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Original article

Increased aortic stiffness in prepubertal girls with Turner syndrome

Katya De Groote (MD)[a,*], Daniel Devos (MD)[b], Koen Van Herck (MD, PhD)[c,d], Daniel De Wolf (MD, PhD)[d], Saskia Van der Straaten (MD)[e], Ernst Rietzschel (MD, PhD)[f], Ann Raes (MD, PhD)[g], Kristof Vandekerckhove (MD)[d], Joseph Panzer (MD)[d], Hans De Wilde (MD)[d], Jean De Schepper (MD, PhD)[h]

[a] Pediatric Cardiology, Department of Pediatrics and Turner Clinic, Ghent University Hospital, Ghent, Belgium
[b] Cardiovascular Radiology, Department of Radiology and Turner Clinic, Ghent University Hospital, Ghent, Belgium
[c] Department of Public Health, Ghent University, Ghent, Belgium
[d] Pediatric Cardiology, Department of Pediatrics, Ghent University Hospital, Ghent, Belgium
[e] Pediatric Endocrinology, Department of Pediatrics, Ghent University Hospital, Ghent, Belgium
[f] Department of Cardiology, Ghent University Hospital and Ghent University, Ghent University Hospital, Ghent, Belgium
[g] Pediatric Nephrology, Department of Pediatrics and Safepedrug, Ghent University Hospital, Ghent, Belgium
[h] Pediatric Endocrinology, Department of Pediatrics and Turner Clinic, Ghent University Hospital, Ghent, Belgium

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ABSTRACT

Background: Aortic dilation and dissection contribute highly to the increased mortality of Turner syndrome (TS) but the exact pathophysiology is not completely understood.
Design: Prospective case – control study.
Methods: 15 prepubertal TS girls (median age 10.64, IQ 8.31–11.04) with a tricuspid (TAV, $n = 9$) or a bicuspid (BAV, $n = 6$) aortic valve, and 31 sex-, age-, and height-matched healthy controls underwent a cardiac and vascular ultrasound to evaluate aortic dimensions and elastic properties of the aortic wall.
Results: TS BAV had significantly larger ascending aortic diameters than controls for absolute diameter, 22.2 ± 5.1 mm vs. 18.6 ± 1.9 mm ($p = 0.014$) and z-score 1.7 ± 2.1 vs. 0.1 ± 0.7 ($p = 0.008$). Distensibility of the ascending aorta was lower in the TS than in controls (40.2×10^{-3} kPa^{-1}, IQ 31.3–56.2 vs. 62.9×10^{-3} kPa^{-1}, IQ 55.5–76.5, $p = 0.003$), both for TS TAV ($p = 0.014$) and BAV ($p = 0.005$). Stiffness index was higher in TS than in controls (5.26, IQ 3.34–5.26 vs. 3.23, IQ 2.55–3.24, $p = 0.005$), both for TS TAV ($p = 0.028$) and TS BAV ($p = 0.006$). Pulse wave velocity was not different between groups. There was no correlation between stiffness and z-score of the ascending aortic diameter.
Conclusions: In prepubertal TS girls, stiffness of the ascending aorta is increased in patients with a BAV and TAV while dilation of the ascending aorta is more frequent in BAV. This suggests an intrinsic aortic wall abnormality making all TS patients at increased risk for severe aortic complications although the risk is the highest for TS with BAV.

Introduction

Turner syndrome (TS) is a chromosomal disorder, occurring in approximately 1 per 2000 live born girls [1] and is typically associated with reduced final height and gonadal failure. Cardiovascular pathology is highly prevalent in TS patients, contributing to the high morbidity and mortality of the syndrome [2]. Structural congenital heart defects are present in 25–50% of TS patients; bicuspid aortic valve and coarctation of the aorta are the most common [3–6]. Additionally, progressive dilation of the ascending aorta is observed in 20–25% of TS patients. Although the prevalence appears to increase with age, abnormal aortic dimensions are present from childhood [7,8]. Hypertension, which affects one-fourth of the children [9] and up to half of the adults with TS [10], coarctation of the aorta, and bicuspid aortic valve are all associated with aortic dilation and dissection. However, dilation and dissection also occur in patients without those risk factors [11–13].

Aortic dilation was found to be inversely correlated with aortic distensibility in a group of TS patients of varying age and an intrinsic abnormal elasticity of the aortic wall has been suggested

* Corresponding author at: Ghent University Hospital, Pediatric Cardiology, 3K12D, De Pintelaan 185, 9000 Ghent, Belgium. Tel.: +32 9 332 24 60; fax: +32 39 332 38 56.
E-mail address: katya.degroote@uzgent.be (K. De Groote).

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as a predictive risk factor for aortic dilatation in TS [14]. In a group of TS patients aged 9–20 years, vasculopathy was observed as compared to obese and lean controls [15].

Since the abnormal aortic dimensions in TS might be the result of a generalized vasculopathy starting from childhood, we examined if abnormal rigidity of the aorta is present from a young age and if it is associated with an increased carotid artery diameter or intima-media thickness.

Therefore, the distensibility and stiffness of the ascending aorta and the whole aortic arch were investigated in young prepubertal TS girls, compared to normal controls matched for sex, age, and height.

Methods

Study population

Patients were recruited in the Pediatric Department of Ghent University Hospital, Belgium. Girls with TS confirmed on karyotype were eligible for the study if they were older than 6 years (to have full cooperation) and prior to puberty induction or spontaneous puberty (to avoid the effect of estrogen). The control group consisted of healthy girls without any medical history, who were matched for age and height.

The study protocol was approved by the ethical committee of Ghent University Hospital. All girls and their parents gave written informed consent.

All examinations were performed during a single visit to the pediatric cardiology department of Ghent University Hospital by a single experienced pediatric cardiologist (KDG).

Anthropometry

Body height was measured with a wall mounted stadiometer and body weight with an electronic scale. Height, weight, and body mass index (BMI) *z*-scores were calculated using Flemish reference growth data, and body surface area (BSA) according to Haycock's formula [16].

Blood pressure

Blood pressure was taken at the 4 limbs, with the patient at rest and in a supine position (Accutorr Plus, Datascope, Mahwah, NJ, USA with an appropriate pediatric cuff). Additionally, blood pressure was taken 3 times at the right arm during the ultrasound examination. The mean of these 3 measurements was used for statistics and the calculation of distensibility and stiffness index. In-office blood pressure was considered normal if below the 95th percentile for sex, age, and height [17]. For Turner girls, an additional 24-h blood pressure registration was performed (Tonoport V, Par Medzintechnik, Berlin, Germany) and analyzed using the normal values for sex and age described by Wuhl et al. [18]. Abnormal nocturnal dipping was defined as:

$$\left[\left(1-\frac{\text{systolic blood pressure during night time}}{\text{systolic blood pressure during day time}}\right)\times 100\right] < 10\%$$

Echocardiography

Echocardiography was performed with the patient in a supine position and with the use of a VIVID 7 ultrasound (GE Vingmed Ultrasound, Horten, Norway) equipped with a 3.5 MHz probe. Data were stored and used for offline analysis by one single observer (KDG) using EchoPAC version 110.1.0 software (GE Vingmed Ultrasound). All patients and controls underwent a complete ultrasound evaluation of the heart to exclude previously unknown pathology such as abnormal aortic valve morphology or aortic coarctation. For each parameter, measurements were performed on at least 3 cardiac cycles and averaged. Diameters of the aorta were measured from the parasternal long axis at the level of the aortic valve annulus, aortic root and ascending aorta at the level of the right pulmonary artery. The interventricular septum, posterior wall and internal diameters were measured on a parasternal short axis and used for calculation of fractional shortening and Devereux index. For each variable, *z*-scores were calculated according to the Sluysmans data [19]. For the aortic root and ascending aorta, *z*-score was calculated using our own previously reported Campens formula [20]. On the parasternal long axis, an M-mode image of the ascending aorta was recorded. Care was taken to place the aorta horizontally on the screen with the cursor perpendicular to the arterial wall at the level of the right pulmonary artery. On the M-mode recording, the diameter of the ascending aorta was measured from inner to inner surface during diastole and systole (Fig. 1). The mean of 10 M-mode measurements and the mean of 3 blood pressure measurements performed during the ultrasound exam were used for calculation of the aortic stiffness index and distensibility as described below [21]

$$\text{Aortic stiffness index}\,\frac{\left[\ln\left(\frac{\text{blood pressure}_{\text{syst}}}{\text{blood pressure}_{\text{diast}}}\right)\right]}{\left[\frac{\text{diameter}_{\text{syst}}-\text{diameter}_{\text{diast}}}{\text{diameter}_{\text{diast}}}\right]}\ (\text{dimensionless})$$

and

$$\text{Distensibility}\left[\frac{\left[\left(\left(\frac{\text{diameter}_{\text{syst}}}{2}\right)^2\times\pi\right)-\left(\left(\frac{\text{diameter}_{\text{diast}}}{2}\right)^2\times\pi\right)\right]}{\left(\left(\frac{\text{diameter}_{\text{diast}}}{2}\right)^2\times\pi\right)*(\text{blood pressure}_{\text{syst}}-\text{blood pressure}_{\text{diast}})\times 1333}\right]\times 10^7\ (\text{in}\ 10^{-3}\ \text{kPa}^{-1})$$

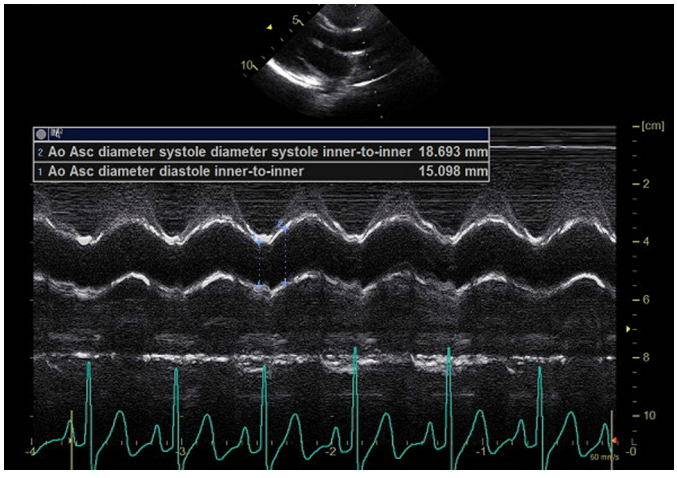

Fig. 1. M-mode recording of the ascending aorta on the parasternal long axis. The diameter of the ascending aorta is measured in diastole and systole.

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