RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Aortic Dimensions in Turner Syndrome

Emilio Quezada,[1]* Jodi Lapidus,[2] Robin Shaughnessy,[1] Zunqiu Chen,[2] and Michael Silberbach[1]

[1]Department of Pediatrics, Division of Pediatric Cardiology, Oregon Health & Sciences University, Portland, Oregon

[2]Department of Public Health & Preventive Medicine, Oregon Health & Sciences University, Portland, Oregon

Manuscript Received: 7 November 2014; Manuscript Accepted: 3 June 2015

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

How to Cite this Article:
Quezada E, Lapidus J, Shaughnessy R, Chen Z, Silberbach M. 2015. Aortic dimensions in turner syndrome.
Am J Med Genet Part A 9999:1–6.

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.

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

Grant sponsor: Turner Syndrome Society of the United States; Grant sponsor: Philips Diagnostic Systems; Grant sponsor: Oregon Clinical and Translational Research Institute; Grant sponsor: National Center for Research Resources, a component of the National Institute of Health and NIH Roadmap for Medical Research; Grant number: UL1 RR024140.

*Correspondence to:
Emilio Quezada, M.D., Department of Pediatrics, Division of Pediatric Cardiology, Oregon Health & Science University, 707 SW Gaines Street, CDRC-P, Portland, OR 97239.
E-mail: emilioquezada@ufm.edu

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2015
DOI 10.1002/ajmg.a.37208

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 ®, 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$^{0.3964}$) X (weight$^{0.5378}$) [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^2)	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^2)

Measurement		Intercept	BSA	BSA^2	MSE	R^2
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 [Roccella, 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 variables and BSA, BSA^2 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:

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

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

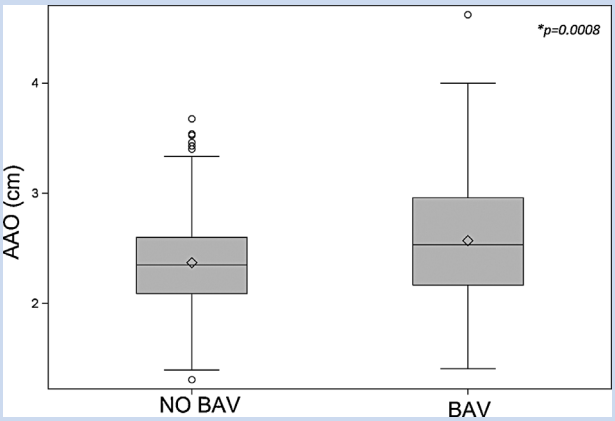

FIG. 1. Box plot comparing size at the level of the ascending aorta (AAO) in Turner subjects without BAV versus patients with BAV*.

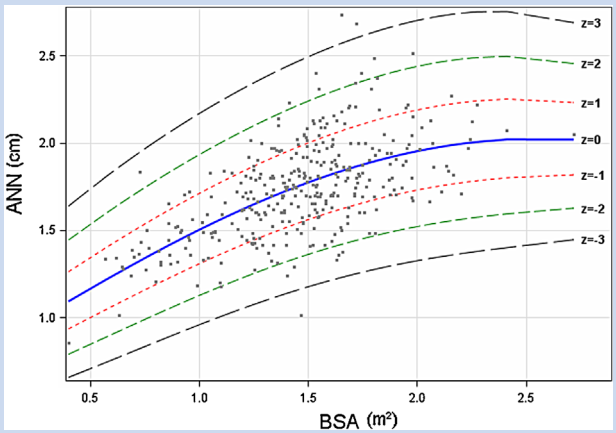

FIG. 2. Normative scatter plot of the aortic annulus (ANN) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

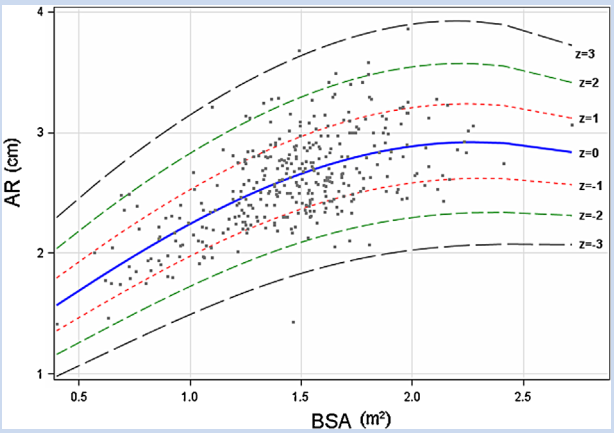

FIG. 3. Normative scatter plot of the aortic root (AR) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

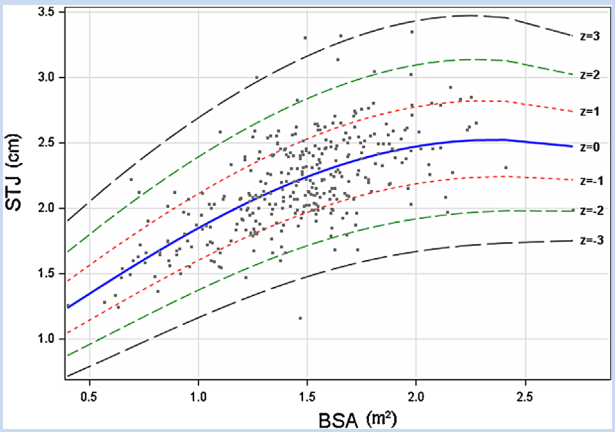

FIG. 4. Normative scatter plot of the sino-tubular junction (STJ) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

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,

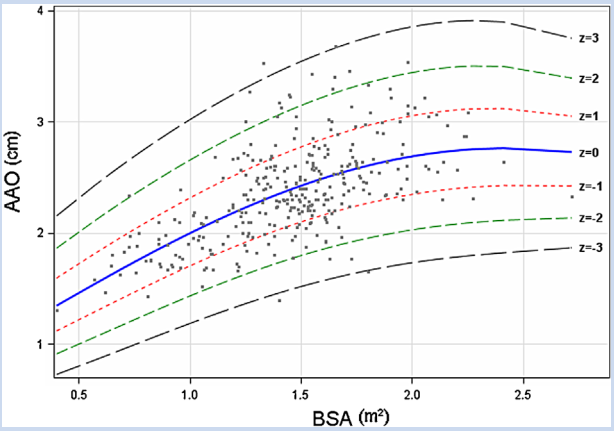

FIG. 5. Normative scatter plot of the ascending aorta (AAO) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

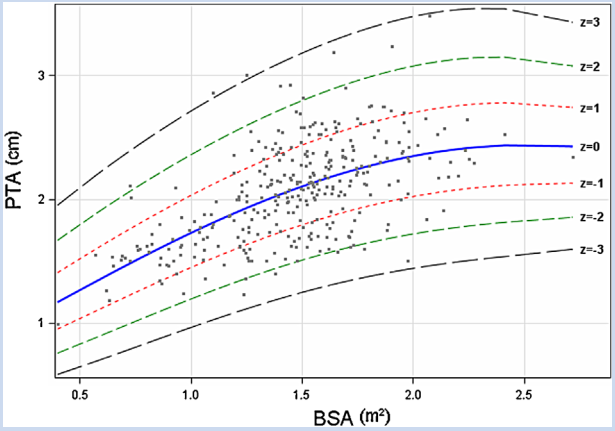

FIG. 6. Normative scatter plot of the proximal transverse aorta (PTA) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

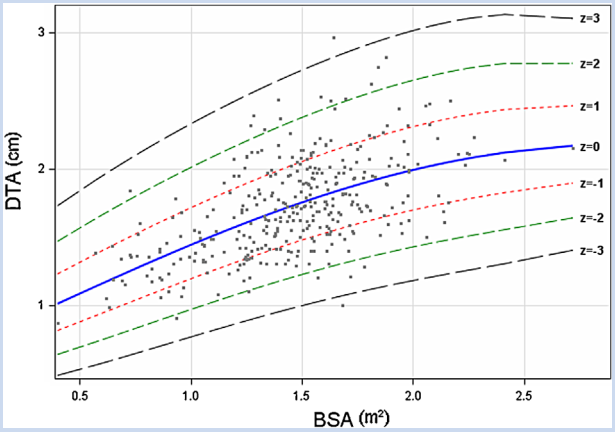

FIG. 7. Normative scatter plot of the distal transverse aorta (DTA) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

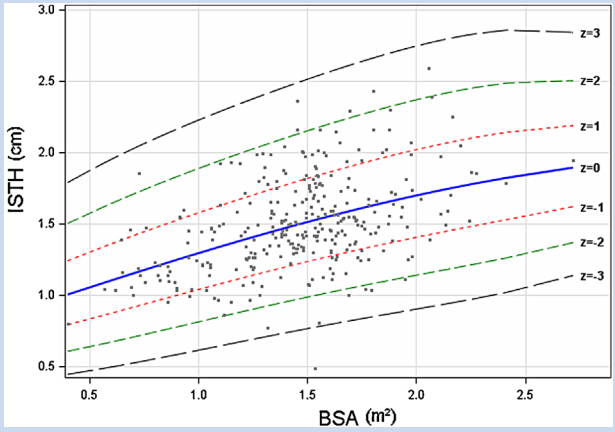

FIG. 8. Normative scatter plot of the aortic isthmus (ISTH) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

hypertension, and renal or urologic disorders. Therefore, values for aortic dimensions were calculated after excluding those with BAV. Figures 2–9 show scatter plots of each subject for a given aortic level compared to BSA. Superimposed are solid lines that represent the estimated regression equation ($Z = 0$). Dashed lines represent the different Z-score values ($Z = \pm 1, \pm 2, \pm 3$) above and below the regression equation.

DISCUSSION

Cardiovascular malformations occur in up to 50% of those affected by Turner syndrome, most commonly aortic diseases: bicuspid aortic valve, aortic stenosis, and aortic coarctation [Sybert, 1998b]. In our study 48% had monosomy X karyotype, 25% BAV and 12% history of aortic coarctation operation, prevalences similar to what Sybert previously observed in a population-based study [Sybert, 1998a]. Furthermore, Gravholt et al. studied a comprehensive Danish registry and reported that aortic dissection occurs in approximately 36:100,000 subject years, six times more common than in the Danish general population [Gravholt et al., 2006]. Among our study cohort we recorded 3 (0.6%) spontaneous aortic dissections in subjects who were ultimately excluded from the normative data calculations. Therefore, in the present study we observed a spontaneous dissection rate of 24:100,000 subject years which is a lower incidence, but comparable to the Danish registry study.

The question of how to compare dimensions of an organ in a growing and aging population is an important one. The aortic size index (ascending aortic diameter/body surface area, ASI) is useful in adult populations where body size is relatively constant [Davies et al., 2006; Carlson et al., 2012]. Furthermore ASI $>2.5\,cm/m^2$ appears to be predictive of aortic dissection risk in adults with Turner syndrome [Carlson et al., 2012]. However, in our healthy subjects who were between the ages 2 and ~15 years of age we found the aortic size index commonly to be $>2.5\,cm/m^2$. It appears that children with Turner syndrome "grow into" their relatively large aortas. Given our finding that aortic size index is strongly age-dependent under ~15 years, we believe that Turner syndrome specific reference curves, which are solely BSA-based should be employed.

Because of the significant risk of aortic dissection in Turner syndrome, even in those without congenital heart disease [Carlson and Silberbach, 2007], longitudinal monitoring of aortic growth is recommended [Bondy, 2007]. Here we performed a large cross-sectional study of healthy subjects with Turner syndrome in order to provide a Turner syndrome-based reference of aortic dimensions that can serve as a tool for caregivers. Future studies based on the longitudinal data available from this same cohort will allow us to characterize the growth of the aorta in Turner syndrome over time.

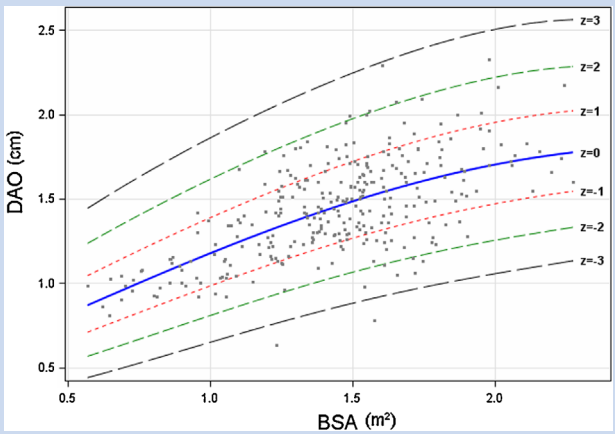

FIG. 9. Normative scatter plot of the descending aorta (DAO) versus BSA. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552–4833.

The information presented here should decrease the bias introduced by making comparisons with a taller and larger non-Turner reference population. Clinical management guidelines for a dilated aorta in Turner syndrome have not been rigorously established. In our practice an ascending aorta Z-score value >3 or an incremental change of >1 for those with baseline Z-score >2 are treated.

There are some limitations to our study. The acquisition of quality echocardiographic images in girls and women with Turner syndrome is particularly challenging. Poor acoustic penetration introduces variability in the measurement of relatively small intrathoracic structures. In this regard, we noted that coefficient of determination (R^2) values are lower in our study than in other studies of the aorta in other normal populations [Pettersen et al., 2008]. Cardiac MRI provides excellent image quality in Turner syndrome and has been recommended for the diagnosis of cardiac disease in these patients [Matura et al., 2007]. However, MRI studies are expensive and carry additional risk to perform in patients under 12 years of age who frequently require deep sedation. Furthermore, expertise in performing and interpreting cardiac MRI is often only available in large centers. Thus, it is important to make available echocardiography-based Turner specific reference values because echocardiography-based decisions remain the standard of care at most institutions.

In conclusion, this work offers clinicians caring for girls and women with Turner syndrome a useful tool for the management of their cardiovascular health. Furthermore, because substantial evidence now exists indicating that Turner syndrome includes a life-threatening aortopathy [Ostberg et al., 2005] and lifelong monitoring of aortic size is recommended [Bondy, 2007], more and more children who live with Turner syndrome have echocardiograms performed. Overestimating aortic size based on non-Turner normative data fosters anxiety among those affected and their families and may lead to unnecessary medical treatment. Our work allows clinicians to compare an individual patient's aorta to a healthy Turner syndrome population. We predict that Z- score values generated by this tool will be lower overall. Consequently more children are likely to be found to have aortic sizes within the normal range. Since aortic dissection is very rare and only is expected to occur with Z-scores far greater than +3, the possibility of missing individuals at risk is very low.

ACKNOWLEDGMENTS

Thuan Nguyen for additional statistical support, Whitney Bodine, Virginia Peterson for logistical support, Sharon Duffy, and Krista Bever for technical assistance.

REFERENCES

Bondy CA. 2007. Care of girls and women with turner syndrome: A guideline of the turner syndrome study group. J Clin Endocrinol Metab 92:10–25.

Carlson M, Airhart N, Lopez L, Silberbach M. 2012. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: Report of the international turner syndrome aortic dissection registry. Circulation 126:2220–2226.

Carlson M, Silberbach M. 2007. Dissection of the aorta in Turner syndrome: two cases and review of 85 cases in the literature. J Med Genet 44:745–749.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. 2003. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 42:1206–1252.

Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, Coe MP, Kopf GS, Elefteriades JA. 2006. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg 81:169–177.

Eagle KA. 2009. Rationale and design of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). Am Heart J 157:319–326.

Gravholt CH, Landin-Wilhelmsen K, Stochholm K, Hjerrild BE, Ledet T, Djurhuus CB, Sylven L, Baandrup U, Kristensen BO, Christiansen JS. 2006. Clinical and epidemiological description of aortic dissection in Turner's syndrome. Cardiol Young 16:430–436.

Haycock GB, Schwartz GJ, Wisotsky DH. 1978. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. J Pediatr 93:62–66.

Lopez L, Arheart KL, Colan SD, Stein NS, Lopez-Mitnik G, Lin AE, Reller MD, Ventura R, Silberbach M. 2008. Turner syndrome is an independent risk factor for aortic dilation in the young. Pediatrics 121:1622–1627.

Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, Lai WW, Geva T. 2010. Recommendations for quantification methods during the performance of a pediatric echocardiogram: A report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 23:465–495.

Matura LA, Ho VB, Rosing DR, Bondy CA. 2007. Aortic dilatation and dissection in Turner syndrome. Circulation 116:1663–1670.

Ostberg JE, Donald AE, Halcox JP, Storry C, McCarthy C, Conway GS. 2005. Vasculopathy in Turner syndrome: Arterial dilatation and intimal thickening without endothelial dysfunction. J Clin Endocrinol Metab 90:5161–5166.

Pettersen MD, Du W, Skeens ME, Humes RA. 2008. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: An echocardiographic study. J Am Soc Echocardiogr 21:922–934.

Roccella E. 2004. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114:555–576.

Sluysmans T, Colan SD. 2005. Theoretical and empirical derivation of cardiovascular allometric relationships in children. J Appl Physiol 99:445–457.

Sybert VP. 1998a. Cardiovascular malformations and complications in Turner syndrome. Pediatrics 101:E11.

Sybert VP. 1998b. Cardiovascular malformations and complications in Turner syndrome. Pediatrics 101:E11.