

Making treatment decisions for those with congenital heart disease in Turner syndrome: The need for evidence-based medicine

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Abstract. Most therapeutic considerations with regard to cardiovascular disease are the same in Turner syndrome (TS) as in the general population with similar problems. However, precious little is known about the unique risks for aortic root enlargement and dissection in TS that would potentially alter treatment decisions. This article highlights the issues related to the medical, surgical and catheter-based approaches to the treatment of congenital heart disease in TS.

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Keywords: Turner syndrome; Cardiac malformation; Aortic dissection; Heart disease treatment

1. Introduction

There is little direct evidence to validate the notion that individuals with Turner syndrome should be treated differently than non-TS individuals with similar problems. On the other hand, in TS, a confluence of worrisome problems including congenital heart malformations, systemic hypertension and aortic root enlargement makes their situation unique. Unfortunately, definitive knowledge regarding the consequences of cardiovascular-related treatment decisions in TS is lacking. This brief article will highlight issues related to the medical, surgical and catheter-based approaches to the treatment of congenital heart disease in TS.

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2. Medical treatment: the issue of aortic root enlargement

The overall medical management of congenital heart disease is the same for those with TS as for those with a normal karyotype. An important exception involves treatment decisions regarding the small but significant risk for aortic enlargement leading to aortic dissection [1]. In patients with significant aortic root enlargement or those who have rapid increases in aortic diameters, the therapeutic choices of therapy are the same as in the non-TS population: beta adrenergic blockade [2], angiotensin converting enzyme inhibition [3] or angiotensin type-1 (AT1) receptor blockade [4]. However, because the norms for evaluating aortic size are based on body size, and those with TS have short stature, the definition of what constitutes significant aortic root enlargement in TS is problematic. Furthermore, whether any of these treatments significantly alter the risk for aortic dissection in TS is unknown. The demonstration of TS vasculopathy by Ostberg et al. [5], presented in another chapter, is the best data, thus far to support the notion that TS individuals have an intrinsic abnormality of the blood vessels wall that may make them more susceptible to significant aortic root enlargement. The problem here is that statistical tools may not adequately control for the well-established risk factors for aortic root enlargement such as bicuspid aortic valve, coarctation of the aorta, systemic hypertension and the effects of aging which are well-known co-morbidities of Turner syndrome. Furthermore, an association of a small, non-progressive increase, in the aortic root size in TS individuals without other known risk factors and the occurrence of aortic root dissection is not established. The International Turner Syndrome Aortic Dissection Registry has been created to gather knowledge about risk factors (http://www.turner-syndrome-us.org/resource/resources_detail.cfm?id=193).

The nearly universally accepted model proposed by Roman et al. [6] for Marfan syndrome to judge the severity of aortic root enlargement by controlling for age and body surface area may not be suitable for assessment of aorta in Turner syndrome population. In Marfan syndrome, the decision to treat aortic enlargement is determined by the number of standard deviations (Z -score) between a Marfan individual's aortic diameter and the mean aortic dimension of a karyotypically normal, non-Marfan population. Thus, the normalized upper limit of aortic sinus of Valsalva diameter for the normal population is thought to be 2.1 cm/m². There is a general consensus that medical therapy in a Marfan patient or an individual with bicuspid aortic valve is warranted when the Z -score for the aortic root is >2 (with a family history of aortic dissection) and >3 (with no family history of dissection). The work of Shores et al. [2] showing that beta blocker therapy halts the progression of aortic root enlargement in Marfan syndrome has not been recapitulated in either the setting of bicuspid aortic valve or TS. In Marfan syndrome, to the extent that the aorta is enlarged independently of connective tissue disease (based on body size-alone the Marfan aorta should be larger), a comparison to non-Marfan norms (smaller body size) will tend to shift the resulting Z -score downward. In other words, the Marfan aorta may appear relatively small because people with Marfan syndrome are big. Accordingly, this will have the potential effect of less medical treatment of the Marfan population. By the same logic, the opposite will be true of the TS population. Namely, to the extent that the aorta is large independently of intrinsic pathology of the aorta, a comparison to 46,XX norms (large body size) will push the Z -score upward, resulting in more treatment of the

TS population. In other words the Turner aorta may look large because people with TS are small.

Since a connective tissue disease or other molecular marker of risk has not been directly demonstrated in TS, the possibility that over-treatment and “medicalization” of the TS population could occur must be considered. As part of the “Healthy Heart Project”, we attended the annual meeting of the Turner Syndrome Society of the United States (TSSUS) from 2003 through 2005. During those 3 years, 365 focused echocardiograms were performed on 288 TS individuals. Aortic root dimensions were adjusted for body surface area and Z-scores were calculated by comparison with 489 phenotypically normal 46,XX females. Twenty-one percent of the TS individuals we studied had Z-scores of 2 or greater. For those over 20 years of age, a value of 28 mm has been suggested to represent aortic root enlargement above the 95th percentile [7]. Using that criteria, of the 195 TS individuals in our study over the age of 19 years, 89 (46%) had aortic root diameters (sinus of Valvula) greater than 28 mm. These data suggest that the decision to treat TS patients with a Z-score >2 or adults with an aorta > 28 mm would result in one-fifth to up to one-half of those with TS being considered for medical therapy and restriction from athletic activity. Such aggressive medical management may or may not be warranted. Clearly, more study is needed. Perhaps, TS-specific norms should be established. Alternatively, a risk score might be devised that includes general population-based Z-scores and the presence of other risk factors. For the time being, it seems reasonable to consider treatment for those with TS who have body size-adjusted aortic root or ascending aortic Z-score >2 , who also demonstrate an increase in the Z-score on a subsequent imaging study.

3. Surgical therapy

Surgeons in the operating theatre anecdotally describe concerningly “thin-appearing” TS aortas. Furthermore, histopathological reports of the TS aneurysmal aorta typically demonstrate cystic medial necrosis which is a final common pathway for arterial injury and is seen commonly in the abnormal Marfan aorta and in aortic aneurysm associated with bicuspid valve aortopathy. While Turner outcomes and risks may well be different than the non-TS population, the current surgical standards for repairing congenital heart malformations are guided solely by lesion-specific and hemodynamic considerations. With further study, we may learn that the TS population has unique risks. For example, whether elongation of the thoracic aorta (ETA), a characteristic of the transverse aorta in TS [8] complicates aortic arch surgery needs to be studied. On the other hand, the so-called Ross operation that involves placing a pulmonary autograft in the aortic position has been performed on several occasions at our institution on TS individuals without complications. In general, abnormal lymphatic circulation is associated with persistent chylous effusions after thoracic surgery and pleural effusions are reported prenatally in TS [9]. However, a review of the available literature reveals no evidence that post-surgical pleural effusions are a significant problem in TS. Again, very little information is available and a careful assessment of this and other questions such as risk associated with the incidence of post-operative renal failure, hypertension, prolonged hospital stay and unforeseen complications is needed.

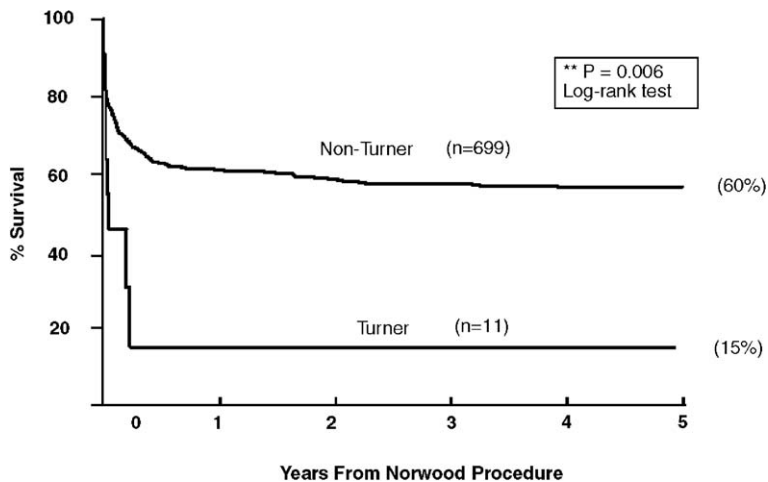


Fig. 1. Kaplan–Meier estimate of survival for 710 infants undergoing stage I Norwood procedure. (Data kindly provided by Dr. Tara Karamlou, MD, Congenital Heart Surgeon Society database.)

The National Congenital Heart Surgery Society (CHSS) database includes information from 24 centers and has compiled clinical features of 18 congenital heart categories including operative death, complications and length of stay, among others. Unfortunately, TS data is not uniformly available in the CHSS database. Outcome data for hypoplastic left heart syndrome (HLHS) in TS was reviewed. Kaplan–Meier survival curves were constructed for the 711 cases of HLHS. There were 11 instances of TS in this population (1.5%). Five-year survival among the non-TS group was 60% and was 15% among those with TS ($p < 0.006$, log-rank test, see Fig. 1). The vast majority of deaths in both groups occurred during the first 30 days after surgery. Whether outcomes for other more common congenital heart surgeries are worse in TS is unknown.

4. Catheter-based therapy

Balloon angioplasty for coarctation and aortic stenosis, common cardiac malformations in TS, are amenable to non-surgical approaches in the cardiac catheterization laboratory. Other catheter-based therapies including device closure of atrial septal defect or patent ductus arteriosus (in the setting of HLHS or interrupted aortic arch), coiling of arteriovenous malformations and aorta-to-pulmonary artery collateral vessels are also performed routinely in the general population. In the future, transcatheter placement of semi-lunar valves will be a reality. Whether any of these procedures are safe in TS is not known.

A recent case report describing fatal dissection of the descending aorta after implantation of a stent in a 19-year-old with TS [10] has elevated the concern that balloon angioplasty of the aorta may carry additional risks in TS. In that case, the mother of the TS individual died a year before with aortic dissection and was found to have fibrillin gene mutation consistent with Marfan syndrome. Other case reports indicate that balloon angioplasty in TS coarctation may be safe [11].

Table 1

Survey of the Congenital Cardiovascular Interventional Study Consortium (CCISC) for complications in catheterization laboratory in Turner syndrome (16 institutions)

	<i>n</i>	Complications
Total cases	49	2 (4.2%)
Coarctation angioplasty	31 (63%)	2 ^a (6.7%)
Native±stent (25)		
Post-op (6)		
Aortic valve angioplasty	5 (10.4%)	–
Coil	6 (12.5%)	–
AVM		
MAPCA		
Pulmonary artery angioplasty	4 (8.3%)	–
Patent ductus stent (HLHS)	1 (2.1%)	–

^a One case report of probable co-existing fibrillin mutation (patient died) [10]. One case small aneurysm repaired surgically. (With the kind assistance of Dr. Grant Burch, MD Doernbecher Children's Hospital Portland OR and Thomas J. Forbes, MD Children's Hospital of Michigan.)

Recognizing the profound lack of information regarding the safety of catheter interventions in TS, we conducted an email-based survey of physicians—members of the Congenital Cardiovascular Interventional Study Consortium (CCISC). The survey included Boston Children's Hospital and The Hospital for Sick Children in Toronto Canada who are not members of the CCISC. It is important to note that no medical records were directly reviewed and the results reported here are based only on our email survey. Sixteen institutions participated. When asked whether the diagnosis of TS was a relative contraindication to catheter intervention, most stated that they lacked sufficient data to make a decision, but that a concern for increased risk was sufficient to warrant a general reluctance to perform catheter-based interventions. Table 1 summarizes the results of 49 interventions that were undertaken in TS individuals. In 31 cases, balloon angioplasty of coarctation was performed. There were two complications, one (described in the above cited case report) resulted in death. The other complication involved the development of a small aneurysm of the descending aorta that was successfully surgically repaired. Thus, the overall complication rate in the survey was 4.2%. In all the other cases, the procedures were considered to be successful. These data suggest that catheter interventions for TS individuals, including balloon angioplasty for native coarctation, are safe and effective. Clearly, however, further study is needed to validate this preliminary impression.

5. Conclusion

The congenital heart surgeon's society is planning to collect more detailed information regarding the outcomes of TS individuals. Still, a long-term natural history study beginning in childhood that defines a subset of those with unique risks for aortic disease is necessary to determine what TS-specific cardiovascular treatment is necessary. In addition, a molecular marker that defines a subset of TS patients who are at more risk for aortic dissection would permit the medical community to make TS-specific treatment recommendations. This information is critical because at the present time it is unclear

how those with TS who have no known risk factors for aortic disease should be monitored, if any limitations of activity are required, or whether early and aggressive therapy for mild aortic root enlargement is warranted. In order to closely examine the clinical profile of TS individuals who have had aortic dissection, along with the Turner Syndrome Society of the United States, we have established the International Turner Syndrome Aortic Dissection Registry. We ask that you place a link from your website to our online dissection registry report form (http://www.turner-syndrome-us.org/resource/resources_detail.cfm?id=193). Alternatively, if someone that you know personally with TS has had aortic dissection, please urge them, their family members or loved ones, to report the event to us at the above URL, or by contacting Dr. Michael Silberbach, MD, email: silberbm@ohsu.edu, phone: 1-503-494-9899 or 1-800-882-9996 (press #3), or write International Turner Syndrome Aortic Dissection Registry, Mail code: CDRC-P, 3181 SW Sam Jackson Park Road, Oregon Health and Science University, Portland, OR 97201.

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