cm/m^2. This method takes into account the considerable size variation of these patients and identifies $\approx$24% of women with TS who should undergo further evaluation. If the aortic valve is abnormal, if other vascular anomalies such as coarctation or elongation of the transverse aortic arch are present, and/or if the patient has hypertension, she is likely at heightened risk for aortic complications. If the initial measurements were by echocardiography, a magnetic resonance study should be performed for additional measurements and detection of aortic abnormalities not visible on transthoracic ultrasound.

We do not have evidence-based recommendations for treatment of TS patients with aortic dilatation. In the absence of such evidence, it may be helpful to borrow from the successful experience in treating patients with Marfan syndrome. Dilatation of the ascending aorta clearly predicts dissection, and treatment with β-adrenergic antagonists (β-blockers) reduces the rate of dilatation in this syndrome.[34] More recently, interruption of angiotensin II signaling via angiotensin-converting enzyme inhibition[35] or angiotensin type 1 receptor antagonism has shown promise in reversing vasculopathy in mice and patients with Marfan and Loeys-Dietz syndromes.[28] Additional management principles used in Marfan syndrome include exercise restriction, frequent cardiovascular imaging, and prophylactic surgical repair when aortic diameter exceeds 5 cm.[36] Admittedly, it is a leap to apply lessons from these other vascular disorders to TS, but it appears that diverse genetic origins may culminate in a common aortic pathology that responds to common intervention.[28] The use of β-blockade in TS may be particularly appropriate because it is a relatively benign treatment and because resting tachycardia is common in TS.[37,38] Likewise, aggressive blood pressure control, frequent imaging, and exercise guidelines for those with aortic dilatation is a very rationale approach.[39]

A major limitation of our study was a lack of correlative information on aortic root anatomy either by more extended magnetic resonance or by echocardiography. It would clearly be very helpful to know whether the sinuses of Valsalva and/or more proximal ascending aorta typically captured by echocardiography also are dilated in patients with dilatation of the ascending aorta at the level of the right pulmonary artery. We are currently investigating these questions intensively and attempting to use magnetic resonance to define the largest diameter of the ascending aorta and to document echocardiographic correlations. We have found magnetic resonance to be extremely valuable in the evaluation of the cardiovascular system in TS in terms of visualizing not only the entire ascending aorta but also the aortic valve (our

unpublished data), and routine use of magnetic resonance for cardiac screening in TS is now recommended.[39]

The criteria on which to base a decision to intervene surgically to prevent aortic dissection in TS are not established. No published experience exists in this area, and no guidelines specific to TS exist at present. However, waiting until an arbitrary aortic diameter of ≥5 cm that was based on adult men clearly is not appropriate given the small stature of most of these patients. This is a difficult issue because it is not known how well TS patients would fare with prophylactic aortic surgery, but at least 3 successful outcomes in cases operated on emergently are noted in the literature.[40] In summary, we found that 24% of TS women have dilatation of the ascending aorta defined as exceeding the 95th percentile of BSA-adjusted aortic diameter for age-matched control women and propose that this group requires close cardiological surveillance. We further identified smaller groups with BSA-adjusted aortic diameter >2.5 cm/m^2 or absolute diameter >3.5 cm who appear to be at highest risk for dissection. Clearly, further study is urgently needed to determine whether β-blocker or renin-angiotensin system blockade may prevent or retard aortic dilatation in patients with TS and if prophylactic surgery may reduce the incidence of aortic dissection and rupture.

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Disclosures

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CLINICAL PERSPECTIVE

Turner syndrome (TS) is a fairly common sex chromosomal disorder found in ≈1/2000 female births. Aortic dissection is a leading cause of premature mortality in these patients. This study reports the first prospective measure of the incidence of aortic dissection in TS and proposes new guidelines for identifying high-risk patients. Data defining specific aortic diameters that threaten dissection in TS have not been available. Because women with TS are typically <147 cm (4 ft 10 in) in height, the 5- to 6-cm threshold used for normal-sized adults is likely too high. To identify highest-risk individuals, we evaluated aortic diameters in a large group of asymptomatic, unselected women with TS and analyzed outcomes in these women, who were followed up for an average of 3 years with respect to premorbid aortic measures. Three cases of aortic dissection occurred among 158 patients during this time. These women had aortic diameters ranging from 3.7 to 4.8 cm and were under a cardiologist's care in their home areas, but with diameters <5 cm, they were not considered candidates for prophylactic intervention. Thirty-three percent of TS women with absolute ascending aorta diameter ≥3.5 cm and 27% of those with body surface area–adjusted aortic diameter ≥2.5 cm/m^2 experienced aortic dissection over 3 years. Hence, we propose that waiting for aortic diameter to reach 5 cm is not appropriate for patients with TS and that women with an actual diameter ≥3.5 cm or body surface area–adjusted diameter ≥2.5 cm/m^2 need evaluation for prophylactic intervention.