Five-Year Randomized Study Demonstrates Blood Pressure Increases in Young Women With Turner Syndrome Regardless of Estradiol Dose

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Abstract—We evaluated the development in blood pressure (BP) and heart rate in young women with Turner syndrome (TS) and investigated potential influencing cofactors. Twenty TS women (mean±SD, 22.9±2.3 years of age) were investigated in a 5-year prospective setting. Data were derived from a randomized controlled clinical trial investigating 2 different doses of estradiol treatment (2 mg 17β-estradiol per day and placebo or 2+2 mg 17β-estradiol per day). A control group of 12 healthy age-matched young women (mean±SD, 23.11±2.2 years of age) was examined at the end of the study. BP and lipids were monitored yearly. At the end of the study, TS (n=15) and controls were examined by 24-hour ambulatory BP monitoring. Systolic and diastolic BPs increased regardless of estradiol dose (P=0.005 and P=0.009) in TS patients, whereas heart rate decreased (P=0.05). Neither body mass index, height, weight, nor lipids contributed significant to the changes. There was no difference in BP, heart rate, or lipids because of treatment. At the end of the study, diastolic BP and heart rate were significantly higher in TS during day, night, and over 24 hours. Systolic BP increased insignificantly. Lipids did not change during the study period, but body mass index determined individual levels. In conclusion, systolic and diastolic BPs increase significantly in late adolescence and early adulthood in TS. It remains an enigma why BP increases early in life in TS.

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The overall mortality rate is increased in Turner syndrome (TS), and mortality caused by cardiovascular disease is 4× higher compared with the general population.[1] Congenital heart disease (CHD) such as bicuspid aortic valve, aortic coarctation, and hypertension are predisposing risk factors for the development of aortic dissection[2–4] and are all found with a higher frequency in TS. The incidence of aortic dissection is 6× higher in TS compared with the general population with an estimation of 36 per 100 000 TS years.[2]

Several cross-sectional studies have examined blood pressure (BP) in TS and found it increased already in childhood or early adolescence.[5,6] In adulthood, hypertension occur in 40% to 50% of TS,[7,8] and a blunted nocturnal dipping pattern is common.[5,9] The nature of hypertension in TS has been investigated, but no consistent signs of secondary hypertension have been found, although dysregulation of the sympathetic nervous system and altered sympathovagal tone may contribute to increased heart rate and hypertension.[10,11] Thus, it remains an enigma why so many individuals with TS develop hypertension and why this also often happens at a young age. Because hypertension directly influences overall morbidity and mortality,[1,12,13] diagnostic delay of TS represents a serious problem as many will not receive timely and appropriate treatment.[6,14]

The aims of the present study were to evaluate the temporal development in BP and heart rate levels during 5 years of early adulthood in a group of young women with TS and to investigate cofactors with a potential influence on BP and heart rate.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Design and Participants

Twenty patients with TS (mean±SD, 22.9±2.3 years of age) were investigated in a prospective 5-year randomized controlled clinical trial using a parallel group design. TS patients fulfilling the inclusion criteria were randomized into 1 of 2 study groups and assigned to

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receive estrogens as follows: the lower-dose group received Trisekvens (days 1–12: 2 mg estradiol; days 13–22: 2 mg estradiol and 1 mg norethisterone acetat days 23–28: 1 mg estradiol) (Novo Nordisk) orally combined with placebo on days 1 to 22 of the menstrual cycle. The higher-dose group received Trisekvens (Novo Nordisk) orally combined with estradiol 2 mg (Novo Nordisk) on days 1 to 22 of the menstrual cycle. Data about other aspects of this trial have previously been published.[15–17] TS patients were recruited from the Danish Turner Syndrome Society, Departments of Pediatrics, Endocrinology and Gynecology and Obstetrics in all parts of Denmark, general practitioners, and advertisements in national Danish newspapers. The criterion for inclusion was diagnosis of TS confirmed by previous karyotyping (45,X [n=8], 45,X/46,XX [n=2], 45,X/46,XY [n=3], isochromosomes [n=3], and deletions [n=4]). The 3 patients with the karyotype 45,X/46,XY had undergone oophorectomy in childhood.

A control group of 12 healthy age-matched young women (mean±SD, 23.11±2.2 years of age) was recruited from the Universities of Copenhagen and Aarhus by advertisement and examined once. Controls had no current or chronic disease, nor history of hypertension or cardiovascular diseases. All had undergone normal pubertal development and received no hormonal treatment.

Individual case notes were reviewed, and data were collected on the complete medical history with emphasis on cardiovascular disease (hypertension and cardiac surgery), puberty and menarche (spontaneous or induced), and age at initiation of hormone replacement therapy. Transcripts of previously performed echocardiographic studies were collected to ascertain aortic valve morphology. As part of the prospective trial, TS patients were also investigated by aortic magnetic resonance imaging. Body weight and height were measured, and body mass index (BMI) was calculated. Body surface area was calculated according to the formula of Dubois and Dubois (body surface area $[m^2]=0.20247\times\text{height}\ [m]^{0.725}\times\text{weight}\ [kg]^{0.425}$). All participants, TS and controls, had undergone an ambulatory BP (AMBP) measurement using an automatic portable apparatus (Spacelabs 90207; Redmond, Washington). The apparatus uses an oscillometric method of BP measurement. An appropriate cuff size placed on the left arm was used, and readings were obtained every 20 minutes for a period of 24 hours on a normal weekday. Time of bed and time of rise in the morning were noted by the participant. A single BP measurement was performed in TS at the yearly examinations as part of the prospective study. Five participants with TS did not complete the AMBP measurement period.

Total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglycerides were measured in TS only using an automated commercially available system (Aeroset; Abbott Diagnostics, North Chicago, IL).

Index of daily activity was studied among TS every year. We asked whether they were sedentary (0 point), little (1 point), moderate (2 points), or hard (3 points) physically active at work/school and how they were transported to work/school. The options were by car/bus/train (0 point), bicycling/walking 1 to 5 km (1 point), bicycling/walking 6 to 10 km (2 points), or bicycling/walking >10 km (3 points). Finally, we asked whether they were physically active in their spare time. The options were not/very little (0 point), little (1 point), moderate (2 points), or very active (3 points). The maximum score was thus 9 and the minimum score 0.

The protocol was approved by the Research Ethics Committees of The Capital Region of Denmark (H-Ø-2004-2-24G). The study was conducted according to the recommendations of the Declaration of Helsinki and the ICH (International Committee on Harmonization) guideline for Good Clinical Practice. This prospective study was registered in the EudraCT database (2004-004778-99) and at ClinicalTrials.gov (NCT00134745). All participants received oral and written information about the study before giving written informed consent.

Statistical Analysis

Statistical analyses were performed using Stata version 14.1. Data were log-transformed when appropriate. It was the case with triglycerides over time. Values are presented as medians and range. Comparisons between groups were performed using paired, unpaired *t* test or Mann-Whitney test as appropriate. Linear regression with individual random intercepts was used to study the development over time for each of the outcome variables. Such a mixed model can handle the design with repeated measurements. A P value <0.05 was considered significant.

Results

At the end of the study, TS had been treated with hormonal replacement therapy for an average duration of 15 years (median, range: 12–18 years). Six (30%) TS had CHD. Of those 4 had a well-functioning bicuspid aortic valve and 2 had aortic coarctation (Table 1). TS and controls were comparable on age and weight, but patients with TS were significantly shorter than controls and therefore had a higher BMI (Table 1). The average level of total cholesterol, HDL, LDL, and triglycerides in TS was within the normal range (Table 1).

There was no difference in BP and heart rate comparing TS receiving higher-dose or lower-dose estradiol during the study (Table 2). In the following computations, we have combined the 2 study groups.

During the study period, both systolic BP (P=0.005) and diastolic BP (P=0.009) increased among TS, whereas heart rate decreased (P=0.05) (Figure 1A through 1C). Using repeated measures linear regression, BMI, height, weight, and different lipid fractions did not contribute significantly to the changes in systolic BP, diastolic BP, or heart rate (data not shown).

At the end of the study, BP and heart rate were measured using AMBP. Diastolic AMBP and heart rate was significantly higher in TS compared with controls, both during day and night and resultantly also during the 24-hour period (Table 3). No difference in systolic AMBP was observed comparing TS and controls. Diastolic night:day ratio was similar in TS and controls, whereas systolic night:day ratio was lower in TS (Table 3). Stratifying on TS with or without CHD, no difference was observed in day and night systolic and diastolic BPs, in day and night heart rate, or in night:day BP ratios. The 45,X karyotype did not influence BP (data not shown).

During the entire study period, there was no change in total cholesterol, HDL cholesterol, or triglycerides (Figure 2), whereas LDL cholesterol increased almost significantly. There was no difference in the course of change in the different lipid fractions because of treatment with lower-dose or higher-dose estradiol. Subsequent computations using BMI as a covariate, both with and without estradiol dose as a covariate, showed that higher BMI was a significant contributor to higher levels of lipids among females with TS, except for HDL cholesterol which was lower with higher BMI (data not shown).

Average index of daily activity was 3 (median, range: 0–7) and did not change over the study period (data not shown).

Discussion

This study presents temporal developments in BP and heart rate in TS at a young age. The principal findings were a significant increase in systolic and diastolic BPs during a 5-year period in a group of young women with TS, without any differences because of estradiol dosing. Concurrently, heart rate decreased significantly, whereas lipid fractions did not change. Because hypertension is associated with aortic dilatation, both in the normal population[18] but especially in TS,[19] early identification of hypertension and timely treatment are cornerstones in preventing aortic disease.

Table 1. Anthropometric Measurements and Lipids at the End of Study for TS and Controls

Demographic	TS (n=20)	Controls (n=12)	*P* Value
Age, y	22.9 (19.4–26.9)	23.1 (20.5–27.4)	0.8
Weight, kg	57.9 (37.2–92)	58.8 (49.7–66.4)	0.9
Height, cm	152.0 (143.5–161.3)	165.4 (155.5–177.6)	0.0001
Body mass index, kg/m^2	25.0 (17.1–42.4)	21.5 (19.7–24.1)	0.04
Race	White	White	
Total cholesterol, mmol/L	4.7 (3.8–5.3)	…	…
HDL, mmol/L	1.9 (1.3–2.6)	…	…
LDL, mmol/L	2.5 (1.6–3.2)	…	…
Triglycerides, mmol/L	0.9 (0.5–1.4)	…	…
Presence of CHD	6	0	…
Bicuspid aortic valve	4	0	…
Aortic coarctation	2	0	…
Aortic insufficiency	1	0	…
Aortic stenosis	1	0	…
Hormonal replacement treatment	20	0	…
45,X/46,XX and other mosaics	8/12	0	…
Spontaneous puberty/menstruation	12/3	NA	…

Data are shown as absolute numbers or as median (range). CHD indicates congenital heart disease; HDL, high-density lipoprotein. LDL, low-density lipoprotein; NA, not applicable; and TS, Turner syndrome.

Hypertension has been found to affect as many as 21% to 42% of girls and adolescents with TS[5,6,20] and >50% of adult TS.[7,8] For comparison only, 3.5% of healthy children and adolescent have hypertension.[21,22] Even though none with TS in this study reached a hypertensive BP level (>130/80 mm Hg[23]), 24-hour diastolic BPs were significantly higher than among controls.

In a large follow-up study with a group of adult TS (38+11 years of age), a model was made for predicting growth of aortic diameter.[19] The study showed that there was a strong association between diastolic BP and aortic growth, which gives a window of opportunity to prevent progressive aortic dilation over time. Although hypertension is not always present in TS with aortic dissection, it is important to treat hypertension aggressively when present because it increases the risk of aortic dissection.[2–4]

Table 2. Twenty-Four–Hour Ambulatory Blood Pressure Measurements in Turner Syndrome Receiving 4 mg (HD) or 2 mg (LD) Estradiol

Measurement	HD (n=10)	LD (n=10)	*P* Value
Day systolic AMBP, mm Hg	120 (109–135)	113 (107–130)	0.1
Night systolic AMBP, mm Hg	101 (96–115)	99 (87–108)	0.4
24-h systolic AMBP, mm Hg	113 (105–127)	107 (100–122)	0.1
Day diastolic AMBP, mm Hg	77 (67–90)	74 (68–82)	0.4
Night diastolic AMBP, mm Hg	62 (58–69)	60 (53–63)	0.1
24-h diastolic AMBP, mm Hg	71 (64–84)	66 (63–76)	0.2
Day heart rate, bpm	80 (70–89)	80 (59–93)	0.6
Night heart rate, bpm	67 (59–87)	67 (52–81)	0.8
24-h heart rate, bpm	75 (67–84)	75 (57–88)	0.8

Data are shown as median (range). The *P* value is found using nonparametric Mann-Whitney *U* test. AMBP indicates ambulatory blood pressure measurement; HD, high dose (4 mg estrogen); and LD, low dose (2 mg estrogen).

Both systolic and diastolic BPs increased significantly over time, whereas heart rate decreased during young adulthood. The participants with a lower or higher AMBP level did also have a lower or higher clinic BP, respectively, measured at the yearly clinical control. In addition, the measurements show that there is greater variability in AMBP in the TS group compared with controls. No other study has performed similar series of BP measurements at regular intervals over several years in young TS. Radetti et al[24] reported the arterial wall in young TS to be functionally and structurally comparable to healthy controls, but they found signs of premature derangement of the arterial function and structure, which could be influenced by age and duration of estrogen treatment. Here, we found TS treated with high-dose estrogen (4 mg) to have similar BP and heart rate compared with those treated with the conventional dose of estrogen (2 mg). It would be interesting to see if there were any structural changes in the arterial wall of the present study group. None of the studied covariates, age, BMI, or lipids, seemed to explain the rise in BP during the study period. However, an even larger sample size may be necessary to see any influence from such covariates. Likewise, we did not see any difference in BP between different karyotypes. Perhaps because the number of individual karyotypes was relatively small. Fewer comorbidities are present among females with other karyotypes than 45,X,[25] and it would thus be of interest to study large groups of individuals with similar TS karyotypes.

The pathophysiology explaining the very frequent occurrence of hypertension among TS remains unexplained but could

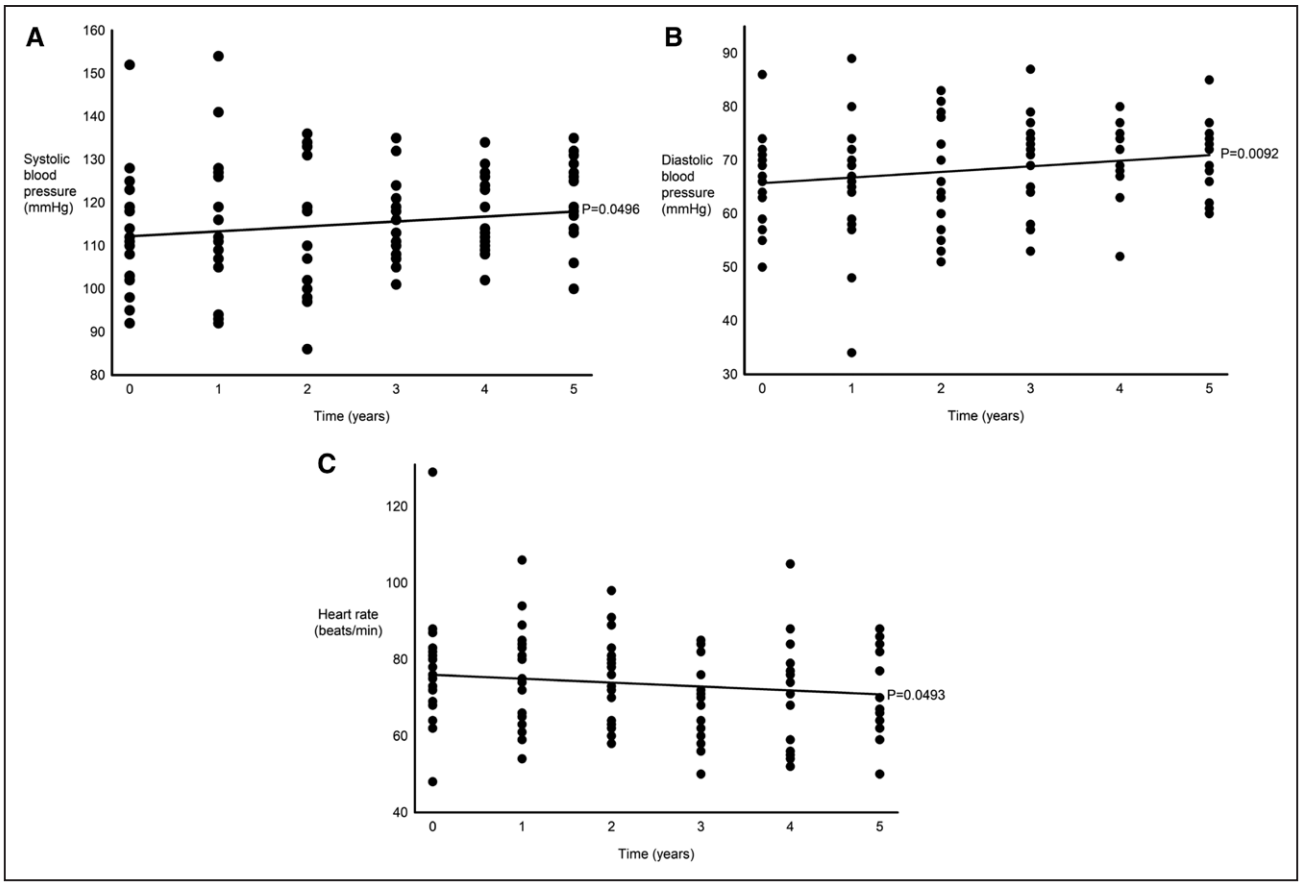

Figure 1. Blood pressure and heart rate in women with Turner syndrome over a period of 5 years. **A**, Systolic blood pressure in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete ambulatory blood pressure measurement (AMBP). The full line illustrates linear regression. Level of significance is depicted in the graph. **B**, Diastolic blood pressure in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete AMBP. The drawn line illustrates linear regression. Level of significance is depicted in the graph. **C**, Heart rate in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete AMBP. The drawn line illustrates linear regression. Level of significance is depicted in the graph.

be because of a combination of influences, such as altered sympathovagal tone, possibly because of CHD of the wiring of the parasympathetic and the sympathetic nervous system with increased resting norepinephrine levels,[10] frequent CHD of the left side of the heart,[26] and dilated branching arteries.[27] Sozen et al[28] found left ventricular thickness significantly increased in normotensive TS patients, and diminished myocardial glucose uptake has also been observed, suggesting myocardial insulin resistance, despite comparable whole-body insulin sensitivity.[29] Such changes could be indicative of early fibrotic changes in the heart and be viewed as a forerunner for diastolic dysfunction.[30] Another study found that TS patients exhibit a predominantly proximal aortic stiffening and dilatation, especially, but not exclusively, if their aortic valve is bicuspid. The increased stiffening in the aorta is observed at an early age. The same changes are not observed in the ascending part of aorta.[31] Thus, even though the majority of girls and young TS women show no signs of clinical cardiovascular disease, including hypertension, it is likely that seeds have been laid early in life, and perhaps even during fetal life.

Table 3. Twenty-Four–Hour Ambulatory Blood Pressure Measurements in Turner Syndrome and Controls

Measurement	TS (n=15)	Controls (n=12)	*P* Value
24-h systolic AMBP, mm Hg	112 (100–127)	109 (100–121)	0.7
Day systolic AMBP, mm Hg	117 (107–135)	115 (103–126)	0.7
Night systolic AMBP, mm Hg	100 (87–115)	99 (93–112)	0.9
Systolic night/day ratio	0.85 (0.80–0.90)	0.88 (0.78–0.95)	0.05
24-h diastolic AMBP, mm Hg	70 (63–84)	64 (59–69)	0.01
Day diastolic AMBP, mm Hg	75 (67–90)	70 (62–79)	0.05
Night diastolic AMBP, mm Hg	62 (53–70)	53 (50–60)	0.0003
Diastolic night/day ratio	0.81 (0.77–0.87)	0.79 (0.65–0.83)	0.1
24-h heart rate, bpm	75 (60–88)	66 (51–78)	0.01
Day heart rate, bpm	80 (59–93)	68 (55–84)	0.02
Night heart rate, bpm	67 (52–87)	56 (42–73)	0.02

End-of-study data. Data are shown as median (range). The *P* value is found using nonparametric Mann-Whitney *U* test. AMBP indicates ambulatory blood pressure measurement; and TS, Turner syndrome.

There is no specific guideline for how to treat TS with hypertension, but the new international guidelines recommend treatment with either a β-blocker or an angiotensin receptor blocker or a combination thereof.[32] Interestingly, there is also no guideline or treatment for isolated elevated diastolic BP alone. It would be obvious to investigate whether a normal circadian BP pattern by use of bed time antihypertensives would be advantageous in TS. In normal hypertensive patients, there is little evidence that bed time antihypertensive medicine reduces cardiovascular morbidity and mortality.[33,34] However,

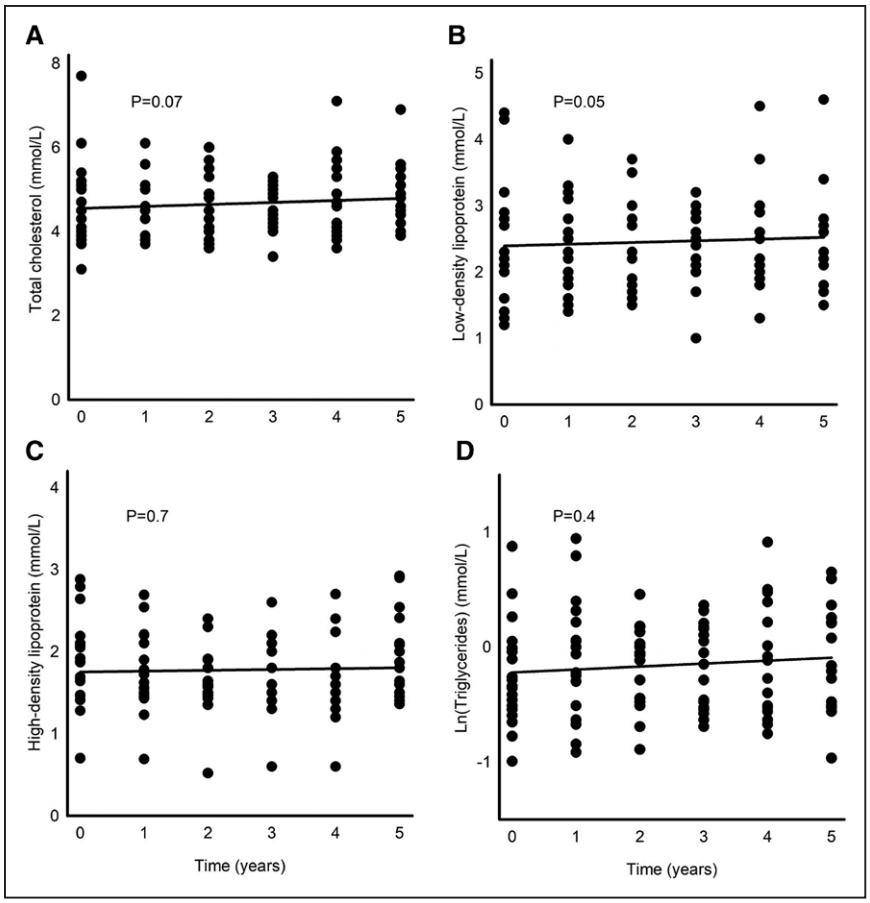

Figure 2. Lipids in women with Turner syndrome over a period of 5 years. **A**, Total cholesterol in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete ambulatory blood pressure measurement (AMBP). The drawn line illustrates linear regression. Level of significance is depicted in the graph. **B**, Low-density lipoprotein in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete AMBP. The drawn line illustrates linear regression. Level of significance is depicted in the graph. **C**, High-density lipoprotein in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete AMBP. The drawn line illustrates linear regression. Level of significance is depicted in the graph. **D**, Triglycerides in women with Turner syndrome over a period of 5 years. N=15—5 participants did not complete AMBP. The drawn line illustrates linear regression. Data for triglycerides are ln transformed. Level of significance is depicted in the graph.

the number of large-scale studies is small, and there is no consensus whether bed time antihypertensive treatment actually reduces cardiovascular risk.[35]

Heart rate decreased among TS over the 5 years. The decrease in heart rate could be because of changes in exercise habits. The activity of the participants did not change over the study period though. In terms of lifestyle habits, it would have been relevant to include information about whether the participants were smokers.

Most studies among TS have found lipids to be within normal levels,[9,14,36,37] although a couple of studies have reported elevated triglyceride levels[38,39] or non-HDL fraction,[40] which, most likely is a consequence of hyperinsulinemia and obesity.[41] This was not the case in this study group. Here, we generally found lipids to be within normal levels, and no change was observed during the study period along with a normal BMI. However, we saw a small but nonsignificant increase in LDL cholesterol, which we deemed to be without clinical significance. Treatment with either higher-dose or lower-dose estradiol did not affect the trajectory of change in the different lipid fractions. Interestingly, the observed differences among TS were solely explained by BMI—the higher the BMI the higher the total cholesterol, LDL, and triglycerides, and the lower the HDL cholesterol.

Limitations

The are some limitations in this research. First, we did not examine the participants with angiography and renal ultrasound to see if any suffered from secondary hypertension because of renal artery stenosis or any other renal pathology. To date, this has not been found in TS, and even though 1 TS patient should have renal artery stenosis, it would not explain the general tendency toward an increase in BP in the total population. Second, our study group is relatively small. We only had 6 of 20 TS patients with CHD and only 15 of 20 TS completed the AMBP measurement. A larger study with more participants would be ideal; however, because of the relative rarity of TS, larger intervention studies over longer periods of time will always be a challenge.

In conclusion, systolic and diastolic BPs increase significantly in late adolescence and early adulthood in TS, whereas heart rate decreases and lipids remain constant. Why BP increases early in life in TS remains an enigma, and further studies are needed.

Perspectives

Already in late adolescence and early adulthood, TS presents with a higher BP compared with age-matched healthy young women independent of both karyotype and presence of CHD. Because hypertension is associated to aortic dilatation, early identification and timely treatment may reduce the burden of aortic disease in TS. Known risk factors like BMI or hyperlipidemia did not contribute to changes in BP; thus, it seems not possible to prevent hypertension by lifestyle changes alone. Moreover, the present study confirmed that the dyslipidemia present among some TS is strongly associated to BMI, emphasizing that a healthy lifestyle is very important in TS to avoid cardiac disease. It would be also relevant to study whether physical exercise capacity has any effect on BP in TS. BP in other patient groups is known to be positively affected by an increase in exercise capacity.

In future studies, it would also be relevant to compare the effect of transdermal and oral estrogen treatment on BP in TS. In a shorter-term study of 6 months, we did compare equivalent doses of transdermal and oral 17β-estradiol and found no difference in AMBP, but we did in both groups see a significant reduction in especially diastolic AMBP, but further studies are clearly warranted.[9]

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Disclosures

C.H. Gravholt has received honorarium from Pfizer in relation to one talk in 2017. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- Blood pressure increases, whereas heart rate decreases in late adolescence and early adulthood in patients with Turner syndrome.

What Is Relevant?

- Up to 40% of girls and adolescents with Turner syndrome have hypertension. For comparison only, 3.5% of healthy children and adolescent have hypertension.
- The pathophysiology explaining the very frequent occurrence of hypertension among females with Turner syndrome remains unexplained, and further research may also lead to better understanding of essential hypertension in the general population.

Summary

Systolic and diastolic blood pressures increase significantly in late adolescence and early adulthood in Turner syndrome, whereas heart rate decreases and lipids remain constant. None of the variables studied, including body mass index, height, weight, different lipid fractions, presence of congenital heart disease, or the specific karyotype 45,X, contributed to the changes in systolic blood pressure, diastolic blood pressure, or heart rate.