

# Aortic Dimensions in Turner Syndrome

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In Turner syndrome, linear growth is less than the general population. Consequently, to assess stature in Turner syndrome, condition-specific comparators have been employed. Similar reference curves for cardiac structures in Turner syndrome are currently unavailable. Accurate assessment of the aorta is particularly critical in Turner syndrome because aortic dissection and rupture occur more frequently than in the general population. Furthermore, comparisons to references calculated from the taller general population with the shorter Turner syndrome population can lead to over-estimation of aortic size causing stigmatization, medicalization, and potentially over-treatment. We used echocardiography to measure aortic diameters at eight levels of the thoracic aorta in 481 healthy girls and women with Turner syndrome who ranged in age from two to seventy years. Univariate and multivariate linear regression analyses were performed to assess the influence of karyotype, age, body mass index, bicuspid aortic valve, blood pressure, history of renal disease, thyroid disease, or growth hormone therapy. Because only bicuspid aortic valve was found to independently affect aortic size, subjects with bicuspid aortic valve were excluded from the analysis. Regression equations for aortic diameters were calculated and Z-scores corresponding to 1, 2, and 3 standard deviations from the mean were plotted against body surface area. The information presented here will allow clinicians and other caregivers to calculate aortic Z-scores using a Turner-based reference population. © 2015 Wiley Periodicals, Inc.

**Key words:** Turner syndrome; aortic dissection; aortic Z-scores; bicuspid aortic valve

## INTRODUCTION

Knowledge of the size of the aorta is particularly important in conditions that cause aortic dilation such as Marfan syndrome, Loeys–Dietz syndrome, bicuspid aortic valve, and Turner syndrome, in which a severely enlarged aorta is more likely to lead to dissection or rupture than in the general population [Eagle, 2009]. The normal aortic phenotype in subjects with Turner syndrome has not been well characterized. This information gap complicates the management of otherwise healthy individuals who live with Turner syndrome.

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Clinical geneticists and pediatric care givers are faced with the challenge of defining normal growth patterns for height and weight. To address this problem the CDC recommends the use of growth percentiles to allow comparison of an individual's growth to that of a healthy population. Analyses of the height and weight as well as the size of heart chambers, valves, and great vessels must take into account the non-constant variance (heteroskedasticity) associated with somatic growth. To accomplish this, raw measurements are transformed and Z-scores based on body surface area are generated [Sluysmans and Colan, 2005]. In most situations, sampling the general population is the appropriate comparator. Predictions of aortic dimensions in Marfan syndrome and Turner syndrome are further complicated because both syndromes affect longitudinal growth. Thus, comparing aortic dimensions to the general population may lead to under-estimates in Marfan syndrome individuals who are quite tall, and over-estimates in Turner syndrome where short stature is a hallmark.

We previously studied a population of healthy subjects with Turner syndrome and found that the prevalence of “abnormal” Z-scores was significantly increased. In fact, the number of subjects with aortic root and ascending aortic Z-scores above the normal range (i.e., greater than 2) was 17% and 22% higher

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when compared to a healthy general female population [Lopez et al., 2008]. This is an important observation because the overestimation of aortic size has the potential to socially stigmatize and “medicalize” girls and women living with Turner syndrome. Overestimation of aortic size in Turner syndrome could lead to inappropriate treatment as well. Therefore, we aim to establish standard values for the aortic size using a large group of healthy girls and women with Turner syndrome who had no evidence of aortic disease.

## METHODS

### Study Population

The protocol was approved by the Institutional Review Board at Oregon Health & Sciences University. The study population consisted of 481 subjects with Turner syndrome who underwent focused echocardiograms at the annual meetings of the Turner Syndrome Society of the United States from 2003 through 2013 as part of the ongoing Turner Syndrome Healthy Heart Project. No subjects had any additional genetic abnormalities. Written consent was obtained from all subjects or their legal guardians. A written assent was obtained from children capable of reading the form. Subjects included in the study were healthy females with Turner syndrome that did not have a history of aortic dissection or heart disease requiring an operation or catheter intervention. Exclusion criteria included the presence of aortic valve stenosis (Doppler-determined aortic valve velocity greater than 2 m/sec), greater than trace aortic insufficiency, un-operated or structural congenital heart disease, those that had elective surgery because of a dilated aorta, or a history of aortic dissection.

### Patient Characteristics

Each individual with Turner syndrome or a legal guardian completed a standardized questionnaire regarding age, karyotype (45,X

versus non-45,X), heart disease, prior cardiac surgery, catheterization, history of hypertension, growth hormone therapy, thyroid disorders, thyroid hormone therapy, other medications and other medical problems including ear/hearing and renal/urologic defects.

### Echocardiographic Examination

All subjects underwent a focused two-dimensional echocardiogram with a Philips Sonos 5500 or IE 33 (Philips Medical Systems, Bothell, WA) ultrasound system. Height, weight and blood pressure (DINAMAP<sup>®</sup>, GE HealthCare) were measured and recorded. For subjects under 18 years of age, blood pressure percentiles were calculated as previously described [Roccella, 2004]. Body surface area was calculated by using the Haycock formula: Body surface area = (0.024265) X (height<sup>0.3964</sup>) X (weight<sup>0.5378</sup>) [Haycock et al., 1978]. All examinations were recorded digitally. Measurements were undertaken offline using a computer workstation (Siemens *syngo* Dynamics). All measurements were made according to a standard laboratory protocol using established techniques [Lopez et al., 2010]. These focused studies included: a) parasternal long axis to measure the diameters along the proximal aorta of the aortic annulus (ANN), aortic root (AR) at the level of the sinuses of Valsalva, sino-tubular junction (STJ) and ascending aorta (AAO); b) parasternal short axis to assess aortic valve morphology; c) suprasternal long axis to exclude coarctation and measure diameters along the aortic arch of the proximal transverse arch (PTA), distal transverse arch (DTA) and aortic isthmus (ISTH); and d) subcostal short axis to assess the abdominal aortic dimension at the level of the diaphragm in systole and the Doppler pattern (DAO). For any given structure, measurements were only made if unambiguous and clear views were available. For each of the eight levels measured 14–24% were excluded from the analysis because of poor image quality. (ANN 14%; AR 14%; STJ 16%; AAO 17%; PTA 16%; DTA 15%; ISTH 23%; and DAO 24%).

TABLE I. Demographic and Clinical Features Among All Subjects (N = 481)

Feature	Mean	SD	Median	IQR
Age (years)	27.7	16.5	25.3	27.4
Height (cm)	139.9	19.5	144.8	14.6
Weight (kg)	52.4	21.0	51.7	23.5
Body surface area (m <sup>2</sup> )	1.4	0.4	1.5	0.4
	Yes	%		
45,X karyotype	220	48.4		
Non-45,X karyotype	177	38.9		
Bicuspid aortic valve	121	25.2		
Hypertension <18 years of age	57	30.0		
Hypertension ≥18 years of age	41	14.1		
History of aortic coarctation repair	57	11.9		
History of previous cardiac surgery	71	14.8		
History of growth hormone therapy	297	62.0		
History of thyroid disorders	129	26.8		
History of hearing disorders	58	12.1		
History of renal or urologic disorders	42	8.7		

**TABLE II. Coefficients for Normative Equations Relating Echocardiographic Measurements and Body Surface Area (BSA), Mean Square Error (MSE), and Coefficient of Determination (R<sup>2</sup>)**

Measurement		Intercept	BSA	BSA <sup>2</sup>	MSE	R <sup>2</sup>
Aortic valve annulus	ANN	0.891	0.414	-0.081	0.007	0.383
Aortic root	AR	1.035	0.589	-0.129	0.009	0.427
Ascending aorta	AAO	0.942	0.593	-0.122	0.012	0.391
Sinotubular junction	STJ	0.895	0.586	-0.124	0.009	0.443
Proximal transverse aorta	PTA	0.881	0.539	-0.107	0.012	0.365
Distal transverse aorta	DTA	0.844	0.428	-0.072	0.012	0.338
Aortic isthmus	ISTH	0.895	0.279	-0.038	0.014	0.203
Descending aorta	DAO	0.676	0.503	-0.094	0.009	0.415

### Statistical Analysis

If a subject had multiple echocardiographic studies only the initial echocardiogram was analyzed. We evaluated the association between subject characteristics and each of the aortic size measurements via linear regression. We evaluated associations for characteristics individually and in combination via multiple linear regression models. In these models, the aortic size measures were square-root transformed to better meet the assumption of normality. Most characteristics were entered as binary predictors (as collected on the patient questionnaire); however, blood pressure was categorized as hypertensive for those under the age of 18 with percentile score >95 [Rocella, 2004], and for those over 18 with systolic blood pressure >140 mmHg as defined by the American Heart Association [Chobanian et al., 2003]. We examined which variables were significant in each regression model, and determined which characteristics were significantly associated at the 0.05 level with two or more of the aortic measurements.

We estimated equations following a procedure analogous to Pettersen et al. [2008]. We first applied a square root transformation to the aortic measurements. We then fit nonlinear regression models with transformed aortic measures as the dependent vari-

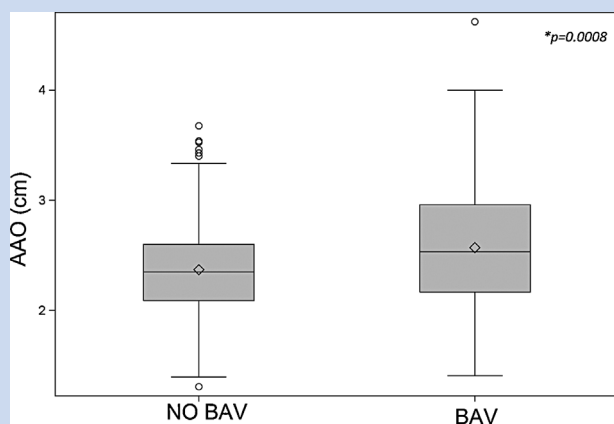
ables and BSA, BSA<sup>2</sup> as predictors. Models were fit for those without BAV because BAV was the only characteristic significantly associated with several of the aortic measurements in previous models. We then computed the expected (predicted) values for each individual from the estimated regression coefficients, which yielded results on the square-root scale, and then transformed back to the original scale for plotting. We plotted the normative values according to the following equation:

$$(expected\ y)^2 = (\hat{\beta}_0 + \hat{\beta}_1 \times BSA + \hat{\beta}_2 \times BSA^2)^2$$

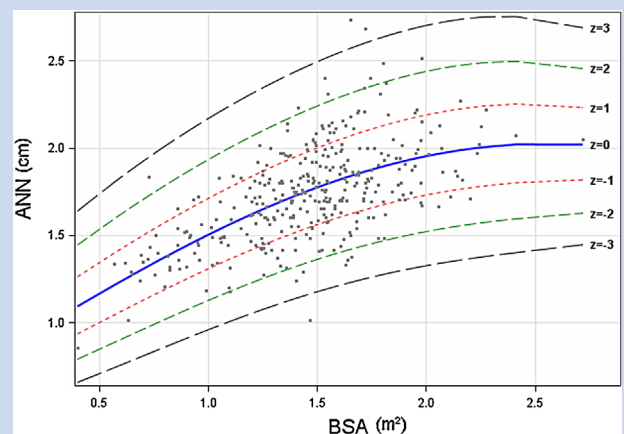
The regression equations for each aortic measurement, as well as Z-scores corresponding to 1, 2, and 3 standard deviations from the mean, were plotted.

### RESULTS

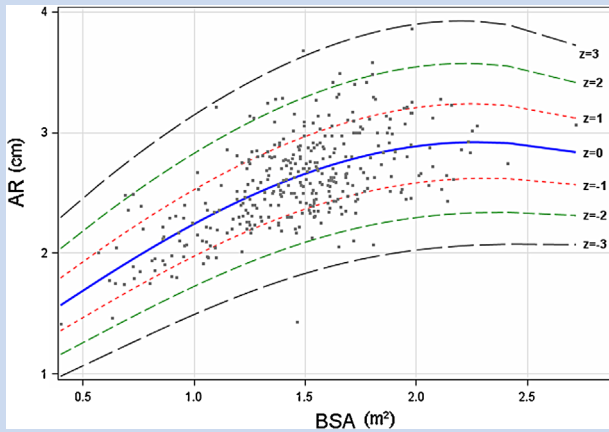
Four hundred eighty one individuals, ages 3–70 years, had at least one echocardiogram over the 10 year study period. 45,X occurred in 220 (48%) subjects. 57 (13%) subjects provided no response. The



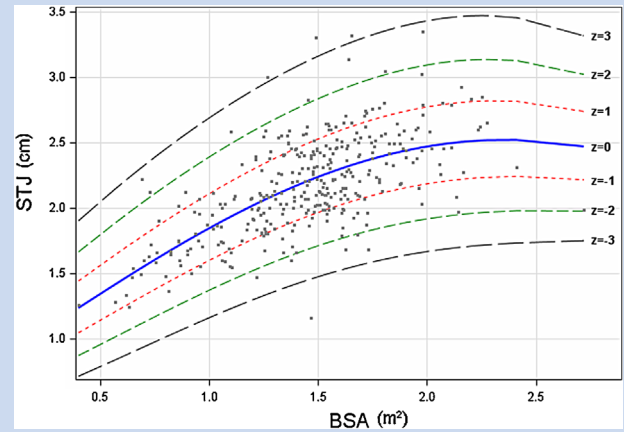
**FIG. 1. Box plot comparing size at the level of the ascending aorta [AAO] in Turner subjects without BAV versus patients with BAV\*.**



**FIG. 2. Normative scatter plot of the aortic annulus [ANN] versus BSA. Color figure can be viewed in the online issue, which is available at [http://onlinelibrary.wiley.com/journal/10.1002/\[ISSN\]1552-4833](http://onlinelibrary.wiley.com/journal/10.1002/[ISSN]1552-4833).**



**FIG. 3.** Normative scatter plot of the aortic root [AR] versus BSA. Color figure can be viewed in the online issue, which is available at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1552-4833](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833).



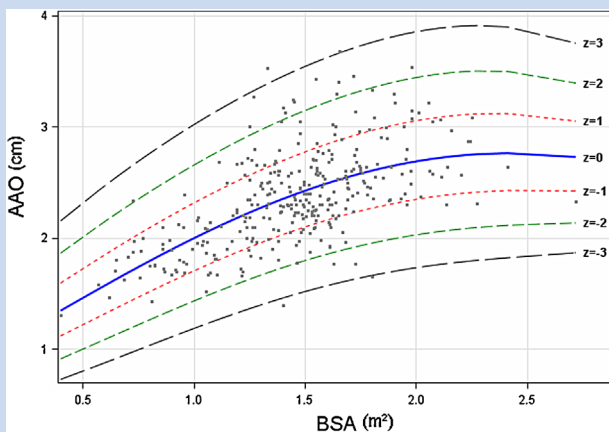
**FIG. 4.** Normative scatter plot of the sino-tubular junction [STJ] versus BSA. Color figure can be viewed in the online issue, which is available at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1552-4833](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833).

remaining 177 (39%) subjects were classified as “non-45,X karyotype”. These subjects represent a heterogeneous group that potentially includes deletions, translocations, mosaics, rings, duplications, or other configurations that were not specifically reported in the questionnaire. Bicuspid aortic valve occurred in 121 (25%) subjects, and 57 (12%) had a history of aortic coarctation operation. No subject had significant aortic valve stenosis as defined by Doppler flow velocity of 2 m/sec or greater, unoperated structural heart disease, significant congenital heart disease or history of aortic dissection.

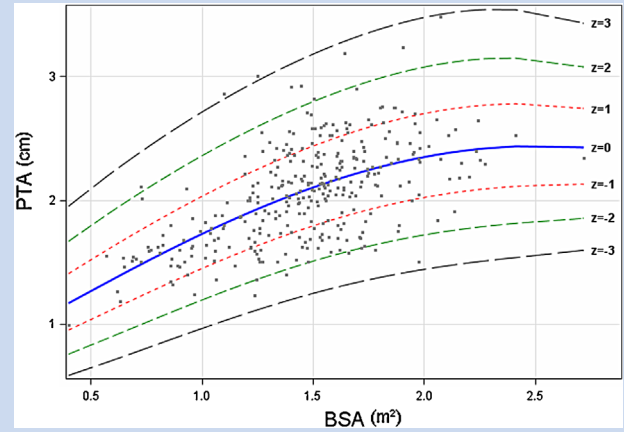
In the course of the 10 years of study, five subjects were excluded, three had spontaneous aortic dissections (two type A and one type B dissections), and two received prophylactic aortic root replacements

because of an enlarged aorta. The remaining 476 subjects comprised 12,765 subject-years free of spontaneous aortic dissection. These 3 (0.6%) cases of spontaneous aortic dissection represent an incidence of aortic dissection occurring in 24:100,000 subject years.

We employed the 15 variables listed in Table I to determine if any correlated with aortic dimensions. Results of the multivariate analysis are shown in Table II. In both univariate and multivariate linear regression models, only the presence of BAV was significantly associated with increased aortic size, Figure 1. The presence of BAV was found to be significant at four levels: aortic annulus ( $P=0.006$ ), aortic root ( $P<0.0001$ ), sino-tubular junction ( $P<0.0001$ ) and ascending aorta ( $P<0.0001$ ), after adjusting for other patient characteristics, such as history of cardiac surgery,



**FIG. 5.** Normative scatter plot of the ascending aorta [AAO] versus BSA. Color figure can be viewed in the online issue, which is available at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1552-4833](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833).



**FIG. 6.** Normative scatter plot of the proximal transverse aorta [PTA] versus BSA. Color figure can be viewed in the online issue, which is available at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1552-4833](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833).



