

# Further Delineation of Aortic Dilatation, Dissection, and Rupture in Patients With Turner Syndrome

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**ABSTRACT.** *Objective.* Although cardiovascular malformations (CVMs) are well-recognized congenital anomalies in Turner syndrome, aortic dilatation and dissection are less common and less familiar. Most of the relevant literature is limited to single cases reports or small series. We sought to increase the information available about the frequency and characteristics of aortic dilatation in patients with Turner syndrome.

*Design.* A 1-page survey of cardiac abnormalities, including aortic dilatation, was mailed to ~1000 (1040 verified) members of the Turner Syndrome Society as an enclosure in the June 1997 newsletter. We also conducted a literature review.

*Participants.* A total of 245 patients or families of patient members of the Turner Syndrome Society responded to the survey (~24% response rate).

*Results.* A CVM was reported in 120 of 232 (52%) respondents to this questionnaire. Obstructive lesions of the left side of the heart predominated and included bicuspid aortic valve (38%) and coarctation (41%).

Aortic dilatation was reported in at least 15 of 237 respondents (6.3%; 95% confidence interval: 3.6%-10.3%); 2 of 15 (13%) had dissection. Twelve of 15 (80%) patients had an associated risk factor for aortic dilatation such as a CVM or hypertension. The 3 (20%) patients who did not have a CVM or hypertension were all younger than 21 years. In the entire group with aortic dilatation, 10 of 15 (67%) patients were younger than 21 years. All patients with aortic dilatation had involvement of the ascending aorta, and 2 had additional involvement of the descending aorta distal to a repaired coarctation.

An update of the literature revealed 68 patients with aortic dilatation, dissection, or rupture. An associated CVM or hypertension was reported in 53 of 59 (90%) informative patients. At least 6 (10%) had no predisposing risk factor (information was inadequate for 9 of 68 patients). The following patterns of aortic involvement were identified: ascending ± descending aorta with coarctation (14); ascending ± descending aorta without coarctation (39); descending aorta with coarctation (3); descending thoracic or abdominal aorta without coarctation (4); and unspecified (8). Dissection or rupture was reported in 42/68 (62%). Two reported patients died suddenly from aortic dissection in the third trimester of assisted pregnancy. At least 20 (29%) patients were younger than 21

years. One of the 6 (17%) patients with isolated aortic dilatation was in this younger group.

*Conclusions.* More information is needed about the frequency and natural history of aortic dilatation in Turner syndrome. This work contributes new patient data and increases the literature review. Despite the well-recognized limitations of self-reporting, this survey detected aortic dilatation with or without dissection in ~6% of patients with Turner syndrome. Although rare, this is a potentially catastrophic occurrence, warranting greater awareness among health professionals.

In this study and the literature, the vast majority of patients with aortic dilatation have an associated risk factor such as a CVM, typically bicuspid aortic valve or coarctation, or systemic hypertension. These patients represent a higher risk group that should be followed appropriately, usually under the direction of a cardiologist. Patients undergoing assisted pregnancy also should be evaluated closely.

It is generally accepted that at the time of diagnosis of Turner syndrome, all patients should have a complete cardiology evaluation including echocardiography. The small number of patients with aortic dilatation without a CVM, who would not be under the long-term care of a cardiologist, makes it prudent to screen all patients with Turner syndrome for this potentially lethal abnormality. The specific timing for this screening is controversial. Our recommendations for prospective imaging do not represent a rigid standard of care. *Pediatrics* 1998;102(1). URL: <http://www.pediatrics.org/cgi/content/full/102/1/e12>; *Turner syndrome, cardiovascular malformation, dysmorphic syndrome, aortic dilatation, aortic dissection.*

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ABBREVIATIONS. CVM, cardiovascular malformation; BAV, bicuspid aortic valve; AS, aortic stenosis; COA, coarctation; AR, aortic regurgitation; AV, aortic valve; ARD, aortic root dilatation; MVP, mitral valve prolapse; MVR, mitral valve regurgitation; PAPVR, partial anomalous pulmonary venous return.

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Cardiovascular malformations (CVMs), or congenital heart defects, are well-recognized anomalies in Turner syndrome, occurring in ~75% of fetuses and 35% of patients.<sup>1,2</sup> Most commonly observed are obstructive lesions of the left side of the heart, including bicuspid aortic valve (BAV), with or without aortic stenosis (AS), and coarctation (COA) of the aorta.<sup>1-3</sup>

Less familiar, and much less common, is aortic dilatation, which in some patients may lead to dissection, rupture, and death (Table 1).<sup>4-33</sup> The dilatation typically involves the root of the ascending aorta, occasionally extending through the aortic arch to the descending aorta, or at the site of previous COA repair. One study estimated a prevalence of aortic

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**TABLE 1.** Literature Reports of Aortic Dilation, Dissection, or Rupture in Turner Syndrome (N = 67)

Patient	Author	Age	CVM	Hypertension	Location of Dilation	Severity of Dilation	Surgery	Status
1	Salgado*	45	—	—	Desc aorta	Dissection	Attempted	Died
2	Anabtawi et al*	34	BAV, COA	Moderate	Distal to COA	Dissection	Attempted	Died
3	Kostich and Opitz*	35	BAV, AS, AR	—	Asc aorta	Dissection	Attempted	Died
4	Youker and Roe*	19	BAV, AS, AR, COA	Mild	Asc aorta	Dissection	Resection of COA and aneurysm, AV replacement	Alive
5	Strader et al*	15	BAV, COA	Moderate	Asc aorta	Dissection	—	Died
6	Lippe and Kogut*	4	COA	Moderate	Asc aorta	Dissection	—	Died
7	Lippe and Kogut*	20	—	Mild	Asc aorta	Dissection	—	Died
8	Jeresaty et al*	54	Pseudo-COA	Moderate	Asc aorta & distal to COA	Dissection	—	Alive
9	Wendel	32	Pseudo-COA, AS	Mild	Asc through desc aorta	Severe	—	Died
10	Guerin	17	Pseudo-COA, AS	—	Asc aorta	Dissection	Resection of aneurysm, AV commissurotomy	Alive
11	Miller	64	—	Moderate	Desc aorta	Dissection	—	Alive
12	Bargman et al	18	(AR)	—	Asc aorta	Severe	—	Alive
13	Edwards et al*	27	BAV	NS	Asc aorta	Dissection	—	Died
14	Asch*	8	BAV, AS, AR, pseudo-COA	—	Asc and desc aorta	Dissection	Resection of aneurysm	Alive
15	Lie*	37	BAV, AS, AR	Moderate	Asc and desc aorta	Dissection	—	Died
16	Slater et al*	40	BAV, AS	—	Asc aorta	Dissection	—	Died
17	Price and Wilson*	29	—	—	Asc and desc aorta	Dissection	—	Died
18	Price and Wilson*	38	(AR)	Mild	Asc aorta	Dissection	—	Died
19	Price and Wilson; Price et al*	30	NS	—	Asc aorta	Dissection	—	Died
20	Goldberg et al*	28	AS, AR	—	Asc aorta	Dissection	Repair of dissection, AV replacement	Alive
21	Lin et al	28	BAV, AS, AR	—	Asc aorta	Dissection	—	Died
22	Lin et al	19	COA, BAV, AS, AR	Mild	Asc aorta	Dissection	COA repair; repair of dissection, AV and root replacement	Alive
23	Lin et al	23	—	—	Sinus of Valsalva	Mild	—	Alive
24	Lin et al	24	BAV	Mild	Sinus of Valsalva	Moderate	—	Alive
25	Lin et al	14	BAV, AS, AR	—	Asc aorta	Mild	—	Alive
26	Lin et al	16	BAV, AR	—	Asc aorta	Mild	—	Alive
27–34 (8 pts)	Allen et al	NS (11–26)	BAV (4/8)	NS	Asc aorta	NS	NS	Alive
35	Boxer et al	NS	NS	NS	NS	NS	NS	NS
36	Hata	10	NS	NS	Asc aorta	Dissection	Attempted	Died
37	Hata	49	NS	NS	NS	Dissection	Attempted	Died
38	Mori	14	Pseudo-COA, BAV	+	Asc aorta	Moderate aneurysm	—	Alive
39	Price et al	39	—	NS	NS	Dissection	NS	Died
40	Price et al	38	—	NS	Arch and desc aorta	Dissection	NS	Died
41	Price et al	18	COA	NS	NS	Dissection	NS	Died
42	Martin	5	COA, AS	—	Site of COA repair	Mild	COA repair	Alive
43	Subramaniam	30	(AR)	+NS	Sinus of Valsalva aneurysm	Severe	Resection of aneurysm and AV replacement	Alive
44	Vesin and Chudanova	23	BAV, AR, MR	NS	Asc aorta and arch	Dissection	—	Alive
45	Dawson-Falk et al	NS	BAV	NS	Asc aorta	NS	NS	Alive
46	Dawson-Falk et al	NS	BAV, AS	NS	Asc aorta	NS	NS	Alive
47	Dawson-Falk et al	NS	—	NS	Asc aorta	NS	NS	Alive
48	Dawson-Falk et al	NS	—	NS	Asc aorta	NS	NS	Alive
49	Dawson-Falk et al	NS	—	NS	Asc aorta	NS	NS	Alive
50	Apostolopoulos	36	BAV, AS	—	Asc aorta and arch	Moderate	—	Alive
51	Cecchi	27	(AR)	Moderate	Asc aorta	Dissection	Resection of aneurysm, AV replacement	Alive
52	Ohuchi et al	27	COA, AS, AR	+	Asc aorta	—	Bypass graft of aneurysm, AV replacement	Alive

**TABLE 1.** Continued

Patient	Author	Age	CVM	Hypertension	Location of Dilation	Severity of Dilation	Surgery	Status
53	Ota et al	14	BAV, COA	Mild	Asc aorta	Dissection	Bypass graft asc to desc aorta; AV replacement	Died
54	Ota et al	18	COA	Mild	COA site desc aorta	Rupture of aneurysm	COA repair; redo COA repair; attempted aneurysm repair	Died
55	Pollak	43	BAV, AR, single LCA	"Labile"	Asc and desc aorta	Dissection	Resection of aneurysm, AV replacement	Alive
56	Rubin	19	—	—	Asc aorta	Dissection	—	Died
57	Lippe	34	—	Mild	Asc aorta	Dissection	—	Died
58	Akimoto	42	—	Mild	Desc aorta	Dissection	Repair of dissection	Alive
59	Kido et al	36	—	Moderate	Asc aorta	Dissection	—	Died
60	Bartlema	27	—	—	Desc aorta	Dissection	—	Alive
61	Cohara et al	25	BAV, AR	—	Asc aorta	Dissection	Resection of aneurysm, AV replacement	Alive
62	Hochberg	48	BAV	+Mild	Asc aorta	Dissection	—	Died
63	Imamura	19	COA, BAV, AS, AR	—	Asc aorta	Dissection	Balloon angioplasty of COA, resection of aneurysm, AV replacement	Alive
64	Kusaba	23	COA	Severe	Asc aorta, desc aorta	Severe	COA repair, resection of aneurysm	Alive
65	Buheitel et al	16	COA, AS	—	Asc aorta	Dissection	COA repair	Died
66	Bueheitel et al	19	AS	Severe	Asc and desc aorta	Dissection	Attempted	Died
67	Nagel	NS	—	+NS	Asc aorta	Dissection	—	Died
68	Nagel	NS	—	—	Asc aorta	Dissection	—	Died

\* As summarized in Lin et al.<sup>4</sup>

Abbreviations: Asc, ascending; Desc, descending; LCA, left coronary artery; NS, not stated.

dilation in 8.8%, although the patient ascertainment was derived from pediatric cardiology clinics, which may have overestimated the true frequency.<sup>4</sup> In Turner syndrome and the general population,<sup>34</sup> most patients with aortic dilation have an associated risk factor, such as a CVM (typically, BAV or COA of the aorta) or hypertension. However, a small number of patients have no apparent predisposing factor.<sup>4</sup> For this reason, it has been suggested that all patients with Turner syndrome be monitored prospectively for aortic dilation.<sup>4,9,35</sup>

The recent report from the Committee on Genetics of the American Academy of Pediatrics proposed a schema to guide pediatricians who care for children with Turner syndrome.<sup>35</sup> Subsequent published criticism was directed at the suggestion for the primary physician to: 1) order echocardiography before consultation with a pediatric cardiologist; 2) repeat the echocardiography in infancy, even if findings from the first were normal, annually between ages 1 and 5 years, biannually between ages 5 and 13 years, and annually or biannually between ages 13 and 21 years; and 3) require echocardiography annually if a cardiac anomaly is present and annually or biannually if a BAV is present.<sup>36-39</sup>

To provide more data about the frequency, patterns, severity, and natural history of aortic dilation in Turner syndrome, we conducted a survey of members of the Turner Syndrome Society and reviewed the literature.

## MATERIALS AND METHODS

### Participants

The study consisted of 245 patients who responded to a single-page, one-sided survey called "Heart Abnormalities in Turner

Syndrome." This was mailed to ~1000 (1040 verified) patient members of the Turner Syndrome Society as an enclosure in the June 1997 newsletter. Responses were collected during the subsequent 4 months. To encourage a high response rate, the survey was limited to 1 page. Some clinical information, eg, karyotype and noncardiac anomalies, was omitted for brevity.

The diagnosis of Turner syndrome in each patient had been established previously, and karyotype documentation was not sought. Participants were asked whether they had been evaluated for a CVM, aortic dilation, and hypertension. Information was requested about cardiology evaluations, echocardiography, overall clinical status, and cardiac and endocrinologic medications.

### Measurements

The self-reported absence of aortic dilation could not be verified because medical records were not requested at the time the survey was mailed. However, the 15 patients who reported aortic dilation were contacted by one of us (AEL) with at least three telephone calls and one written inquiry. Medical records were requested to analyze the magnitude (mild-moderate, severe, aneurysmal, dissection) and specific location (ascending or descending thoracic aorta, site of previous COA repair) of aortic dilation. In selected cases when medical records were available, aortic dilation was determined by comparing the measured dimension with published normative tables based on body surface area.<sup>40</sup>

The severity of aortic dilation was based on the cardiologist's description as noted in the clinic or echocardiography report. In general, the dilation was called mild if the aortic diameter exceeded the 98th percentile for body surface area by  $\leq 8$  mm. Severe dilation referred to cases associated with dissection or the need for surgical correction. Moderate dilation was used arbitrarily to describe patients in between these categories. In addition to defining the degree of dilation, attempts were made to determine whether the aortic diameter was measured at the sinus of Valsalva (where most of the unspecified aortic dimensions were made) or supraaortic ridge.<sup>40</sup>

## RESULTS

### Response to Survey

Of ~1000 patients with Turner syndrome or parents of patients who received the newsletter, there

were 245 respondents (24%). The surveys were completed by the adult patients themselves or parents of girls younger than 16 years. Physicians or other health professionals did not complete the questionnaires. Thirteen of the 15 (87%) patients who reported aortic dilation were contacted to verify their responses, and all 13 provided additional medical records. Two respondents could not be reached because of incomplete return addresses.

### Age and Outcome

The ages of 244/245 patient/family respondents were as follows: 86 (35%) were 10 years and younger, 65 (27%) were 11 through 20 years inclusive, 60 (25%) were 21 through 40 years, and 33 (14%) were 41 years and older. Thus, 38% were 21 years or older. This proportion of older patients is similar to the general patient membership (~1000) of the Turner Syndrome Society, of which one third are older than 21 years (L. Tesch, personal communication).

Because of the study design, deaths among former members could not be assessed. Two respondents reported knowing someone who had died from aortic dissection. No survey was completed by the parents or relative of a deceased patient.

### CVMs and Procedures

Table 2 lists the types and frequency of CVMs occurring in 112 of 232 (48%) respondents. In addition, 20 of the 112 with a CVM (18%) volunteered information (not specifically queried, thus underestimating the true frequency) about a surgical procedure. Eight of these 20 had aortic dilation, 3 of whom

**TABLE 2.** CVMs in Turner Syndrome (Based on 232 Respondents)

Not Present or Patient Not Sure	112 (48%)
Present	120 (52%)
BAV	
Isolated	23
AS	5
MVP	1
ASD	2
Total	31/120 (26%),with COA46/120 (38%)
COA	
Isolated	22
BAV	15
AS	3
MVP	2
VSD	1
PAPVR	1
BAV, PAPVR	2
BAV, VSD	1
BAV, VSD, MS	1
dextrocardia	1
Total	49/120 (41%)
AS	
Not stated if also BAV	4
MVP	16
With MR, AR	1
TVP	1
Total	18/120 (15%)
PAPVR	2
ASD	4
VSD	3
Not specified	1

Abbreviations: ASD, atrial septal defect; TVP, tricuspid valve prolapse; VSD, ventricular septal defect.

had related surgery of the aorta. Of 12 without aortic dilation, the operations included repair of COA of the aorta,<sup>9</sup> and ventricular septal defect, repair of partial anomalous pulmonary venous return, and coronary artery bypass graft (1 each). One patient reported balloon dilation angioplasty of COA, and 1 had had aortic valvuloplasty.

### Aortic Dilation and Dissection

#### Survey Patients

Of 245 total patients, 237 responded to the questions about aortic dilation and 173 of the 237 (73%) stated specifically that they did not believe that they had aortic dilation. Fifteen patients reported aortic dilation with or without dissection (Table 3). The frequency of aortic dilation can be calculated in several ways using assorted denominators. Excluding the 49 (21%) patients who reported that they had "not been checked for it by echocardiogram or catheterization," aortic dilation was reported in 15/188 (8.0%) of those who had been checked. Considering all respondents, 15/237 (6.3%; confidence interval: 3.6%-10.3%) had aortic dilation. At the very least, 15 of 1000 (1.5%) patient members of the Turner Syndrome Society who were sent the newsletter were affected. In 2 of 15 (13%) of patients with aortic dilation, the dilation was reported as severe and accompanied by dissection.

In most patients (12/15, 80%), a CVM also was present. Ten of these 12 (83%) patients had a type of CVM known to be a risk factor for aortic dilation,<sup>4</sup> ie, BAV or AV stenosis,<sup>6</sup> or COA, with or without BAV.<sup>4</sup> These 10 patients represent 12% of the 84 study patients who had BAV or COA. Patient 12 had partial anomalous pulmonary venous return, and patient 13 had mitral valve prolapse (MVP), CVMs not previously considered risk factors. The isolated aortic regurgitation (AR) in patient 3 was not counted as a CVM. This patient and 2 other survey patients with aortic dilation did not have a CVM or hypertension. Three patients reported mild hypertension, all of whom had a CVM as well.

All patients with aortic dilation had involvement of the ascending aorta, and 2 had additional involvement of the descending aorta distal to a repaired COA. Two patients described themselves as "resembling Marfan syndrome." Patient 8, with BAV and COA, reported that some physicians thought her appearance suggested Marfan syndrome. However, a recent genetic evaluation did not find sufficient evidence to support this impression. In addition to aortic dissection, patient 13 had MVP, with aortic and mitral valve regurgitation, and described herself as having a "connective tissue disorder like Marfan syndrome."

Ten of 15 (67%) patients with aortic dilation were younger than 21 years, 8 of whom had an associated CVM. Two of the 3 patients who had aortic dilation without a CVM or other risk factor were in this younger age group.

Thirteen patients who reported aortic dilation were asked whether they had been reported previously, and all replied they had not. It was not possi-

**TABLE 3.** New Patients With Turner Syndrome and Aortic Dilation (*n* = 15)

Patient	Age	Age at Dx	CVM	Hypertension	Location	Severity of Dilation*	Surgery	Status	Hormone
1	10	NS	BAV	—	Asc aorta	Mild*	—	Good	GH currently
2	10	5	BAV, AS, AR	—	Asc aorta	Moderate aneurysm*	Aortic valvotomy (2 mo)	Good	GH currently
3	11	11	(AR)	—	Asc aorta	Mild*	—	Good	GH currently
4	14	13	Pseudo-COA, AR, BAV	NS	Asc aorta	Mild*	—	Few problems	GH currently estrogen currently
5	15	14	COA	—	Asc aorta	Mild*	COA repair (3 wk)	Few problems	GH currently estrogen currently
6	17	NS	—	—	Asc aorta	Mild†	—	Good	GH in the past estrogen currently
7	18	NS	BAV, MVP	—	Asc aorta	Mild*	—	Good	GH in the past estrogen currently
8	19	?13	BAV, COA	Mild	Asc and desc aorta	Moderate*, aneurysm	COA repair (7 y); aneurysm repair (15 y)	Significant problems	GH in the past estrogen currently
9	18	4	COA	Mild	Asc and Desc aorta	Moderate*	COA repair (4 y); COA redo with bypass graft (12 y)	Good	GH in the past estrogen currently
10	20	16	AS	—	Asc aorta	Mild*	—	Good	GH in the past estrogen currently
11	22	17	—	—	Asc aorta	Mild*	—	Good	GH currently estrogen currently
12	22	12	PAPVR	—	Asc aorta	Moderate†	PAPVR repair (12 y)	Good	GH in the past estrogen currently
13	30	19	MVP, MR, AR	—	Asc aorta	Severe*, dissection "Marfan-like"	AV replacement and aortic graft (19 y); MV replacement (24 y)	Significant problems	GH currently estrogen currently
14	31	28	BAV	—	Asc aorta	Severe*, dissection	AV replacement and aortic graft (28 y)	Few problems	Estrogen currently
15	48	44	BAV	Mild	Asc aorta	Moderate*, aneurysm	CABG (45 y)	Few problems	—

\* Aortic dilation verified.

† Patient name and/or address not available, verification not possible.

Abbreviations: CABG, coronary artery bypass graft; GH, growth hormone; NS, not stated.

ble to verify their responses to ensure that no patient would be reported twice.

#### Literature Patients

Among 68 reported patients with aortic dilation, dissection, or rupture (Table 1), the following patterns of involvement of the aorta were identified: ascending ± descending aorta with COA (14); ascending ± descending aorta without COA (39); descending aorta with COA (3); descending thoracic or abdominal aorta without COA (4); and unspecified (8). Dissection or rupture was reported in 42/68 (62%).

Fifty-three of 59 (90%) informative patients had an associated CVM or some degree of hypertension. At least 6 (10%) had neither a CVM nor hypertension (information was inadequate for 9 of 68 patients).

Age was not available for 12/68 (18%). Twenty of 55 (36%) were younger than 21 years, 2 of whom had isolated aortic dilation.<sup>8,23</sup> Twenty-eight of these reported patients had died (42%).

Of 41 patients with aortic dissection, 2 died suddenly in the third trimester of pregnancies assisted by egg donation.<sup>33</sup> One patient had essential hypertension since childhood and had been treated with an unspecified antihypertensive. Before pregnancy, an echocardiogram was interpreted as showing a "mildly dilated aortic root." The second patient had neither a CVM nor hypertension. Neither patient had toxemia of pregnancy.

#### Miscellaneous Cardiac Problems

Among survey patients, miscellaneous nonstructural anomalies not listed in Table 2 included murmur (6), endocardial fibroelastosis (1), and "left ventricular hypertrophy" without specified CVM (1). Other vascular problems were early onset coronary artery disease necessitating bypass surgery (2) and cerebral stroke (1).

Hypertension was reported in 40 of 238 (17%) survey respondents. In 37 patients, the degree of hypertension was described as mild or moderate. In 3 patients, it was described as severe hypertension; none had aortic dilation.

#### Patient Management

Of 238 respondents, 47 (20%) had never been seen by a cardiologist. Three had been seen once by a cardiologist, but had not undergone echocardiography. Seventy-six (32%) had been seen once and had undergone electrocardiography at least once. One hundred twelve (47%) had been seen more than once and had undergone echocardiography at least twice.

#### DISCUSSION

That aortic dilation occurs in Turner syndrome is not disputed. What remains unanswered is its natural history and prevalence and, by implication, the extent of recommendations for follow-up. Despite its limitations, the results of this survey provide a con-

servative estimate of the frequency of aortic dilation in Turner syndrome. Surveys were completed by motivated patient members or parents of patients over a brief period (4 months). Telephone follow-up of all members might have increased the response rate but was not feasible. This survey provides one of the largest reported databases of cardiac abnormalities in Turner syndrome patients. The proportion of older patients (>21 years; 38%) is valuable because cardiac abnormalities have been studied less frequently in adults with Turner syndrome than in the pediatric age group.

The frequency and type of CVMs in this series (Table 2) were similar to what has been reported, ie, almost half had a CVM, typically a BAV and/or COA.<sup>1,3,9</sup> This similarity between self-reported CVM data and the literature provides some reassurance of the reliability of self-reporting. In this series, obstructive lesions of the left side of the heart predominated. There also appears to be an increase of MVP, which may be accompanied by mitral regurgitation, tricuspid valve prolapse, and AR.

### Aortic Root Dilation (ARD)

Multiple risk factors exist for aortic dilation and dissection, including CVMs (typically, BAV with or without AS, or COA) and systemic hypertension.<sup>34</sup> Isolated AR sometime is considered a risk factor, but it has not been established whether this is cause or effect. For this study, isolated AR was not considered a risk factor. The vast majority of Turner syndrome patients in this survey and the literature have an associated risk factor for dilation. Of concern, ARD not associated with a risk factor has been observed in a small number of patients in the literature (Table 1, 6/59, 10%) and the current survey (Table 3, 3/15, 20%).

In the published criticism of the American Academy of Pediatrics recommendations, several centers stated that they “had not encountered a child with Turner syndrome with aortic dissection” or performed aortic root or ascending aorta replacements.<sup>37</sup> Awareness about aortic dilation in Turner syndrome may be related to the age of the patients followed. Among patients younger than 21 years, aortic dilation without a risk factor was observed in only 3 of 15 surveyed and 1 of 67 patients reported in the literature (Table 1).

Of interest, this survey also detected 2 women (29 and 45 years of age) with coronary artery disease of sufficient severity to require bypass surgery. This may reflect an earlier onset of atherosclerosis in some Turner syndrome patients.

### Study Strengths and Limitations

The greatest strength of this survey was the response of almost 250 patients, which included a large number of older Turner syndrome patients. Although this represents approximately one fourth of the entire Turner Syndrome Society patient readership, this database represents the largest published series of older Turner syndrome patients and one of the largest reports of cardiac anomalies of all age

groups. The current literature review more than triples what was reported in 1986.<sup>4</sup>

A limitation of this study, and self-reporting surveys in general, is possible ascertainment bias and inaccuracy. One cannot predict, however, whether the bias is one of over- or underestimation of aortic dilation. It might be assumed that the most severely affected patients are more likely to report their aortic abnormality, leading to an inflated frequency. Somewhat reassuring is that the 13 (of 15 total) patients who reported aortic dilation and who consented to medical record review were verified as having it in the manner they reported.

Severely affected patients may be underrepresented because of disability. Another source of underascertainment was the inability to identify deaths attributable to aortic dilation, dissection, and rupture. We are aware anecdotally of approximately 5 patients who died of dissection, but who have not been reported previously. Because these patients are deceased, they are not tabulated in this survey. Furthermore, aortic enlargement may be underestimated because of inconsistent prospective or inadequate echocardiography, especially among older Turner syndrome patients. Indeed, 20% had never had a cardiology consultation with echocardiography. Another potential source of underascertainment would be those patients with mild-moderate aortic dilation that was not communicated by the cardiologist to the patient/parent, or was misunderstood. At the very least, a crude (and probably conservative) prevalence of aortic dilation or dissection was calculated as 15 of ~1000 (1.5%) Turner Syndrome Society members. One could argue that this figure does not differ from the general population if one defines an enlarged aorta as exceeding the 98th percentile. However, aortic aneurysm and dissection in women in the general population, especially younger women, are extremely rare, and what was found in this Turner syndrome population deviates markedly from the norm.

### Aortic Dilation in Pregnancy

It has been suggested that there is an increased risk of aortic dissection in pregnancy.<sup>41</sup> Three studies of the outcome of a small number of pregnant women with Turner syndrome did not report aortic dissection or rupture.<sup>42-44</sup> Nevertheless, a recommendation was made to screen for cardiac abnormalities, especially aortic dilation, in women with Turner syndrome who are participating in egg donor programs.<sup>45</sup> Subsequently, 2 pregnant patients who died of aortic dissection were described, 1 of whom underwent echocardiography before pregnancy that showed mild dilation.<sup>33</sup> Presumably, this patient did not undergo echocardiography during the early part of pregnancy. It is unproven whether such serial imaging studies would have detected an evolving dilation or whether progressive changes ever occur in Turner syndrome, as found in Marfan syndrome.<sup>39</sup>

Clearly, as more women with Turner syndrome contemplate pregnancy, it will become increasingly important to identify women with aortic dilation to prevent a catastrophic outcome. Those women with

a previous risk factor (CVM, hypertension) should be reevaluated thoroughly to determine the magnitude of dilation, if any. Those women without known risk factors also require attention, either as a first-time cardiology consultation or as follow-up to evaluations performed in childhood.

### Connective Tissue Abnormality in Turner Syndrome

Cystic medial necrosis similar to what is seen in aortic dissection in Marfan syndrome has been reported in Turner syndrome.<sup>4,11,13,16-18,20,23,25,32</sup> Furthermore, 2 of the patients in this survey with aortic dilation were described by their physicians as having features suggesting a connective tissue disease "like Marfan syndrome." This was disproved in patient 8. Nevertheless, the observations support the notion that aortic dilation in Turner syndrome may represent or be similar to an inherited disorder of connective tissue.<sup>4,9</sup> In addition to patients with thoracic aorta dilation, 1 patient had isolated abdominal aortic ectasia and dissection with no involvement of the ascending or descending thoracic aorta.<sup>29</sup> Because this patient had no predisposing atherosclerosis, an intrinsic weakening of the aorta was suggested.

Observations about the apparent friability of the aortic wall and hemorrhage prompted warnings about the operative risk for COA repair in Turner syndrome.<sup>46,47</sup> Balloon angioplasty for COA relief has been performed in 1 reported patient<sup>30</sup> and 1 patient in the current survey; its safety in patients with Turner syndrome probably should be studied more closely.

Increased awareness among health professionals is needed. Although patients with Turner syndrome may become symptomatic at the time dissection occurs, their chest pain and dyspnea at the time of presentation may be misinterpreted as a noncatastrophic condition such as gastroenteritis<sup>23</sup> or atelectasis.<sup>24</sup> Chest radiography and echocardiography usually are the initial testing modalities, but computed tomography and magnetic resonance imaging provide superior imaging for women who lack an adequate echocardiographic acoustic window.<sup>10,19</sup>

Inextricable from this discussion about aortic dilation is a plea for more information about the natural history of patients with Turner syndrome, especially in regards to cardiac morbidity and mortality. This present study provides more data about older patients, whom many pediatric cardiologists do not encounter. In a study of life expectancy and morbidity among 156 patients with Turner syndrome in the United Kingdom, aortic dissection was the cause of death in 4 patients. One patient had COA, but 3 did not have a CVM or hypertension (Table 1).<sup>13</sup>

Shortly after this study was submitted, a review of 244 women with karyotype-proven Turner syndrome was published in the electronic pages of *Pediatrics* (Sybert VP. Cardiovascular malformations and complications in Turner syndrome. *Pediatrics*, 1998;101(1) URL: <http://www.pediatrics.org/cgi/content/full/101/1/e11>). There were 3 (1.2%) patients with aortic dissection associated with trauma and previous COA repair, and chronic hypertension and obesity in 1 each. The frequency of aortic dilation

without dissection in that series was not reported. Because the risk for aortic dissection appeared to be small in the absence of structural cardiac malformations or hypertension, the author did not recommend serial echocardiography or magnetic resonance imaging. It was suggested that additional monitoring be individualized. The author emphasized the importance of a systematic longitudinal and cross-sectional evaluation of aortic dilation in Turner syndrome.

### RECOMMENDATIONS

Based on information available in the literature and on this survey, we propose the following recommendations for monitoring the cardiac status of patients with Turner syndrome:

1. At the time that Turner syndrome is diagnosed, all patients of any age should have a baseline cardiology evaluation, including echocardiography. In most cases, echocardiography should not be ordered as an isolated test, but only in the broader context of a careful clinical examination. Depending on the age of the patient and availability of medical care, this is optimally performed under the direction of a pediatric or adult cardiologist, who is usually best qualified to correlate clinical and diagnostic findings.
2. If the consultation detects a CVM or other cardiac abnormality, additional care should be directed by the cardiologist, as with any patient with a cardiac problem. This should occur in collaboration of variable degree with the primary physician. Monitoring for aortic dilation would be guided by the type of cardiac problem present. As noted, aortic dilation and dissection is more prevalent in patients with BAV and COA of the aorta.
3. If the initial evaluation done in early childhood does not show a CVM, the patient with Turner syndrome should have another cardiology evaluation and echocardiography to look for aortic dilation at some time during adolescence. At this time, the girl can be given an understanding of the need for additional care. This is a cautious recommendation, based on limited information, and does not necessarily represent a rigid standard of care. As noted previously, echocardiography should not be ordered as an isolated test, because of subtleties of interpretation. The accuracy of aortic measurement probably will vary with the experience of the echocardiography laboratory. This must be kept in mind because false-positive and false-negative results could have an adverse impact. Attention should be directed not only at the aortic dimension, but also to the development of AS (even if BAV had not been noted in the past), AR, and hypertension. If aortic enlargement is present, a cardiologist should monitor the situation and obtain additional echocardiograms based on the severity of the dilation present. Echocardiography may be supplemented by computed tomography or magnetic resonance imaging as needed.

4. Until the natural history of aortic dilation is delineated fully, prospective imaging is prudent for those patients without a risk factor (CVM, hypertension). If aortic dilation is not present on echocardiography performed in adolescence, another study should be repeated in the asymptomatic patient approximately every 3 to 5 years, to be repeated at a similar interval thereafter into adulthood. Again, the suggested timing should not be interpreted as a fixed schedule. Needless to say, when dilation is detected, the frequency of imaging studies should be increased appropriately.
5. For women who have spontaneous pregnancy or are undertaking assisted pregnancy, careful monitoring of the aortic dimension before and during pregnancy under the guidance of a cardiologist seems warranted.

In general, as more children with malformation syndromes grow into adulthood, adult specialists must become more aware of their special needs. This includes internists, adult cardiologists, reproductive endocrinologists, and obstetrician-gynecologists. Pediatricians and pediatric specialists should try to facilitate the transfer of care. Regardless of their current state of health, women with Turner syndrome should be advised to remain under general medical care. Patients with Turner syndrome with asymptomatic BAV, repaired AS or COA, or mild hypertension frequently drift from cardiology care when their overall health is good. The risk of aortic dilation mandates that they continue with follow-up.

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## Further Delineation of Aortic Dilation, Dissection, and Rupture in Patients With Turner Syndrome

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