Background—Congenital aortic valve fusion is associated with aortic dilation, aneurysm, and rupture in girls and women with Turner syndrome. Our objective was to characterize aortic valve structure in subjects with Turner syndrome and to determine the prevalence of aortic dilation and valve dysfunction associated with different types of aortic valves.

Methods and Results—The aortic valve and thoracic aorta were characterized by cardiovascular MRI in 208 subjects with Turner syndrome in an institutional review board–approved natural history study. Echocardiography was used to measure peak velocities across the aortic valve and the degree of aortic regurgitation. Four distinct valve morphologies were identified: tricuspid aortic valve, 64% (n=133); partially fused aortic valve, 12% (n=25); bicuspid aortic valve, 23% (n=47); and unicuspid aortic valve, 1% (n=3). Age and body surface area were similar in the 4 valve morphology groups. There was a significant trend, independent of age, toward larger body surface area–indexed ascending aortic diameters with increasing valve fusion. Ascending aortic diameters were (mean±SD) 16.9±3.3, 18.3±3.3, and 19.8±3.9 mm/m² (P<0.0001) for tricuspid aortic valve, partially fused aortic valve, and bicuspid aortic valve+unicuspid aortic valve, respectively. Partially fused aortic valve, bicuspid aortic valve, and unicuspid aortic valve were significantly associated with mild aortic regurgitation and elevated peak velocities across the aortic valve.

Conclusions—Aortic valve abnormalities in Turner syndrome occur with a spectrum of severity and are associated with aortic root dilation across age groups. Partial fusion of the aortic valve, traditionally regarded as an acquired valve problem, had an equal age distribution and was associated with an increased ascending aortic diameters. (Circ Cardiovasc Imaging. 2013;6:1018-1023.)

Key Words: abnormalities ■ aorta ■ echocardiography ■ magnetic resonance imaging ■ Turner syndrome

T

Turner syndrome (TS) or monosomy X is a relatively common genetic disorder characterized by the loss of all or part of 1 of the sex chromosomes in a phenotypic female patient. It affects 1 in every 2500 live-born females1 and presents with a relatively variable phenotype, with short stature, premature ovarian failure, and physical traits including webbed neck, low-set or malrotated ears, ptosis, and skeletal abnormalities.2,3 The most serious clinical aspect of TS is the presence of congenital heart disease, particularly aortic valve disease, coarctation of aorta, and partial anomalous pulmonary venous return.4,6 There is a higher rate of prenatal diagnosis of TS and a higher rate of major cardiac malformations such as hypoplastic left heart syndrome, which may account for the high rate of observed fetal demise (80%) among all fetuses with TS between 10 weeks and term.5,7 There was a significant trend, independent of age, toward larger body surface area–indexed ascending aortic diameters. The most common defects being aortic valve disease and coarctation of the aorta. Aortic valve disease is associated with valve dysfunction, aortic dilation, and even aortic dissection and aortic rupture in 1% to 2% of these women5,12-15 which underlies the importance of early identification of these defects in asymptomatic women. Previously, Sachdev et al16 reported the incidence of bicuspid aortic valve (BAV) among asymptomatic, unselected female subjects with TS as 30%, and a significant proportion of these patients had aortic dilation, elevated peak flow across the aortic valve, and aortic regurgitation. However, in this study, a BAV was defined as partial or complete fusion of 2 aortic cusps, leading to the loss of a functional commissure between the fused leaflets. Partial fusion of the aortic valve is not a clearly defined entity and generally refers to the calcific changes of the aortic valve that are commonly acquired with age. Waller et al17 have described various forms of this abnormality, emphasizing the differentiation between a classic congenital BAV and acquired cusp fusion. Various pathology reports, autopsy series, and imaging studies have postulated an association of the nonsyndromic BAV with aortic dilation, calcific aortic stenosis, and aortic regurgitation.18-22 Although patients with partial fusion...
were included, these reports did not specifically focus on partial fusion of the aortic valve and did not report its prevalence in the general population. In many cases, the morphological structure of partial commissural fusion in these studies could not be determined with certainty, usually attributable to extensive valve destruction and heavy calcific deposits that prevented differentiation between a congenitally bicuspid and acquired valvular fusion. Therefore, no published description of this lesion and its prognosis in living patients exists in the literature.

The purpose of this study is to classify aortic valve abnormalities in a large group of girls and women with TS and to determine the prevalence of valve dysfunction and degree of aortic dilation associated with different types of aortic valve abnormalities.

Methods

Study Subjects

Between January 2007 and December 2010, 208 female patients between 7 and 67 years of age (mean age, 32.9±15.5 years) with genetically proven TS participated in an ongoing National Institute of Child Health and Human Development Institutional Review Board–approved TS genotype-phenotype protocol at the National Institutes of Health. This study was approved by an institutional review committee, and the subjects gave informed consent. Included in the study were phenotypic females ≥7 years of age who on a 50-cell peripheral karyotype had ≥70% cells demonstrating complete or partial loss of the second sex chromosome. The karyotype based on analysis of 50 metaphase spreads for this study group was 45,X in 66%, 46,X,delXp or 46,X,iXq in 9%, mosaic for 45,X, and a second abnormal cell line in 18% (commonly 45,X/46,X,iXq) and mosaic for 45,X and a normal cell line in 7%.

No patients were referred by a cardiologist, thus minimizing bias for patients with congenital heart disease. All subjects underwent cardiovascular magnetic resonance (CMR) imaging to define aortic valve anatomy, ascending aorta, and the aortic root, as well as transthoracic echocardiography to evaluate valve function. All adult subjects gave written informed consent, and all minors gave informed assent. Body surface area was calculated using the DuBois and DuBois formula.

CMR Imaging

CMR imaging techniques, including cine MRI, black blood imaging, 3-dimensional (3D) magnetic resonance angiography with and without contrast (for subjects ≥18 years of age or in the presence of known pathology in subjects <18 years of age), and velocity-encoded cine phase-contrast pulse sequences, were used in dedicated study of the aortic valve, aortic root, and thoracic aorta with a Siemens 1.5-T Avanto or Espree (Siemens, Erlangen, Germany). Cross-sectional measurements of the aortic valve annulus, sinuses of Valsalva, and sinotubular junction were performed on 3D noncontrast magnetic resonance angiography data sets. Measurements of the ascending and descending thoracic aorta were performed on axial black blood images at the level of the pulmonary artery bifurcation. Contrast-enhanced magnetic resonance angiography data sets were used to examine the anatomy of the thoracic aorta, arrangement of the head and neck vessels, and presence of aortic dilation or coarctation in adults. Finally, velocity-encoded cine phase-contrast imaging was used to examine the aortic valve, to classify valve defects, and to detect aortic stenosis and regurgitation if present. Images were interpreted by 2 readers. Both readers were blinded to clinical history and other diagnostic images.

Tricuspid aortic valves (TAVs) were noted to have 3 cusps, 3 commissures that opened completely, and a triangular shape on phase-contrast imaging. Partially fused aortic valves (PFs) had 3 cusps, 2 commissures that opened freely, 1 commissure that was partially fused, and a puckered orifice appearance on phase-contrast imaging. BAVs were noted to have 3 cusps, a completely fused commissure between 2 cusps and an oval-shaped orifice on phase-contrast imaging. Finally, a unicuspid aortic valve (UAV) was noted to have 3 cusps and fusion of ≥2 commissures: typically 1 completely fused commissure and 1 partially fused commissure. The shape of the orifice on phase-contrast imaging was irregular and eccentrically located within the valve area. To differentiate between BAV and PF, a BAV was defined as complete fusion of 2 aortic valve leaflets with or without a central raphe such that a functional commissure between the fused leaflets was absent, whereas a PF was defined as fusion to a lesser extent (Figure 1B). Although there are no accepted imaging-based criteria for partial fusion of the aortic valve, autopsy data from the 1980s defined a PF in an adult patient as fusion of 2 cusps <5 mm extending from the wall of the aorta along the commissure.

Echocardiography

Transthoracic 2D and Doppler echocardiography using commercially available echocardiography machines was obtained. Standard parasternal, apical, and subcostal views were obtained with the subject in a left lateral recumbent position. Images were stored digitally and on VHS videotape, which were subsequently analyzed. Echocardiography was used as a secondary modality to ascertain aortic valve function by the presence and degree of aortic regurgitation and stenosis only. Degree of aortic regurgitation was graded as trivial, mild, moderate, or severe on the basis of the size of the regurgitant jet determined by color Doppler and the downward slope of the continuous-wave Doppler. Peak flow velocity across the aortic valve was assessed by continuous-wave Doppler. The classification of both valvar stenosis and regurgitation was made according to the American Society of Echocardiography Guidelines.

Figure 1. Aortic valve structure shown on cardiac MRI. Gradient echo (left) and phase-contrast (right) images of (A) tricuspid aortic valve, (B) partially fused aortic valve (PF), (C) bicuspid aortic valve, and (D) unicuspid aortic valve. A PF was defined by 3 main criteria: the degree of fusion (subjectively assessed by how much of the commissure was still visible at peak systole), the shape of the phase contrast at peak systole, and the centeredness of the orifice in the valve.
Limited echocardiographic data from a subset of our cohort were reported in an earlier study on the prevalence of aortic valve disease in TS.16

Valve Classification
The anatomic features of the aortic valve were examined, and valves were classified according to the appearance of the cusps/commissures on cine CMR imaging and the shape of the valve orifice on phase-contrast imaging. Four distinct valve morphologies were noted: TAV, PF, BAV, and UAV. Figure 1 illustrates the 4 types of aortic valves observed in the cohort. Aortic valve classification was based on CMR imaging and was completed by 2 independent reviewers (κ=0.82).

Statistical Analysis
Continuous data are presented as means with SD; nominal data are given as number and percent. Because there were just 3 subjects in the UAV group, these subjects were combined with the BAV group. ANOVA was used to compare age across valve-structure groups, and ANCOVA adjusted for age using ANCOVA (Fig-3). The mean age-adjusted ascending aorta diameters for TAV, PF, BAV, and UAV, 1% (n=3). Right-left coronary cusp (92%) fusion predominated over right-noncoronary cusp (8%) fusion within both the BAV and PF groups, which is consistent with previously reported studies.16.18.23 No significant differences in age, height, weight, or body surface area were found among the 4 groups.

Echocardiography/CMR Comparison
All 208 participants underwent transthoracic echocardiography, including anatomic assessment of the aortic valve. Of these, 28 echocardiographic studies (13%) could not establish aortic valve anatomy attributable to inadequate views. An additional 20 (10%) echocardiographic studies described aortic valve anatomy that was discrepant with CMR findings. The majority of discrepancies involved valves determined to be partially fused by CMR. The 48 inadequate and misclassified echocardiographic studies included 11 PFs and 4 BAVs. Of the 20 misclassified echocardiographic studies, 9 aortic valves were misclassified as normal and were found to have pathology by CMR. The remainder of the discrepancies involved severity of the aortic valve lesion. Table 2 illustrates comparison of echocardiographic and CMR aortic valve diagnoses.

The frequency of inadequate and discrepant echocardiographic studies among the pediatric subjects (11% [n=5] and 9% [n=4], respectively) was comparable to those of the adult subjects (14% [n=23] and 10% [n=16], respectively).

Aortic Valve Function
Aortic valve stenosis and regurgitation were assessed using standard techniques based on transthoracic echocardiography. Valve dysfunction was classified as trivial, mild, moderate, or severe according to established guidelines. Subjects were placed in 1 of 3 cohorts: those with trivial or less, mild, and moderate or greater valvular dysfunction. Table 3 depicts results of valvular function by type of valve.

Overall, there was a low incidence of clinically significant valve dysfunction within the cohort. Only 8 of 208 subjects had greater than mild stenosis or insufficiency or both, demonstrated in Table 3. Any degree of valve fusion, including PF, BAV, and UAV, was significantly associated with mild aortic regurgitation and stenosis.

Thoracic Aorta Dimensions
Aortic dimensions increased with degree of valve fusion at all levels of the arch, and this was significant from the level of the aortic valve to the ascending aorta (Figure 2). No significant differences in aortic size were observed distal to the ascending aorta in the groups. There was a significant trend toward larger body surface area-indexed ascending aorta diameters from TAV to BAV/UAV after adjustment for age using ANCOVA (Figure 3). The mean age-adjusted ascending aorta diameters for TAV, PF, and BAV/UAV were (mean±SD) 16.6±3.3, 17.85±3.3, and 19.70±3.9 mm/m² (P<0.0001). A post hoc analysis evaluating the ascending aorta diameters while excluding the 8 subjects with more than mild valve dysfunction revealed an identical relationship between ascending aorta diameters and valve type.

Forty subjects had aortic dilation with an aortic size index >2.0:15 with TAV, 6 with PF, 17 with BAV, and 2 with UAV.

Table 1. Baseline Characteristics of the 4 Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>TAV (n=134)</th>
<th>PF (n=25)</th>
<th>BAV (n=46)</th>
<th>UAV (n=3)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>33.6 (16.5)</td>
<td>33.9 (12.9)</td>
<td>30.8 (13.3)</td>
<td>28.0 (15.7)</td>
<td>0.763</td>
</tr>
<tr>
<td>Pediatric age, n (%)</td>
<td>28 (20.9)</td>
<td>2 (8)</td>
<td>10 (21.7)</td>
<td>1 (33.3)</td>
<td>0.666</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>146.1 (9.6)</td>
<td>147.5 (8.2)</td>
<td>148.6 (7.8)</td>
<td>145.7 (8.1)</td>
<td>0.426</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>60.3 (19.4)</td>
<td>56.4 (12.2)</td>
<td>58.8 (17.3)</td>
<td>51.1 (3.4)</td>
<td>0.648</td>
</tr>
<tr>
<td>BSA, mean (SD), m²</td>
<td>1.50 (0.25)</td>
<td>1.47 (0.16)</td>
<td>1.51 (0.22)</td>
<td>1.4 (0.09)</td>
<td>0.899</td>
</tr>
<tr>
<td>Mean SBP (SD), mm Hg</td>
<td>116 (11)</td>
<td>116 (10)</td>
<td>118 (13)</td>
<td>106 (11)</td>
<td>0.441</td>
</tr>
<tr>
<td>Mean DBP (SD), mm Hg</td>
<td>71 (8)</td>
<td>71 (8)</td>
<td>72 (7)</td>
<td>70 (5)</td>
<td>0.859</td>
</tr>
</tbody>
</table>

BAV indicates bicuspid aortic valve; BSA, body surface area; DBP, diastolic blood pressure; PF, partially fused aortic valve; SBP, systolic blood pressure; TAV, tricuspid aortic valve; and UAV, unicuspid aortic valve. There were no significant differences in mean age, BSA, height, weight, or blood pressure between groups.
Table 2. Comparison Grid of Valve Morphology as Determined by Echocardiography and Cardiac MRI

<table>
<thead>
<tr>
<th></th>
<th>Echocardiography</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAV</td>
<td>PF</td>
</tr>
<tr>
<td>TAV</td>
<td>113</td>
<td>3</td>
</tr>
<tr>
<td>PF</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>BAV</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>UAV</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All values represent the number of patients. BAV indicates bicuspid aortic valve; PF, partially fused aortic valve; TAV, tricuspid aortic valve; and UAV, unicuspid aortic valve.

In terms of valve function, 25 of the 40 subjects had trivial or no aortic insufficiency, 12 had mild aortic insufficiency, and 3 had greater than mild aortic insufficiency. Thirty-four had no aortic stenosis, 4 had mild aortic stenosis, and 2 had more than mild aortic stenosis. In terms of the aortic isthmus geometry, 30 subjects had no coarctation of the aorta, past or present, whereas 4 had a history of coarctation repair, 4 had evidence of a pseudocoarctation of the aorta, and 2 had evidence of a trivial coarctation. There were no significant differences in ascending aorta size between right-left and right-nonfused valves, with any degree of fusion (PF or BAV).

The probability of having a dilated ascending aorta was analyzed using backward stepwise regression analysis with the following independent variables: type of aortic valve, presence or absence of aortic valve dysfunction, presence or absence of coarctation, age, and average systolic and diastolic blood pressures. The probability of a dilated ascending aorta was significantly associated with abnormal aortic valve leaflets (odds ratio, 2.61; 95% confidence interval, 1.66–4.23; \( P < 0.0001 \)), aortic valve dysfunction (odds ratio, 2.45; 95% confidence interval, 1.02–5.99; \( P = 0.045 \)), and age (odds ratio, 1.08; 95% confidence interval, 1.05–1.11; \( P < 0.0001 \)).

Discussion

The present study of asymptomatic, unselected female subjects diagnosed with TS confirms that congenital aortic valve disease in TS is common and suggests that it occurs along a spectrum of severity, as opposed to the traditional binary classification of TAV or BAV. This is particularly notable because partial fusion of the aortic valve has previously been described as an acquired valve disorder, the incidence of which increases with age. Prior studies have reported the incidence of BAV in TS ranging from 12.5% to 30% in their patients.5,16,24–26 In most cases, echocardiography was used to image the valve, and the criterion for diagnosis of a BAV was either not defined or no distinction between partial and complete fusion of the aortic valve leaflets was made. It is likely that echocardiograms in the earlier studies may not have captured partial fusion of the aortic valve, reporting them as normal valves, or BAV and PF were combined into 1 category. Echocardiography is widely available and is an excellent tool for evaluation of valve dysfunction. However, in certain cases, direct visualization of the aortic valve morphology in women with TS by ultrasound may be limited by chest wall anomalies associated with fetal lymphedema, the barrel-shaped chest, and obesity. Our study shows that up to 23% of transthoracic echocardiograms were inaccurate or inadequate in their anatomic description of the aortic valve, whereas no CMR studies were deemed inadequate. Given these limitations, cardiac MRI is a reliable alternative, with reliable direct visualization of the aortic leaflets at high resolution in both adults and older children.27 By using cardiac MRI to classify valve structure, we have eliminated any potential bias from inadequately imaged, abnormal valves.

A correlation between aortic valve defect and aortic dissection in women with TS has been reported in recent studies.13,14,28 Aortic dissection is often preceded by aortic dilation, which in turn is influenced by established risk factors such as BAV, coarctation of aorta, and uncontrolled hypertension.12,16,29 Lanzarini et al30 have reported a slow, clinically irrelevant progression of aortic dilation in women with TS during a median follow-up of 37 months. Presence of baseline dilation, hypertension, and congenital cardiovascular disease, including coarctation of the aorta, was not found to influence the increase in aortic diameters during the follow-up period.30 Similarly, a slow progression of aortic dilation has been reported in adult subjects with BAV.22

PFs are associated with aortic root remodeling, albeit less severe than a BAV, which can progress to significant aortic dilation in some cases. Aortic root dilation can potentially progress to an aortic dissection. Therefore, the diagnosis of

Table 3. Echo Evidence of Aortic Valve Dysfunction by Valve Type

<table>
<thead>
<tr>
<th>Aortic Valve Dysfunction</th>
<th>TAV (n=134)</th>
<th>PF (n=25)</th>
<th>BAV/UAV (n=49)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficiency, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/trivial</td>
<td>127 (97.8)</td>
<td>20 (80)</td>
<td>25 (51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (4.5)</td>
<td>5 (20)</td>
<td>20 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>1 (0.7)</td>
<td>0</td>
<td>4 (8.2)</td>
<td></td>
</tr>
<tr>
<td>All with insufficiency, n (%)</td>
<td>7 (5.2)</td>
<td>5 (20)</td>
<td>24 (49)</td>
<td></td>
</tr>
<tr>
<td>Stenosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>134 (100)</td>
<td>23 (92)</td>
<td>42 (85.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>1 (4)</td>
<td>4 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>0</td>
<td>1 (4)</td>
<td>3 (6.1)</td>
<td></td>
</tr>
<tr>
<td>All with stenosis, n (%)</td>
<td>0</td>
<td>2 (8)</td>
<td>7 (14.3)</td>
<td></td>
</tr>
</tbody>
</table>

BAV indicates bicuspid aortic valve; PF, partially fused aortic valve; TAV, tricuspid aortic valve; and UAV, unicuspid aortic valve. Aortic stenosis and insufficiency were graded as absent, trivial, mild, moderate, or severe, and these groups were coarchored into 3 groups: none/trivial, mild, and moderate/severe.
PF in TS is clinically relevant and may follow a course similar to a BAV. The diagnosis of PF should warrant a baseline evaluation by a cardiologist including 2D echocardiography, ECG, and close follow-up similar to a diagnosed BAV. Theoretically, PFs may also be subject to different age-related aortic valve calcification when compared with normal TAV.

At present, the pathogenesis of BAV in TS and the cause behind its association with aortic dilation and proximal aortic anomalies are still not known. Most recent studies have postulated an intrinsic abnormality of this entire region involving the aortic valve and aorta simultaneously, a so-called aortopathy. In 1999, Bonderman et al suggested premature apoptosis of the smooth muscle cells of the medial muscular layer of the aorta, before aortic dilation, as part of a genetic program that causes progression to aneurysms and dissections in patients with abnormal aortic valve morphology. This is in agreement with the histological observation of cystic medial necrosis that has been reported in a majority of cases of aortic dissection in patients with a BAV. Abnormal elastic properties of the aorta and altered collagen resistance in the aortic wall have also been suggested. Recently, Ostberg et al reported enlargement of the extra aortic conduit arteries and increased carotid thickening in women with TS, likely attributable to estrogen deficiency predisposing to intimal hyperplasia in TS. These findings are in support of the hypothesis that abnormal aortic valve morphology and proximal aortic pathology, that is, dilation, aneurysms, and dissections, occur along a spectrum of severity in TS. It is likely that PF and BAV represent variable phenotypic expression of these genes such that PF represents a less severe but clinically significant pathology in this region.

Whether type of valve fusion correlates with valve dysfunction and aortic dilation in TS as it does in the general population is contentious. A recent review of BAV in a general pediatric population confirmed that right-left leaflet fusion is more common and usually associated with coarctation of the aorta. Right-nonleaflet fusion was associated with more significant valve pathology and dilation of the aorta. Recently, a phenotypic classification for BAV that includes aortic root shape and leaflet morphology has also been proposed. A significantly different pattern of dilation has been reported that is based on the leaflets involved in fusion such that possible differences in development, hemodynamics, and possibly tissue composition between the different valve types may be inferred. In our study of unselected, asymptomatic women with TS, we found no differences in the distribution of valve dysfunction or aortic dimensions based on this classification; however, the young mean age and asymptomatic clinical status are likely factors that would bias our group toward having less valvular dysfunction.

Limitations of this study include lack of an age-matched group of 46,XX women to determine and compare the incidence and prognosis of a PF in the general population. Despite the lack of an age-matched control group, we believe that the described spectrum of aortic valvulopathy in TS is informative. Confirmation of the effects of PF on valve function and aortic dimensions in the general population has to come from longitudinal studies in young children and adolescents because the relationship may be confounded by acquired valve fusion in the aging, calcified valves.

Conclusions

Aortic valve abnormalities occur in more than one third of patients with TS, occur with a spectrum of severity, and are associated with aortic root dilation across age groups. Partial fusion of the aortic valve, traditionally regarded as an acquired valve problem, had an equal distribution across age groups and had an increased ascending aortic diameter in subjects.
with TS. Patients with TS require a clear, focused visualization of the aortic root and aortic valve, and if traditional echocardiography is inadequate, CMR should be considered.

Acknowledgments
We thank all the girls and women who were a part of this study.

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Disclosures
None.

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Laura J. Olivieri, Ridhwan Y. Baba, Andrew E. Arai, W. Patricia Bandettini, Douglas R. Rosing, Vladimir Bakalov, Vandana Sachdev and Carolyn A. Bondy

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