



# Vasculopathy in Turner Syndrome

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**Abstract.** Dissection or rupture of the aorta accounts for death in 2–8% of women with Turner Syndrome (TS). Dilatation of the root of the aorta, hypertension and bicuspid aortic valve have been reported as predisposing factors for aortic dissection but the underlying pathogenesis of vascular dilation in TS is unknown. Recent papers have revealed that dilatation of the arterial tree in TS extends beyond the aorta to conduit vessels including the carotid and brachial arteries. The distal extent of this dilation is unknown. This finding of widespread arterial dilation appears to represent an unusual ‘vasculopathy’ in Turner’s syndrome. In trying to understand the pathogenesis of this vasculopathy, several aspects of arterial wall integrity lend themselves to scrutiny. There may be a defect of composition or remodelling of connective tissue, an inflammatory process or abnormal smooth muscle contractility thinking particularly of the nitric oxide pathway. Such processes can be exacerbated other features of TS including oestrogen deficiency, hypertension and accelerated atherosclerosis. © 2006 Published by Elsevier B.V.

*Keywords:* Intima medial thickness; Arterial dilation; Aortic dissection; Cardiovascular disease

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## 1. Introduction

Dissection or rupture of the aorta accounts for death in 2–8% of women with Turner Syndrome (TS) [1,2] Dilatation of the root of the aorta, hypertension and bicuspid aortic valve (BAV) have been reported as predisposing factors for aortic dissection [3,4]. The pathogenesis of vascular dilation in TS is unknown and comparisons with Marfan’s syndrome, although commonly made, may not be appropriate. Several aspects of vascular wall integrity lend themselves to scrutiny. There may be a defect of composition or remodelling of connective tissue, an inflammatory process or abnormal smooth muscle contractility thinking particularly of the nitric oxide pathway. Such processes can be

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exacerbated other features of TS including oestrogen deficiency, hypertension and accelerated atherosclerosis.

There are several methods available that can be used to assess the arterial wall that might give insight into the profile of defects in TS and allow stratification of risk factors. Such a profile has several components:

- Arterial wall structure can be assessed by measuring the diameter and intima media thickness of various vessels.
- Arterial stiffness can be assessed using pulse wave velocity and augmentation index.
- Endothelial function can be assessed using flow-mediated dilatation.

## **2. Examples of methodologies in the study of vasculopathy**

### *2.1. Artery diameter*

Internal carotid artery diameter can be measured at a standard reference point usually 1 cm below the common carotid artery bifurcation using high resolution B-mode real-time ultrasound. The vessel diameter is calculated from the end-diastolic distance between the lumen–intima interfaces measured in three sequential R-wave-triggered frames. Similar measurements can be taken of the brachial artery. The ascending aorta can be measured by echocardiography usually at the level of the annulus but also defined intervals up the ascending limb. Magnetic resonance scanning can be used to measure the ascending and descending aorta.

### *2.2. Intima media thickness*

Intima media thickness (IMT) is defined by the lumen–intima and media–adventitia interfaces of the far wall of a given vessel as measured by ultrasound. The mean of three measurements are usually taken for both parameters on each side, and the mean of right and left taken as the overall average. Increased IMT is a marker of early carotid atherosclerosis and an independent predictor of an adverse cardiovascular prognosis in the general population [5].

### *2.3. Pulse wave velocity*

Pulse wave velocity (PWV) is measured using a transcutaneous pressure tonometer (e.g. Sphygmocor system) to record the pulse pressure waveform consecutively at the carotid and femoral artery. The distance travelled by the pulse wave is measured over the body surface, and the pulse wave velocity (in m/s) is derived from the mean time difference between the R-wave measured in a simultaneously recorded ECG and pressure wave in relation to the arterial path length.

PWV is an independent marker of cardiovascular risk [6] and is associated with other cardiovascular risk factors such as blood pressure, insulin resistance, central obesity and greater carotid IMT in the general population [7].

#### 2.4. Augmentation index

Augmentation index (AIx) is calculated using the radial pulse pressure waveform to derive the central pressure waveform using a validated generalised transfer function. AIx is influenced by both heart rate and body height and should therefore be corrected for both [8]. Data on the prognostic value of AIx are still emerging and some studies suggest that it may have even greater predictive power than PWV.

#### 2.5. Flow-mediated dilatation (FMD) measurement

Using high resolution ultrasound, the change in brachial artery diameter in response to the hyperemic stimulus mediated by 5 min of forearm ischemia and also in response to 25 µg glyceryl trinitrate (GTN) as previously described can be measured [9]. It has been shown that endothelium-dependent vasodilator function reflects underlying cardiovascular risk factor burden [10] and independently predicts cardiovascular prognosis [11].

### 3. The problems of control groups in the study of TS

The evaluation of vascular data in the study of women with TS is hampered by the complexity of the syndrome making selection of relevant control groups of vital importance. Normal women differ from women with TS in several ways including stature and oestrogen status which strongly influence vascular measurements and function. Differences in stature can be controlled for statistically and the relative merits of correcting for height or body surface area have been discussed [12]. Increasingly studies have included controls that share oestrogen deficiency but have a normal karyotype and in this regard the earlier the onset of oestrogen deficiency the better as this hormone may have a ‘programming’ role in arterial development. Lastly, some of the vascular parameters are affected by heart rate which is consistently raised in TS and although there is routine adjustment for heart rate for augmentation index for instance, this systematic difference must always be taken into account.

### 4. Vascular studies in TS

Several studies have shown the increase in aortic diameter in women with TS [4,13,14]. Increased aortic diameter has been associated with the presence of BAV, aortic coarctation and hypertension. Of note, both the ascending and the descending aorta are of greater calibre in those with any constriction at the coarctation site [12].

In exploring other vessels Baguet et al. reported on 24 females with TS in whom both IMT and carotid artery diameter were increased compared to controls when corrected for height [15]. In a study of 93 adults with TS Ostberg et al. reported increased aortic root, carotid artery and brachial artery diameters in women with TS compared to both oestrogen deficient and oestrogen replete controls (Fig. 1) [16]. Both Baguet and Ostberg found an increase in IMT in women with TS and that this difference was oestrogen dependent was shown by Ostberg who found a similar difference in

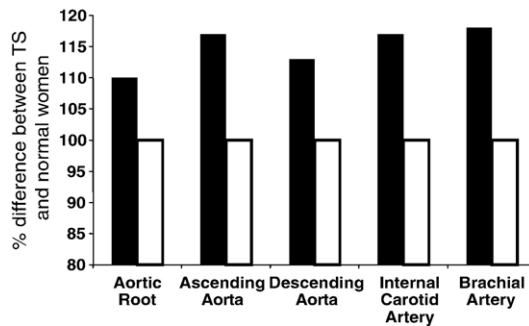


Fig. 1. Arterial diameter measurements in women with TS (solid bars) presented as a percent of measurements from controls (open bars) taken from Ostberg et al. [12, 16].

oestrogen deficient controls. The increases in carotid artery diameter and IMT are inter-related variables. IMT measurements are also associated with age and blood pressure in women with TS.

Three studies have reported on arterial dynamics in TS. Two studies have explored the effects of exogenous oestrogen in women with TS. Both augmentation index [17] and the vasodilator response to bradykinin in a plethysmography study [18] have been shown to improve when oestrogen deficient women with TS are treated with oestrogen. In cross sectional studies Baguet et al. found a higher augmentation index compared to controls whereas Ostberg found no alteration in either augmentation index or pulse wave velocity when corrected for height. In light of the effect of oestrogen found in the intervention studies, it might be relevant that nearly half of the subjects in the Baguet study were not receiving oestrogen. Also, PWV measurements may be distorted when the abdominal aorta becomes more tortuous with age [19], which may be an important factor in women with TS who frequently have greater tortuosity of the descending aorta [12] and elongation of the transverse arch [20].

Flow mediated dilation and vasodilator responses to GTN were studied by Ostberg et al. and no differences were found compared to controls [16].

## 5. Discussion

The latest group of studies in women with TS demonstrate widespread structural vascular differences in women with TS characterized by enlargement not only of the aorta but also of conduit arteries. The distal extent of this dilatation is unknown and it will be interesting to see assessments of arterial calibre from elsewhere in the arterial vascular tree. Whether there is any common process with the distortion of lymphatic vessels that is common in TS one consideration and it now seems logical to extend research to the venous network.

A relationship between generalized arterial dilatation and increased IMT has been observed outside of TS with the ‘Glagov phenomenon’ [21]. This refers to the outward remodelling and enlargement of atherosclerotic arteries as a consequence of complex inflammatory changes in the vascular wall that compensates for luminal occlusion in the

earlier stages of disease development. For example, increased carotid artery diameter was associated both with IMT and with the presence of atherosclerotic plaques and increased blood pressure in a population based study [22].

From the studies in TS and women with ovarian failure we see that oestrogen deficiency probably the dominant determinant of intimal hyperplasia in these subjects. Oestrogen deficiency may, therefore, be the focus for intervention in TS to reduce progression of intimal thickening, and ultimately clinical atherosclerotic disease. In postmenopausal women, exogenous oestrogen has been shown to reduce IMT slightly [23–25] but this is not a universal finding [26,27]. It may be that in younger women with greater tissue turnover, the effects of oestrogen on IMT would be greater.

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