Improving Detection of Hypertension in Girls with Turner Syndrome Using Ambulatory Blood Pressure Monitoring

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Key Words

Blood pressure · Cardiovascular disease · Cardiovascular risk · Hypertension · Karyotype · Turner syndrome

Abstract

Background/Aims: Turner syndrome (TS) is associated with increased mortality due to cardiovascular disease and a dramatically higher rate of aortic dissection. The recognition and treatment of hypertension in this population is critical. We sought to assess the ability to detect blood pressure (BP) abnormalities comparing ambulatory blood pressure monitoring (ABPM) with conventional BP measurement methods. We hypothesized that ABPM would improve detection of hypertension and alter management strategies. **Methods:** Twenty-three girls with TS underwent BP measurements using an automated oscillometric method and a manual mercury sphygmomanometer. Twenty-four-hour ABPM was performed (Spacelabs 90217, Issaquah, Wash., USA). BP values were compared to normative data based on height and sex for ABPM, and for age, height and sex for automated oscillometric and manual measurements. **Results:** Five (22%) subjects were found to have ambulatory hypertension (3 of these with severe hypertension). Three subjects had prehypertension using ABPM measurements. Only 1 of the 5 patients with ambulatory hypertension was categorized as hy-

pertensive using manual BP measurements. Twelve subjects (52%) had nocturnal hypertension. ABPM data led to a change in medical management of hypertensive patients with initiation of antihypertensive therapy. **Conclusions:** ABPM is advantageous in TS, as it improves detection of hypertension, identifies those with non-dipping BP patterns, and changes medical management of patients.

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Introduction

Turner syndrome (TS) is a genetic disorder that affects 1:2,000 newborn girls [1] and is caused by loss of all or part of the second sex chromosome. The recognition of increased cardiovascular mortality in this population has emphasized the need for aggressive treatment of hypertension in TS. TS confers a threefold increase in mortality with 41% of the excess mortality accounted for by circulatory disorders [2].

Approximately 40% of patients with TS have congenital cardiac defects demonstrable by echocardiography, including bicuspid aortic valve (16%), coarctation of the aorta (11%), hypoplastic left heart (10%) and aortic stenosis (5%) [3]. More recently, cardiac magnetic resonance imaging (MRI) has identified venous anomalies in-

cluding partial anomalous pulmonary venous return in approximately 15%, and persistent left superior vena cava in 7%. In addition, almost half of individuals with TS have an abnormal angulation and elongation of the aortic arch (elongated transverse arch) [4]. Due to the high prevalence of cardiac defects in TS, clinical guidelines recommend cardiac imaging at diagnosis and re-imaging at 5- to 10-year intervals unless indicated earlier. Imaging is generally performed by echocardiography in early childhood and MRI in adolescents and adults. The relative prevalence of hypertension in those with or without identifiable cardiac abnormalities has not been described.

Individuals with TS have a dramatically increased lifetime risk of aortic dissection (~1.4%) which is often fatal [5]. Aortic dissection occurs at an earlier mean age (30 years) compared to 67 years in the general population. Many children have died from aortic dissection, including a 4-year-old child [6]. Susceptibility to aortic dilatation and dissection is thought to be due to a generalized vasculopathy inherent in TS. Indeed, greater intimal medial thickening and dilatation of large caliber vessels is observed in those with TS [7]. Ascending aortic diameters are increased in TS, and aortic dilatation tends to be progressive [8]. Hypertension has been reported in up to 54% of cases with aortic dissection and is the most important modifiable risk factor [6]. Therefore, recognition and treatment of hypertension in this high-risk population is critical.

In a study of 75 girls and young women with TS, Nathwani et al. [9] found that 21% had hypertension using 24-hour ambulatory blood pressure monitoring (ABPM) and that 50% had abnormal diurnal variation in blood pressure (BP), defined as less than 10% decrease in nighttime mean ambulatory BP compared to daytime mean ambulatory BP. Absence of normal diurnal variation in BP has been associated with increased cardiovascular risk and target-organ damage in other populations [10, 11].

BP measurements in the clinic can be problematic. White coat hypertension (BP $\geq$ 95th percentile in a medical setting, but normal elsewhere) certainly occurs in this population in which anxiety is relatively common [12]. By relying on intermittent BP measurements in the clinic, healthcare providers may ignore true hypertension by assuming that the reading is attributable to white coat hypertension related to anxiety from the clinic visit.

ABPM allows for characterization of BP changes during daily activities and at rest, is less dependent on observer bias than conventional, intermittent measurements, and is able to detect nocturnal hypertension [13]. Furthermore, it is helpful in differentiating white coat hy-

pertension from true hypertension, especially in those with borderline or mildly elevated clinic BPs. The prevalence of white coat hypertension in children and adolescents with elevated clinic BPs has been reported as 22–32.6% [14, 15]. The likelihood of white coat hypertension in children decreases as clinic BP measurement increases [16]. Studies in both adults and children suggest that ABPM data correlate more closely with cardiovascular risk and target-organ damage than does clinic BP monitoring [17–20]. ABPM is not currently considered standard of care for individuals with TS [21], although a recent American Heart Association (AHA) statement cites TS as a population for which it is indicated [22]. The use of ABPM for improving detection and monitoring the treatment of hypertension may be an important step in reducing cardiovascular morbidity and mortality in the TS population.

We sought, therefore, to assess the rate of detection of BP abnormalities in girls with TS comparing ABPM with conventional BP measurement methods. We hypothesized that ABPM would be superior at detecting hypertension, that some subjects would have nocturnal hypertension identified by ABPM, and that ABPM would differentiate white coat hypertension from true hypertension in this population. In addition, we investigated the relationship of ABPM parameters to presence of structural cardiovascular defects with TS, hypothesizing that hypertension will occur in a significant percentage of patients, including young girls, both with and without structural cardiovascular defects as evaluated by echocardiography or MRI.

Materials and Methods

Patients

Twenty-three girls with karyotype-proven TS (ages 7–20 years) were recruited from the University of North Carolina (UNC) pediatric TS clinic. Patients attending the TS clinic were informed about the study and offered participation. Of the 23 subjects, 13 had a family history of hypertension in a first- or second-degree relative; none were taking antihypertensive medications; 15 of the subjects were receiving growth hormone therapy; 5 girls were receiving transdermal estradiol replacement and 4 were taking a combination of oral estrogen and progesterone, and 2 of the subjects were taking oxandrolone and 3 were prescribed levothyroxine replacement.

Methods

Subjects were evaluated by a member of the study team in a single visit in conjunction with a routine pediatric endocrinology clinic appointment in the UNC pediatric TS clinic. Anthropometric data were obtained including weight and height by standard methods. Body mass index (BMI) was also calculated. BMI SDS

was calculated using data from the First National Health and Nutrition Examination Study (NHANES) [23].

BP Measurements

BP assessment was performed using the oscillometric portable pediatric device Dynamap (Critikon, Tampa, Fla., USA) as routinely performed during every clinic visit. In addition, BP was measured using a manual mercury sphygmomanometer. Clinic visits occurred at variable times during the day. Dynamap and manual mercury sphygmomanometer measurements were obtained at the end of the clinic visit. Phase 1 of the Korotkoff sounds (onset of tapping sounds) corresponded to the systolic BP, and the diastolic BP was determined by phase 5 (the disappearance of tapping sounds) unless Korotkoff sounds could be heard to very low pressures. In these cases, BP measurement was repeated with less pressure on head of stethoscope. Only if Korotkoff sounds persisted at very low pressures, Korotkoff phase 4 was used (muffling of sounds).

An average of three readings was used for data analysis. An appropriately sized BP cuff (one which extended completely around the circumference of the upper arm with a bladder width that covered at least two thirds of the upper arm) was used for all measurements.

The ABPM monitoring device (Spacelabs 90217, Issaquah, Wash., USA) was applied and calibrated as described [22]. This device uses an oscillometric method of BP measurement. The device was placed on a weekday and worn for 24 h while the subjects continued normal activities. They were advised to avoid vigorous exercise including contact sports. BP recordings were obtained every 20 min during the daytime (08:00–22:00 h) and every 60 min at night (22:00–08:00 h). An acoustic signal before recordings during the daytime reminded the subject to relax the arm. During the nighttime this signal was programmed to be off so as not to interrupt the sleep. Each subject completed an activity log to record events during the 24-hour period which could affect BP (period of physical activity, rest, etc.). The ABPM device and activity log were returned to the clinic by mail.

Data were downloaded and analyzed by Spacelabs software. Interpretable studies included at least one valid recording per hour, and at least 40 readings for the 24-hour period. ABPM recordings were edited for outlying values as recommended by the AHA Scientific Statement of ABPM in children and adolescents [22]: systolic BP values were discarded if <60 or >220 mm Hg and diastolic BP values were discarded if <35 or >120 mm Hg.

Mean systolic and diastolic BP values were calculated by Spacelabs software for the 24-hour period, as well as day- and nighttime periods. BP load (the percentage of BP values >95th percentile for age and height) was calculated for systolic and diastolic readings. To evaluate nocturnal change in BP, the nighttime mean was divided by the daytime mean, and the change was expressed as a percentage of the daytime mean.

Interpretation of BP Readings

The Fourth Report on Blood Pressure by the National High Blood Pressure Education Program was used to stage manual BP readings [24]. Hypertension was defined as systolic or diastolic BP >95th percentile for sex, age and height based on normative data for manual BP measurements. Prehypertension was diagnosed if systolic or diastolic BP readings were between the 90th and 95th percentiles.

ABPM data were categorized using the criteria suggested by the AHA adapted from Wühl et al. [25] using normative data for ABPM in children stratified by sex and height [22]. Normal ambulatory BP was defined as mean ambulatory systolic BP <95th percentile and systolic BP load <25%. Prehypertension was defined as mean ambulatory systolic BP <95th percentile, but systolic BP load 25–50%. Ambulatory hypertension was defined as mean ambulatory systolic BP >95th percentile and systolic BP load 25–50%. Severe ambulatory hypertension was defined as mean ambulatory systolic BP >95th percentile and systolic BP load >50%. A nocturnal decrease in BP less than 10% compared to the daytime mean was considered abnormal.

Cardiac Imaging

Each subject's cardiac imaging data (echocardiogram and/or cardiac MRI) was interpreted by UNC pediatric radiologists with expertise in structural cardiac disease in TS. All of the subjects had echocardiograms and 10 had cardiac MRI in the past. Information regarding the patient's karyotype, medications and previous BP measurements were extracted from the medical record and confirmed by patient interviewing.

Statistical Analysis

χ^2 analysis was used to evaluate interaction between variables which were analyzed, including karyotype (monosomic 45,X vs. mosaic), presence of structural heart disease, presence of ambulatory hypertension, nocturnal hypertension or increased BP load.

This study was approved by the institutional review board of the UNC. Informed consent and assent were obtained from each patient and her parents prior to participation. Participation was voluntary.

Results

ABPM Data

The clinical data for the subjects is shown in table 1. Of the 23 subjects, 5 were found to have ambulatory hypertension, 3 of whom met criteria for severe ambulatory hypertension. Three additional subjects had prehypertension based on elevated BP load, but mean ambulatory SBP which was <95th percentile. The distribution of mean 24-hour systolic and diastolic BP values are shown for each subject compared to ABPM normative data for height-specific percentiles in females in figure 1. Six subjects had mean 24-hour diastolic BP >95th percentile. The mean 24-hour systolic BP in this group tended to be higher with 3 subjects having this parameter >95th percentile, 1 subject's measurements between the 90th and 95th percentile, and 2 subjects' values between the 75th and 90th percentile. Four of the 5 subjects with ambulatory hypertension were obese defined as BMI SDS >2, while 1 subject had a normal BMI.

Of the subjects, 12 (52%) lacked the normal 10% dip in BP during the nighttime, 9 of whom had normal cardiac anatomy by echo or MRI. Interestingly, only 2 of the 5

Fig. 1. Distribution of mean 24-hour BP measurements recorded by ABPM compared to normative data in children stratified by height adapted from Wühl et al. [25].

subjects with ambulatory hypertension had a non-dipping BP pattern, whereas the other 3 subjects with hypertension dipped normally. Two of the subjects with a non-dipping BP had normal BMI, while the 10 others had BMI SDS consistent with overweight (1 subject) or obesity (9 subjects) using WHO criteria. The average BMI SDS for the study group was 2.58.

Structural Cardiac Defects

Ten of the 23 patients had a history of one or more structural cardiac defects including: bicuspid aortic valve (7 subjects), coarctation of the aorta [repaired] (3 subjects), patent ductus arteriosus [repaired] (3 subjects), ventricular septal defect [repaired] (1 subject), and atrial septal defect [repaired] (1 subject). Four of the subjects with structural heart disease had completely normal ABPM parameters and manual BP measurements. Of the 8 subjects diagnosed with ambulatory prehypertension or hypertension, 4 (50%) had normal cardiac anatomy. The

3 subjects with severe ambulatory hypertension all had structural heart disease.

Comparing Manual BP and ABPM Parameters

The ability to detect hypertension using manual sphygmomanometry compared to ABPM is shown in table 2. Only 1 of the 5 patients determined to have ambulatory hypertension was categorized as hypertensive using BP measurements obtained by manual mercury sphygmomanometer at the time of the study. Therefore, 4 of the 5 subjects with ambulatory hypertension would not have been detected using manual clinic BP measurements alone. None of the subjects had elevation in manual clinic BP measurements alone (white coat hypertension). Four of the 8 (50%) patients with ambulatory hypertension or prehypertension had a history of an elevated BP measurement (>95th percentile) at a clinic visit in the past. Only 2 of the remaining 15 subjects had a history of elevated clinic BP at previous clinic visits.

Table 1. Patient characteristics including karyotype, BMI, mean 24-hour ambulatory systolic BP, clinic manual systolic BP, systolic BP load, percent dip in nocturnal systolic BP, and presence of structural cardiac defects

Age, years	Karyotype	BMI (SDS)	Mean ambulatory SBP (percentile for gender and height)	Clinic manual SBP (percentile for gender, age and height)	24 h SBP load, %	% dip in nocturnal SBP	Cardiac defects
7.1	45,X/46,X psu idic (X)/48,X psu idic (X)	16.3 (0.33)	121 (95–99)	99 (50–90)	35	0.1	n
8.2	45,X	21.3 (2.01)	108 (50–75)	109 (90)	11	14.3	CoA; PDA
8.9	45,X/46,X,i(X)	16.7 (0.171)	103 (<50)	91.5 (<50)	0	9.4	n
9.3	45,X	24 (2.38)	107 (50–75)	88 (<50)	2	13.3	n
10.2	45,X/46,XY	22.3 (1.80)	102 (<50)	98 (<50)	2	17.6	BAV
10.5	45,X	25.9 (2.49)	116 (90–95)	102 (50–90)	40	6.8	n
11.2	45,X/46,X,r(X)	26.4 (2.45)	100 (<50)	87 (<50)	3	9.7	BAV
11.4	45,X/46,XX	25.9 (2.32)	121 (95–99)	110 (50–90)	35	17.5	n
11.7	45,X	24 (1.86)	112 (75–90)	110 (50–90)	35	14.5	CoA; PDA
12.0	45,X/46,XX	35.4 (3.47)	108 (<50)	100 (<50)	11	14.1	n
12.4	46,X,del(X)	30.4 (2.86)	110 (50–75)	97.5 (<50)	2	8.1	n
12.7	45,X/46,XX	30.4 (2.82)	131 (>99)	111 (50–90)	75	10.4	PDA, VSD, ASD
13.0	45,X	29.8 (2.70)	124 (>99)	120 (90–95)	58	23.4	BAV
14.5	45X/46,X,i(X)	37.4 (3.43)	103 (<50)	100 (<50)	0	12.2	BAV
14.5	45,X	36.8 (3.38)	125 (75–90)	107 (50–90)	0	8.6	n
14.8	45,X/46,X,+mar/46,idic(Y)	32.5 (2.87)	107 (<50)	110 (50–90)	3	15.4	n
15.0	45,X	34.8 (3.13)	130 (>99)	131 (95–99)	69	9.8	BAV
15.0	45,X	28.2 (2.19)	97 (<50)	89 (<50)	0	0.01	BAV; mild ARD
15.3	45,X	31.9 (2.75)	102 (<50)	98 (<50)	49	6.8	n
15.7	46,X,der(X)t(X;Y)	45.1 (3.98)	112 (50–75)	102 (<50)	4	7.9	n
16.7	46,X,i(X)	50.8 (4.30)	105 (<50)	102 (<50)	3	7.6	n
18.1	45,X/46,XX/47,XXX	27.8 (1.83)	93 (<50)	90 (<50)	0	8.3	n
20.2	45,X	43.9 (3.83)	120 (75–90)	102 (<50)	0	13.8	CoA; BAV

BAV = Bicuspid aortic valve; ARD = aortic root dilatation; CoA = coarctation of aorta; PDA = patent ductus arteriosus; VSD = ventricular septal defect; ASD = atrial septal defect; SBP = systolic blood pressure; SDS = standard deviation score; n = none; SBP load = percent of the day in which SBP is >95th% (<25% non-hypertensive); nocturnal blood pressure dip = percentage decrease in SBP during sleep (>10% normal).

Correlation with Karyotype

Karyotype (45,X compared to mosaic karyotype) was not associated with increased risk of ambulatory hypertension, abnormal diurnal variation in BP, or elevated BP load.

Discussion

Individuals with TS have a significantly increased risk of cardiovascular mortality [2]. Hypertension occurs commonly in this population and is one of the most readily modifiable risk factors for prevention of coronary artery disease and aortic dissection, as well as for reduction in overall cardiovascular mortality [9]. In our study, ABPM was superior in detecting hypertension in this population compared to clinic BP measurements. Only 20% of our hypertensive subjects would have been diagnosed using clinic BP measurements. Furthermore, only half of those subjects with prehypertension or hyperten-

Table 2. Detection of prehypertension and hypertension using ABPM compared to manual clinic measurements (n = 23)

	90–95th percentile	>95th percentile
Mean manual systolic BP	n = 1 (4%)	n = 1 (4%)
Mean 24 h systolic ABPM	n = 1 (4%)	n = 5 (22%)
Mean manual diastolic BP	n = 2 (9%)	n = 1 (4%)
Mean 24 h diastolic ABPM	n = 3 (13%)	n = 6 (26%)

sion had an elevated BP at any of their past clinic visits. ABPM-obtained data led to a change in medical management of the hypertensive patients with initiation of anti-hypertensive therapy. In addition, ABPM provided enhanced surveillance for hypertension in subjects.

In our study, 4 of the 8 (50%) subjects diagnosed with ambulatory prehypertension or hypertension had normal cardiac anatomy. However, the 3 subjects with severe am-

bulatory hypertension all had structural heart disease. Therefore, hypertension was found in those with and without identifiable structural cardiac defects in TS.

Nocturnal hypertension, or non-dipping BP pattern, was found in approximately half (52%) of our study population. Interestingly, 8 of the 12 subjects with non-dipping BP patterns did not meet criteria for ambulatory prehypertension or hypertension. In addition, only half (4/8) of those with ambulatory prehypertension or hypertension had a non-dipping BP pattern. These data suggest multiple mechanisms involved in the development of hypertension in this population including abnormal vasculature, obesity, obstructive sleep apnea (OSA), and metabolic syndrome.

One factor in the development of hypertension in TS is structural heart disease. The 3 subjects with severe ambulatory hypertension had structural heart defects indicating that this is an important risk factor. However, nocturnal hypertension was also found frequently in those without structural cardiac defects suggesting that other factors likely play a role. For example, increased vascular stiffness has been reported in TS, and is thought to be related to a TS-specific vasculopathy which likely contributes to hypertension [26]. In addition, pharyngeal airway space is reduced in TS predisposing to OSA [27]; even mild degrees of OSA are associated with increased nocturnal BP as the result of hypoxemia, sympathetic activation, mechanical changes, and disruption of normal sleep [28]. Girls and women with TS have higher frequencies of obesity and insulin resistance which may be involved in the development of hypertension [29].

In normal and hypertensive populations, nocturnal hypertension is a potent predictor of cardiovascular morbidity and mortality independent of 24-hour BP levels [30]. In addition, a non-dipping BP pattern has been associated with early atherosclerosis [31]. Because of the association of non-dipping BP pattern with increased cardiovascular mortality, it has been suggested from studies in adults that administration of antihypertensive therapy in the evening (chronotherapy) may be warranted. Recently, the MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares) study demonstrated that bedtime administration of BP-lowering medications, compared to conventional morning therapy, decreased the prevalence of non-dipping, more effectively controlled BP, and significantly reduced cardiovascular morbidity and mortality [32]. The most important predictor of lowering cardiovascular risk in these investigations was the decrease in asleep BP mean assessed by ABPM [33]. These findings could be applicable to the TS

population in which aggressive BP control is an important factor in reducing risk of aortic dilatation.

Indeed, intensive BP control and reduction of hemodynamic stress have been shown to slow the rate of progression of aortic dilatation and risk of dissection in Marfan syndrome (MS), a genetic disorder caused by mutations in the gene encoding fibrillin-1 (FBN-1) predisposing those affected to aortic dilatation and rupture. In MS, β -adrenergic blockade reduces the rate of aortic root growth, decreases risk of cardiovascular endpoints such as surgery, heart failure and death, and improves survival [34]. In mouse models of MS, angiotensin receptor blockade reduced aortic growth [35]. As individuals with MS are highly predisposed to thoracic aortic aneurysms and dissection (almost every patient with the disorder has evidence of aortic disease during their lifetime), treatment with β -blockers is standard of care [36]. Aortic dilatation is not uncommon in TS with 33% of women found to have aortic dilatation defined as an ascending-to-descending aortic diameter ratio >1.5 [37]. Approximately 1.4% of patients progress to aortic rupture which is often fatal. It is unclear when antihypertensive therapy should be initiated to reduce the risk of aortic dissection in TS; however, it seems reasonable to begin therapy in those patients with early aortic dilatation based on data available in MS. In addition, the use of ABPM data to diagnose and treat nocturnal hypertension in this population might be an important step in reducing the rate of aortic dilatation and dissection.

A major limitation of our study is the small sample size. In addition, it is unclear if these results are reproducible as our study design was not able to repeat ABPM in each patient over time. Future studies with repeated ABPM measurements are necessary to determine reproducibility. A wide range of BP values were found between subjects, and larger studies would be beneficial to determine if this is characteristic of TS, or a result of small sample size. Larger population studies are needed to evaluate the association of nocturnal hypertension with markers of end-organ damage such as left ventricular hypertrophy and whether antihypertensive therapy improves these markers. In addition, further studies are needed to establish the optimal BP goals for this population and whether normotensive non-dippers should be treated with antihypertensive therapy and when to start antihypertensive treatment for aortic dilatation.

In summary, our study demonstrates that ABPM is advantageous in the TS population. It improves detection of hypertension, identifies those with non-dipping BP patterns, and changes medical management of patients.

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