one context (everyday life or routine examinations) to another context (nonbeneficial research). As such, we must consider the equivalence of risks. Fourth, the assessment of the risks of interventions or procedures that do not offer the prospect of direct benefit must be independent of the inclusion of other interventions that offer the prospect of direct benefit in the same research protocol.[16] These recommendations have been endorsed by more than one federal panel and have recently been forwarded to the Secretary of Health and Human Services for incorporation into guidance and/or policy.[16,17]

The implementation of the above guidelines would be a reasonable first step toward a uniform interpretation of the definition of minimal risk. It is unlikely, and perhaps unnecessary, that these guidelines eliminate the documented variability in applying the definition to specific research procedures.[5] On the assumption that the federal definition of minimal risk will not change, we are left with the ambiguity introduced by the juxtaposition of the two different standards, that is, the "routine examination" and "everyday risks" standards. The concept of minimal risk was introduced by The National Commission to reflect the boundaries of appropriate parental decision-making about children's exposure to research risk.[14] We may gain some moral insight into parental decision-making by reflecting on the appropriateness of a child participating in different charitable activities. This insight, however, will reflect the degree to which such parental decisions are value-laden and not the degree to which we can use data about the risks of charitable participation to decide about the appropriateness of nonbeneficial research risks. Finally, the value-laden nature of this risk assessment will not be eliminated by simplifying the definition of minimal risk to include either the "routine examination" standard or the "everyday risks" standard, but not both.

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REFERENCES

1. Department of Health and Human Services. 45 CFR Part 46: Additional Protections for Children Involved as Subjects in Research. Federal Register 1983;48:9814.
2. Food and Drug Administration. 21 CFR Parts 50 and 56: Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products. Federal Register 2001;66:20589-600.
3. Kopelman LM. Minimal risk as an international ethical standard in research. J Med Philosophy 2004;29:351-78.
4. Kopelman LM, Murphy TF. Ethical concerns about federal approval of risky pediatric studies. Pediatrics 2004;113:1783-9.
5. Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? JAMA 2004;291:476-82.
6. Nelson RM, Ross LF. In defense of a single standard of research risk for all children. J Pediatr 2005;147:565-6.
7. Wendler D, Belsky L, Thompson KM, Emanuel EJ. Quantifying the federal minimal risk standard: implications for pediatric research without a prospect of direct benefit. JAMA 2005;294:826-32.
8. Wendler D, Emanuel EJ. What is a 'minor' increase over minimal risk? J Pediatr 2005;147:575-8.
9. Ross LF, Nelson RM. Pediatric research and the federal minimal risk standard. JAMA 2006;295:759.
10. Wendler D, Varma S. Minimal risk in pediatric research. J Pediatr 2006;149:855-61.
11. Department of Health and Human Services. 45 CFR Part 46: Federal Policy for the Protection of Human Services. Federal Register 1991;56:28003-23.
12. Food and Drug Administration. 21 CFR Parts 50 and 56. Federal Register 1991;56:28025-9.
13. Wendler D, Glantz L. A Standard for assessing the risks of pediatric research: pro and con. J Pediatr 2007;150:579-82.
14. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Research Involving Children: Report and Recommendations. Washington, DC: US Government Printing Office; 1977.
15. Ross LF. Do healthy children deserve greater protection in medical research? J Pediatr 2003;142:108-12.
16. Field MJ, Behrman RE, eds. Ethical Conduct of Clinical Research Involving Children. Washington, DC; The National Academies Press; 2004.
17. SACHRP Chair Letter to HHS Secretary Regarding Recommendations. Dated July 21, 2005. Accessed March 4, 2007. Available from: http://www.hhs.gov/ohrp/sachrp/sachrpltrtohhssec.html.

Focus on the Heart and Aorta in Turner Syndrome

In this issue of *The Journal*, Matura et al[1] examine the effect of growth hormone (GH) treatment on cardiac dimensions in females with Turner syndrome (TS). In concert with previously published data,[2] they provide further evidence that GH does not increase cardiac size or mass out of proportion to linear growth. This work should be viewed as a companion piece to a recent publication by the same group reporting that GH also has no effect on the size of the aorta.[3]

GH	Growth hormone
MRI	Magnetic resonance imaging
TGF	Transforming growth factor
TS	Turner syndrome

WHY SHOULD WE CARE ABOUT THIS NEGATIVE STUDY?

The most compelling reason to study the impact of an anabolic hormone on the myocardium and aorta itself is the growing recognition of a poorly understood aortopathy

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in individuals with TS that predisposes them to fatal aortic dissection.[4-6] Ostberg et al[7] have described a generalized vasculopathy in TS characterized by intimal-medial thickening of the blood vessel wall reminiscent of the histopathology of blood vessels in animal models of Marfan syndrome.[8] Indeed, recent studies by Dietz and colleagues at Johns Hopkins University have begun to elucidate the disease-causing role of growth factor signaling in seemingly diverse aortopathies, including Marfan syndrome and Loeys-Dietz syndrome. They have demonstrated that up-regulation of transforming growth factor (TGF)-β signaling induces a fibroproliferative process that weakens the aorta. These studies support the notion that other similar growth-causing agents, such as GH, could play a deleterious role in the pathogenesis of aortic disease in TS.[9,10] Because pharmacologic doses of GH are routinely administered at increasingly younger ages to girls with TS to treat short stature, we must be certain that we are first doing no harm. Matura et al provide some reassurance that GH is not the culprit in TS. Perhaps TGF-β signaling is involved; further research into this possibility is warranted.

HOW SIGNIFICANT IS THE PROBLEM OF AORTIC DISSECTION IN TS?

Our recent review of the literature on TS identified 85 cases of aortic dissection reported in 40 publications since 1960. The average patient age at aortic dissection was 31 years, and less than half of these patients survived the event.[11] Gravholt et al[4,6] used data from excellent Danish national registries to calculate a population-based incidence of 36:100,000 TS years (1.4% among individuals with TS), compared with 6:100,000 in the general Danish population. Other clinical series had suggested a similar frequency, although referral and case ascertainment may have introduced a bias toward overestimation.[4,5]

It is clear that the risk of aortic dissection is significantly lower in patients with TS compared with those with Marfan syndrome. However, the mean age of death from aortic dissection in women without TS is 68 years,[12] almost 4 decades later than in the population with TS. Concerned clinicians, individuals with TS, and the devastated families of victims of aortic dissection are correct to ask why dissection occurs preferentially in TS and to demand that the general medical community take notice of the problem. We, like others, have found that 90% of the cases reported with dissection had known risk factors for dissection: cardiac malformations (primarily bicuspid aortic valve or coarctation of the aorta), systemic hypertension, or both. The remaining 10% of cases that lacked a known risk factor simply may have been poorly documented. We suspect that it is more likely that TS itself independently contributes vulnerability, which lowers the threshold for this event.

CAN AORTIC DISSECTION IN TS BE PREVENTED?

In the clinical setting of Marfan syndrome, we can be confident that the enlarged aorta can be adequately monitored and appropriately managed because the natural history of aortic disease in Marfan syndrome has been extensively documented, the molecular underpinnings of the disease are becoming well understood, and there is a broad awareness of the problem in the medical community. Unfortunately, very little is known about the pattern of growth of the aorta in individuals with TS and the mechanism of aortic aneurysm formation. The risk of dissection in this population is not generally appreciated beyond the pediatric medical community.[13] Thus, well-established, evidence-based recommendations for monitoring and treatment of aortic disease in patients with TS are not currently available.

To define the clinical profile of individuals with TS who are at risk for aortic dissection, we have established the International Aortic Dissection Registry. Individuals with TS who have survived aortic dissection, as well as caregivers,

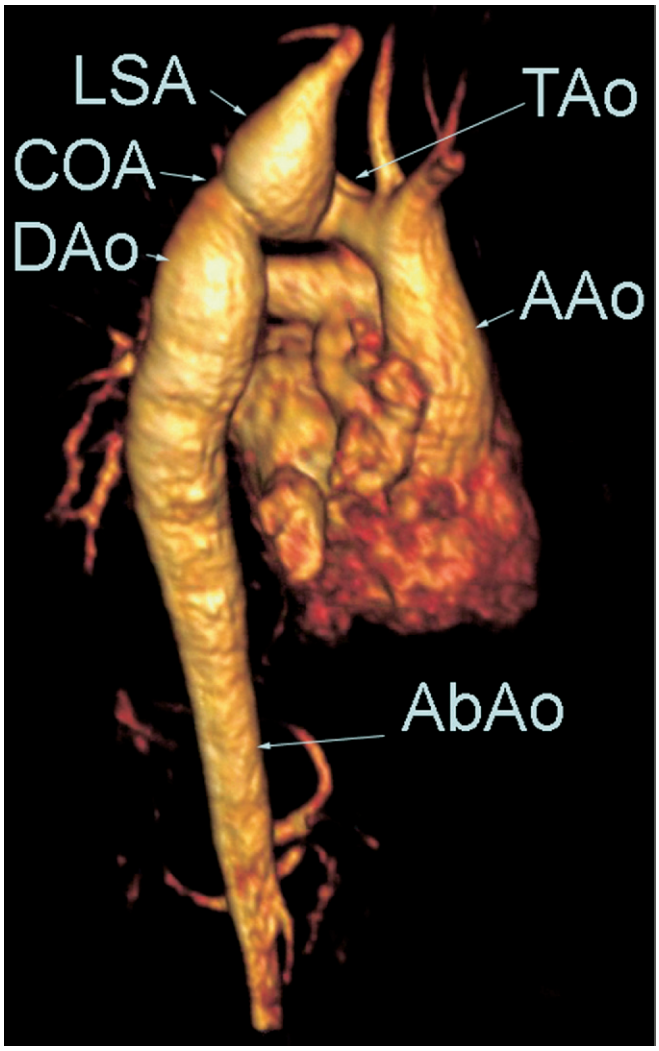

Figure. Gadolinium-enhanced MRI image of the thoracic and abdominal aorta in a 17-year-old female with TS. The ascending aorta (*AAo*) is dilated, and the transverse aorta (*Tao*) is elongated. There is a large aneurysm of the left subclavian artery (*LSA*). There is a mild aortic coarctation (*COA*) and the descending aorta (*DAo*) and the abdominal aorta (*AbAo*) is dilated. (Available in color at www.jpeds.com.)

Table. Cardiovascular screening and monitoring algorithm for girls and women with TS

Screening: All patients at time of diagnosis
- Evaluation by a cardiologist with expertise in congenital heart disease
- Comprehensive exam including blood pressure in all extremities
- All require clear imaging of heart, aortic valve, aortic arch, and pulmonary veins
  - Echocardiography is usually adequate for infants and young girls
  - MRI and echo for older girls and adults
  - Electrocardiogram

Monitoring: Follow-up depends on clinical situation
- For patients with apparently normal cardiovascular systems and age-appropriate blood pressure:
  - Reevaluation with imaging at timely occasions, e.g. at transition to adult clinic, before attempting pregnancy or with appearance of hypertension. Girls that have only had echocardiography should undergo MRI when old enough to cooperate with the procedure
  - Otherwise, imaging about every 5 to 10 years
- For patients with cardiovascular pathology, treatment and monitoring determined by cardiologist

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family members, or friends of a patient with TS who has suffered aortic dissection, are urged to contact the registry online at http://www.tssus.org/readweb.asp?wid=3092.

In lieu of direct evidence on which to base recommendations, the Cardiovascular Section of the Turner Syndrome National Institutes of Health Consensus Study Group was convened by Dr Caroline Bondy (the senior author of the paper by Matura et al) in April 2006 to establish guidelines for monitoring and managing aortic disease in patients with TS.[14] This document summarizes new information in the field, including the evidence of the superiority of cardiac magnetic resonance imaging (MRI) over echocardiography to visualize the transverse and descending aorta (Figure). The challenge of transitioning young women with TS to adult caregivers who are committed to the need for ongoing cardiovascular care is discussed. The Table outlines the algorithm for screening and monitoring for the progression of aortic disease proposed in the guideline. The notion that the aorta in patients with TS is enlarged even in the absence of the risk factors of cardiac malformation or systemic hypertension has led to the suggestion by the Consensus Group that the aorta in patients with TS be monitored (preferably by MRI) every 5 to 10 years.

As the pathophysiology and natural history of disease progression to aortic dissection in TS become better delineated, specific remedies may become available. In the meantime, clinicians must be content with making decisions based on imperfect evidence and the well-considered opinions of consensus groups. The tragic consequence of failure to identify the signs and symptoms of aortic dissection remains the most pressing issue. Primary pediatric caregivers, endocrinologists, and pediatric cardiologists need to educate adult caregivers regarding the potential for worsening aortic disease as girls with TS transition into their care. Emergency room physicians and first responders must be vigilant in their evaluation of complaints of chest, back, or abdominal pain; change in phonation (due to traction from the rapidly enlarging aorta on the recurrent laryngeal nerve); or weakness in 1 or both legs or arms, particularly if the complaint persists.

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REFERENCES

1. Matura LA, Sachdev V, Bakalov VK, Rosing DR, Bondy CA. Growth hormone treatment and left ventricular dimensions in Turner syndrome. J Pediatr 2007;150:587-91.
2. Sas TC, Cromme-Dijkhuis AH, de Muinck Keizer-Schrama SM, Stijnen T, van Teunenbroek A, Drop SL. The effects of long-term growth hormone treatment on cardiac left ventricular dimensions and blood pressure in girls with Turner's syndrome. J Pediatr 1999;135:470-6.
3. Bondy CA, Van PL, Bakalov VK, Ho VB. Growth hormone treatment and aortic dimensions in Turner syndrome. J Clin Endocrinol Metab 2006;91:1785-8.
4. Lin AE, Lippe B, Rosenfeld RG. Further delineation of aortic dilation, dissection, and rupture in patients with Turner syndrome. Pediatrics 1998;102:e12.
5. Sybert VP. Cardiovascular malformations and complications in Turner syndrome. Pediatrics 1998;101:e11.
6. Gravholt CH, Landin-Wilhelmsen K, Stochholm K, Hjerrild BE, Ledet T, Djurhuus CB, et al. Clinical and epidemiological description of aortic dissection in Turner's syndrome. Cardiol Young 2006;16:430-6.
7. Ostberg JE, Donald AE, Halcox JP, Storry C, McCarthy C, Conway GS. Vasculopathy in Turner syndrome: arterial dilatation and intimal thickening without endothelial dysfunction. J Clin Endocrinol Metab 2005;90:5161-6.
8. Pereira L, Andrikopoulos K, Tian J, Lee SY, Keene DR, Ono R, et al. Targeting of the gene encoding fibrillin-1 recapitulates the vascular aspect of Marfan syndrome. Nat Genet 1997;17:218-22.
9. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788-98.
10. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 2006;312:117-21.
11. Carlson M, Silberbach M. Dissection of the aorta in Turner syndrome: Two new cases and review of 85 cases in the literature. (Submitted to Pediatrics).
12. Meszaros I, Morocz J, Szlavi J, Schmidt J, Tornoci L, Nagy L, et al. Epidemiology and clinicopathology of aortic dissection. Chest 2000;117:1271-8.
13. Silberbach M. Making treatment decisions for those with congenital heart disease in Turner syndrome: the need for evidence-based medicine. International Congress Series 2006;1298:131-6. (Eds. Bondy CA, Gravholt C, Elsevier).
14. Bondy CA. Care of girls and women with turner syndrome: a guideline of the turner syndrome study group. J Clin Endocrinol Metab 2007;92:10-25.