Received: 4 February 2019 | Revised: 30 March 2019 | Accepted: 31 March 2019

DOI: 10.1111/cen.13983

ORIGINAL ARTICLE

WILEY

Blood pressure, sympathovagal tone, exercise capacity and metabolic status are linked in Turner syndrome

Sara Brun[1] | Agnethe Berglund[2] | Kristian H. Mortensen[3] | Britta E. Hjerrild[1] | Klavs W. Hansen[4] | Niels H. Andersen[5] | Claus H. Gravholt[1,2]

[1]Department of Endocrinology and Internal Medicine and Medical Research Laboratories, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark

[3]Cardiorespiratory Unit, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK

[4]Diagnostic Centre, Regional Hospital Silkeborg, Silkeborg, Denmark

[5]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

Correspondence
Niels H. Andersen, Department of Cardiology, Aalborg University Hospital, DK-9000 Aalborg, Denmark.
Email: holmark@ki.au.dk

Funding information
This work was supported by grants from the Lundbeck Foundation, the Augustinus Foundation, The Toyota Foundation, the Aase og Einar Danielsen Foundation, the Novo Nordisk Foundation (NNF13OC0003234, NNF15OC0016474), 'Fonden til lægevidenskabens fremme' and the Familien Hede Nielsen Foundation.

Abstract

Objectives: We studied cardiac autonomic changes in relation to metabolic factors, body composition and 24-hour ambulatory blood pressure measurements in Turner syndrome patients without known hypertension.

Design: Cross sectional.

Patients: Participants were 48 TS women and 24 healthy female controls aged over 18 years.

Methods: Short-term power spectral analysis was obtained in supine-standing-supine position. Bedside tests included three conventional cardiovascular reflex tests of heart rate response to standing up, heart rate response to deep breathing and blood pressure response to standing up. Mean heart rate during the last 2 minutes of work was used to calculate the maximal aerobic power (VO_{2max}).

Results: We found a significantly higher mean reciprocal of the heart rate per second (RR) in TS. Testing for interaction between position and status (TS or control), there were highly significant differences between TS and controls in high-frequency (HF) power, the coefficient of component variation (square root of HF power/mean RR) and low-frequency (LF): HF ratio, with a dampened decline in vagal activity among TS during standing. Bedside test showed TS had a significantly higher diastolic BP in the supine position compared to controls, and the adaptive rise in BP, when changing to upright position was reduced. VO_{2max} and self-reported level of physical activity were significantly correlated to systolic ambulatory blood pressure both 24-hour and night diastolic ambulatory blood pressure.

Conclusion: Vagal tone and modulation of the sympathovagal balance during alteration in body position are impaired in TS. These changes can be risk factors for cardiovascular disease.

KEYWORDS

autonomic nervous system, biomarkers, blood pressure, heart rate, physical conditioning, human

1 | INTRODUCTION

The new international guidelines on Turner syndrome (TS)[1] recommend thorough cardiovascular evaluation of all women with TS, due to a very high frequency of congenital malformations,[2] a high frequency of early onset hypertension[3] and an increased cardiovascular morbidity and mortality.[4,5]

The risk of hypertension in TS is increased already at a young age and later in life as many as 50% have hypertension when assessed by 24-hour AMBP.[6] Several studies have evaluated blood pressure (BP) levels in TS and consistently found elevated BP levels early in life with a frequent presence of nondipping hypertension.[7,8] A reduced nocturnal BP dip (nondipping) can be a sign of impairment of the physiological increase in parasympathetic tone and a decrease in sympathetic tone during sleep. Cardiac autonomic neuropathy has in other study populations been associated with several components of the metabolic syndrome[9,10] as well as increased cardiac mortality in diabetic patients,[11] and in patients with cardiovascular disease.[12]

Impaired sympathovagal tone, suggestive of discrete autonomic cardiac neuropathy, has been found in a small group (n = 8) of normotensive women with TS,[7] as well as dysregulation of the sympathetic nervous system.[13] The present study was initiated with the aim of understanding the frequent occurrence of high BP and altered autonomic innervation of the heart in TS. We studied cardiac autonomic changes in relation to metabolic factors, body composition and 24-hour AMBP in a much larger group of TS women without known hypertension.

2 | MATERIALS AND METHODS

The TS women were a subgroup of 75 participants from a prospective study evaluating aortic dimensions by magnetic resonance imaging (MRI).[14,15] TS was verified by karyotyping (45, X: n = 41 (55%); other karyotypes: n = 34 (45%)). From this group, 27 women with TS and pre-existing hypertension were excluded. The resultant 48 women with TS were without known nonpharmacologically or pharmacologically treated hypertension, prior to inclusion in the study, and they all had a clinic BP < 140/90 mm Hg and a normal resting ECG. None of the participants had either symptoms or had any history of autonomic dysfunction. Twenty-four healthy control women served as the control group.

Patients were included consecutively through the National Society of Turner Contact Groups in Denmark and the outpatient clinic at the Department of Endocrinology, Aarhus University Hospital, Denmark. Participants were all aged over 18 years. Patients with malignant disease, clinically significant liver disease and artificial heart valves, were excluded. As controls, 24 healthy women (aged 43 ± 10 years, range: 25-63) using no daily medication (oral contraceptives accepted) were recruited through advertising. The protocol was approved by the Aarhus County Ethical Scientific Committee (# 20010248).

All trial participants were admitted to the research laboratory at 8 AM after an overnight fast (10 hours (h)). Body weight was measured to the nearest 0.1 kilogram (kg) on an electronic scale, and body height was measured to the nearest 0.5 cm with participants barefooted. Information on the age at menarche, age when exogenous oestrogen was introduced (oral 17-β oestradiol in all cases), age at premature menopause and duration of hormone replacement therapy (HRT) was registered, enabling summation of total oestrogen exposure (in years). Years of oestrogen insufficiency was estimated as the number of years between the age of 13 and 53 years, where participants were not receiving HRT and had no spontaneous menstrual bleedings.

2.1 | 24-Hour ambulatory blood pressure measurements

Twenty-four-hour AMBP was measured by Spacelabs, 90207 using an oscillometric technique. An appropriate cuff size placed on the left arm was used and readings were obtained every 20 minutes (min). Day- and night-time was set according to diary registered bedtime and get-up time. The degree of nocturnal systolic BP fall was calculated by dividing the difference between $AMBP_{sys}$ day and $AMBP_{sys}$ night with $AMBP_{sys}$ day.

2.2 | Short-term spectral analysis of heart rate variability—supine and upright

The autonomic tests were performed after 10:00 AM in a quiet room with subdued lighting, between 20 and 22°C, with only the patient and the laboratory technician who conducted the examination present. Patients had to refrain from smoking, eating and drinking 2 h before the examination. After resting in the supine position for 15 min, the reciprocal of the heart rate per second (RR) intervals was measured using an online telemetrical transmitter (VariaPulse TF3; Sima Media Olomouc).

2.2.1 | Spectral analysis

Short-term power spectral analysis was obtained in three positions (supine-standing-supine), each of at least 5-min duration, resulting in 3x 256 artefact-free heartbeats. In addition to automatic filtering (using a recognition algorithm), each record was visually scrutinized for ventricular ectopic beats. For the calculations, a modified fast Fourier transformation (coarse graining) was used; this allows the extraction of broadband nonharmonic noise, particularly contaminating the lower frequencies.[16] LF (0.05-0.15 Hz, mediated by the interaction of sympathetic and vagal activity, and strongly influenced by baroreflex activity)[17] and HF (0.15-0.50 Hz, representing a pure estimate of vagal activity) power[17] (expressed as natural log milliseconds squared) and frequency were determined. The intra-individual coefficient of variation of two measurements performed within 1 week in our laboratory was 15.9% (LF power) and 11.3% (HF power). The coefficient of component variation

TABLE 1 Clinical characteristics of participants

	TS (n = 48)	Control (n = 24)	*P*-value
Age (y)	35.0 ± 10.1	42.7 ± 10.4	0.002
Height (cm)	148.0 ± 7.2	168.2 ± 5.9	<0.001
Weight (kg)	56.6 ± 10.0	69.4 ± 7.3	<0.001
BMI ($kg*m^2$)	25.9 ± 4.6	24.6 ± 3.2	0.2
BSA (m^2)	1.49 ± 0.14	1.79 ± 0.09	<0.001
Waist (cm)	79.1 ± 9.9	82.0 ± 9.5	0.2
Hip (cm)	95.2 ± 8.4	104.3 ± 6.1	<0.001
WHR	0.83 ± 0.06	0.79 ± 0.06	0.003
VO_{2max} mL $O_2*kg^{-1}*min^{-1}$	37.8 ± 10.5	38.1 ± 12.4	0.8
Physical activity (self-reported)	2.5 (0-6)	3.5 (2-6)	0.002
Fat mass (kg)	15.1 ± 7.5	17.6 ± 5.5	0.1
Fat mass (%)	25.6 ± 9.0	25.1 ± 5.7	0.8
Fat-free mass (kg)	41.5 ± 4.7	51.8 ± 4.5	<0.001
Fat-free mass (%)	74.3 ± 9.2	74.9 ± 5.7	0.8
AMBP 24 h (mm Hg)			
Systolic	119.4 ± 13.7	115.0 ± 9.4	0.2
Diastolic	75.6 ± 11.4	72.5 ± 7.3	0.2
AMBP day (mm Hg)			
Systolic	125.1 ± 14.2	121.3 ± 9.5	0.2
Diastolic	80.4 ± 11.7	78.3 ± 7.9	0.4
AMBP night (mm Hg)			
Systolic	108.4 ± 13.8	102.3 ± 11.2	0.06
Diastolic	67.1 ± 11.7	60.3 ± 6.9	0.01
Night/day ratio			
Systolic	0.87 ± 0.06	0.84 ± 0.05	0.8
Diastolic	0.83 ± 0.07	0.77 ± 0.05	<0.001
Heart rate day	81.1 ± 9.0	73.8 ± 13.5	0.003
Heart rate night	69.7 ± 8.5	60.4 ± 10.2	<0.001
Heart rate night/day ratio	0.86 ± 0.060	0.071 ± 0.081	0.03

Note. Baseline data of participants and control subjects. AMBP represents average values of 24-h ambulatory blood pressure registration. Values are mean ± standard deviations.
Abbreviation(s): AMBP, ambulatory blood pressure; BMI, body mass index; BSA, body surface area; VO_{2max}, maximal aerobic capacity; WHR, waist-hip ratio.

(square root of HF or LF power/mean RR) (CCVHF and CCVLF, respectively) was calculated for the two components. This parameter accounts for a possible impact of the mean RR level on the amplitude of the HF and LF component.[18] The distribution of the power and central frequency of LF (0.05-0.15 Hz) and HF (central frequency of HF) power (0.15-0.50 Hz) were assessed. The LF:HF ratio is considered an indicator of sympathovagal balance.[19] In addition, the mean RR interval was calculated (the reciprocal of the heart rate per second).

2.2.2 | Bedside tests

These included three conventional cardiovascular reflex tests of heart rate response to standing up (30:15 ratio), heart rate response to deep breathing (inspiration-expiration difference, average of two measurements) and BP response to standing up.[20]

2.3 | Body composition

Resistance and impedance were measured, and total body water (TBW), fat mass (FM), and fat-free mass (FFM) were calculated using bioelectrical impedance (Body Impedance Analyzer BIA 101/S; Akern).[21]

2.4 | Maximal oxygen uptake and questionnaire concerning physical activity

2.4.1 | Maximal oxygen uptake

A 6-min submaximal exercise test with continuous monitoring of heart rate was performed on a bicycle ergometer (Monark Ergometric 829 E; Monark Exercise) using a workload of 300-1200 kpm/min, depending on age and reported physical activity by the subject. The mean heart rate during the last 2 min of work (>120 beats/min) was used for calculation of $VO_{2\text{-}max}$,[22] which in our hands previously has been shown to have a day-to-day intra-individual coefficient of variation of 9%.[22] This indirect measure of $VO_{2\text{-}max}$ correlates well with a direct measure of VO_{2max}, with a coefficient of variation of <10%.

2.4.2 | Physical activity

Participants were interviewed concerning their level of daily activity, during work, leisure and sports; the results were quantified using a questionnaire as described; and a combined index of physical activity is presented.[3]

2.5 | Biochemical analyses

Fasting plasma glucose was measured in duplicate on a Beckman Glucoanalyzer by the glucose oxidase technique (Beckman Instruments, Palo Alto, CA, USA). Plasma lipids and triglycerides were measured using an automated commercially available system (Aeroset, Abbott Diagnostics, Abbott Park Laboratories). The coefficient of variation was <5%. Haemoglobin A1c (HbA1c) was measured by commercially available high-performance liquid chromatography. Hepatic enzymes were determined on a Cobas INTEGRA (Roche).

2.6 | Statistical methods

All statistical calculations were done using SPSS 15.0. Normality of the data was tested with Shapiro-Wilk test of normal distribution. To

TABLE 2 Glucose and lipids in TS and controls

	TS (n = 48)	Control (n = 24)	*P*-value
Fasting glucose[a]	5.4 ± 1.9	5.0 ± 0.6	0.3
HbA1c[b]	0.053 ± 0.008	0.055 ± 0.004	0.4
Cholesterol (mmol/L)	5.2 ± 1.1	5.0 ± 1.0	0.3
HDL-cholesterol (mmol/L)	2.0 ± 0.6	1.6 ± 0.4	0.01
LDL-cholesterol (mmol/L)	2.9 ± 1.0	2.9 ± 1.0	0.8
Triglyceride (mmol/L)	1.0 ± 0.7	0.9 ± 0.4	0.6

Note. Values are mean ± standard deviations. HbA1c, haemoglobin A1c.
Please note that glucose and HbA1c values were not available on all TS participants ([a]n = 35; [b]n = 36).

examine the correlation between parameters, Pearson or Spearman correlation test was used as appropriate. Spectral analysis data were analysed by two-way analysis of variance (ANOVA). For this, ANOVA (general linear model, SPSS) was used to study the influence of changes in measures derived from spectral analysis as a result of changes in the position of the body (supine-standing-supine). The interaction term 'position (supine-standing-supine) * status (TS or control)' was considered the term of interest. Because age is known to influence heart rate variability measures, we repeated the ANOVA model with age as explanatory covariates in the latter ANOVA model, but this did not change the outcome significantly.

Multiple backward stepwise linear regression models were constructed to examine the principal determinants of the autonomic variables, where independent variables were omitted from the model when $P > 0.1$. *P*-values <5% were considered significant.

3 | RESULTS

3.1 | Metabolic parameters

This TS population consisted of 25 women with 45, X (52%), vs other karyotypes in 23 cases (48%) (N = 48). No TS women had significant congenital heart disease (ie, coarctation of the aorta, corrected aortic arch obstruction or minor arch anomalies); however, 16 women had a bicuspid aortic valve and the remaining a tricuspid valve. The TS women and controls were comparable regarding body mass index (BMI), measures of body composition (FM (%) and FFM (%)) and VO_{2max}, while waist-hip ratio (WHR) was higher in TS and age was lower (Table 1). No clinically significant differences were found in metabolic variables such as glucose, HbA1c and lipids (total cholesterol, HDL, LDL and triglycerides; Table 2). Glucose and lipid parameters, WHR, FFM and FM (%) were not different between TS who were or were not receiving HRT at the time of the study visit.

3.2 | Blood pressure

Daytime AMBP was similar in TS and controls, while nocturnal AMBP was elevated in TS leading to an increased night/day diastolic ratio. Heart rate was significantly increased in TS both during day and night (Table 1). Other AMBP measures were similar in the two groups. AMBP was neither found to be different among TS with bicuspid aortic valves (n = 16) compared to tricuspid aortic valves (n = 32), nor when looking at 45, X individuals compared to TS with other karyotypes.

3.3 | Short-term spectral analysis of heart rate variability

In the supine, the standing and the resumed supine position, there was a significant difference between TS and controls in mean RR (indicating a higher heart rate in TS), whereas in the upright position there were significantly higher levels of HF power, CCVHF and a resultant lower LF:HF ratio in TS (Table 3 and Figure 1). When testing for repeated measurements (ie, testing for the interaction between position and status [TS or control]), there were highly significant differences between TS and controls in HF power, CCVHF and LF:HF ratio, with a dampened decline in vagal activity (ie, HF and CCVHF) among TS during standing. Likewise, when testing for repeated measurements we found a highly significant difference in RR TS had a much higher pulse in the supine condition but did not experience a comparable increase in pulse (ie, decrease in RR) during standing, but a return to similar values upon resuming the supine position. Also, the HF and the CCVHF response was significantly different when tested by ANOVA (Table 3). No difference between TS and controls was found in the LF band or in CCVLF. When separating the TS group in two, depending on karyotype (45, X or other), no significant difference was found in heart rate variability parameters between the subgroups.

3.4 | Regression analyses among females with Turner syndrome

3.4.1 | 24-hour blood pressure and heart rate

Among TS, there was no correlation between AMBP and body size (weight, BSA, BMI or WHR). Both VO_{2max} and self-reported level of physical activity were significantly correlated to systolic AMBP both 24 h and night (VO_{2max}: $AMBP_{systolic}$ 24 h: $R = -0.24$, $P = 0.05$; $AMBP_{systolic\ night}$: $R = -0.32$, $P = 0.008$) and night diastolic AMBP (VO_{2max}: $AMBP_{diastolic\ night}$: $R = -0.31$, $P = 0.01$). Likewise, an association was found between VO_{2max} and heart rate both day and night (heart $rate_{day}$: $R = -0.38$, $P = 0.002$; heart $rate_{night}$: $R = -0.32$, $P = 0.007$), while physical activity levels only correlated to the heart $rate_{night}$ ($R = -0.276$, $P = 0.006$).

TABLE 3 Heart rate variability in relation to position

	TS (n = 48)	Control (n = 24)	*P*-value (TS vs C)	*P*-value (ANOVA)*
Mean RR (s)				
Supine	0.867 ± 0.129	1.04 ± 0.152	<0.001	0.003
Standing	0.720 ± 0.097	0.776 ± 0.123	0.02	
Supine	0.874 ± 0.131	1.05 ± 0.149	<0.001	
LF power (ln ms^2)				
Supine	5.66 ± 1.30	5.81 ± 1.52	0.7	0.9
Standing	5.88 ± 1.22	5.91 ± 1.23	0.9	
Supine	5.62 ± 1.32	5.88 ± 1.28	0.4	
HF power (ln ms^2)				
Supine	6.31 ± 1.54	6.74 ± 1.42	0.2	0.02
Standing	5.15 ± 1.50	4.39 ± 1.40	0.03	
Supine	6.56 ± 1.55	7.03 ± 1.20	0.2	
CCVLF (ln)				
Supine	0.681 ± 0.619	0.575 ± 0.762	0.5	0.96
Standing	0.973 ± 0.622	0.917 ± 0.568	0.7	
Supine	0.653 ± 0.641	0.597 ± 0.633	0.7	
CCVHF (ln)				
Supine	1.01 ± 0.70	1.04 ± 0.69	0.8	0.046
Standing	0.611 ± 0.715	0.157 ± 0.650	0.007	
Supine	1.12 ± 0.71	1.17 ± 0.57	0.8	
cf LF (mHz)				
Supine	103 ± 29	87 ± 32	0.0	0.6
Standing	88 ± 24	81 ± 29	0.3	
Supine	107 ± 29	94 ± 28	0.1	
cf HF (mHz)				
Supine	227 ± 52	233 ± 67	0.6	0.8
Standing	211 ± 56	205 ± 53	0.6	
Supine	237 ± 52	242 ± 71	0.7	
Ratio LF: HF (ln)				
Supine	-0.649 ± 1.20	-0.938 ± 1.09	0.3	0.002
Standing	0.726 ± 1.19	1.53 ± 1.10	0.02	
Supine	-0.937 ± 1.33	-1.143 ± 1.11	0.3	

Note. Values are mean ± standard deviations.
Abbreviation(s): cf LF/cf HF, the distribution of central frequency of low frequency/high frequency; CCVLF/CCVHF, coefficient of component variation of low/high frequency power; LF/HF power, low/high-frequency power; ln, the natural logarithm; ms, milliseconds; RR, the reciprocal of the heart rate per second.
*Analysis of variance (ANOVA) in Turner syndrome vs controls; *P*-value is given for the interaction term "position (supine–standing-supine) *status (Turner syndrome or control)".

3.4.2 | Heart rate variability

LF power and HF power, CCVLF and CCVHF all correlated with age ($r = -0.39$ to -0.47; $P < 0.001$ for all), while LF:HF ratio did not. Even though HbA1c was only available in a subgroup of TS (n = 35), a consistent association was present between HbA1c and LF power, HF power, CCVLF and CCVHF ($r = -0.23$ to -0.43; $P < 0.001$ to $P = 0.04$). Associations to systolic AMBP, cholesterol and triglyceride were also present (data not shown).

3.4.3 | Final regression models

Based on these findings, models of multiple linear regression were constructed with age, HbA1c, triglycerides, WHR, systolic AMBP and pulse as independent variables, and LF power, HF power, CCVLF and CCVHF consecutively as the dependent variables. In combined analyses with both TS and controls, age, $AMBP_{systolic}$ 24 h and status (being TS or control) were significant contributing covariates to the change in HF power, LF power and CCVHF (results not shown).

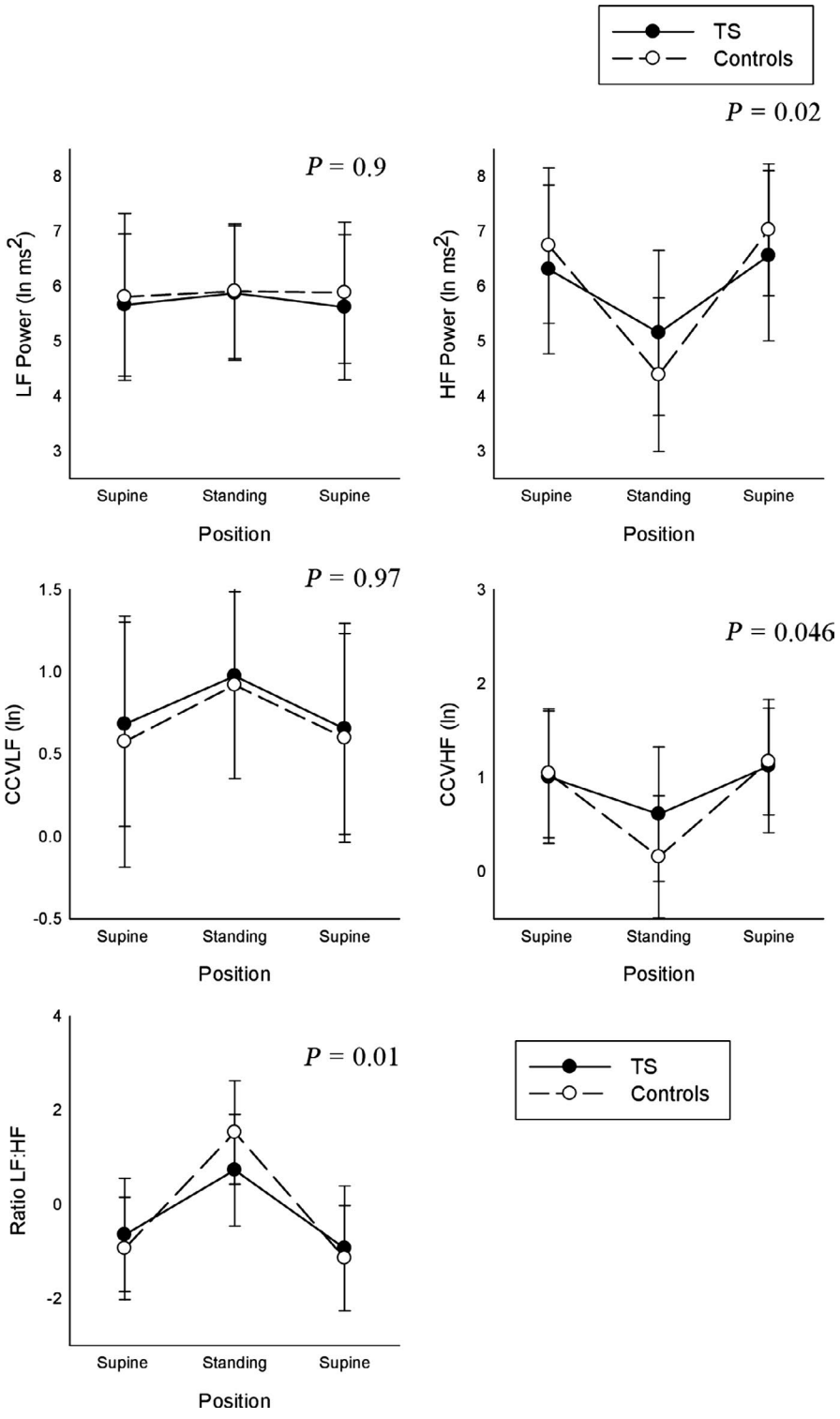

FIGURE 1 Adaptation in heart rate variability from supine to standing and back to the supine position, with a reduced response in TS. N = 48 for TS. N = 24 for controls

Among TS alone, age, $AMBP_{systolic}$ 24 h, triglycerides, and HbA1c were determining for the change in LF and HF power (data not shown). Adding VO_{2max} to the model, we found that VO_{2max} was of importance for HF power and CCVHF (HF power: $r = -0.21$-0.39, $P = 0.001$-0.06; CCVHF: $r = 0.001$-0.32, $P = 0.001$-0.03), but not LF power or CCVLF.

Oestrogen treatment and years with oestrogen insufficiency did not have any influence on the results (data not shown).

4 | DISCUSSION

The principal result of this study was a difference in markers of autonomic innervation and heart rate variability in TS compared to a control population. We have previously shown this at a smaller scale,[7] and the present study supports and elaborates on these findings. Here, we show that HF power and CCVHF, as well as mean RR and the LF: HF ratio, are significantly changed in TS, despite only

marginally higher BP during the night. These findings are indicative of altered vagal tone of heart rate variability and may be part of the pathophysiology behind the frequent cardiac disease burden in TS.[23] Especially, the reduced change in HF power during the sequence supine-standing-supine suggests a reduced plasticity of the parasympathetic system among females with TS. In addition, we show that 24-hour heart rate is unequivocally increased in TS.

Through life, cardiovascular mortality in TS is primarily associated with congenital abnormalities, aortic dissection and ischaemic heart disease.[2] However, in the general population, resting heart rate is associated with increased all-cause and cardiovascular mortality,[24] and this factor may also contribute to the increased mortality in TS. Especially, the incidence of heart failure is not completely explained by the burden of ischaemic heart disease, and there may be an association between heart failure and heart rate variability needs to be investigated further.[4,5] Larger cohorts and follow-up studies are warranted before we can include heart rate variability in the overall risk assessment. Interestingly, we found a significant negative association between VO_{2max} and AMBP measures, including heart rate, reinforcing that also among females with TS it is beneficial to have a large aerobic capacity, because this seems to positively impact both BP and heart rate.

In our earlier study on 8 women with TS, the differences were in the LF band, which comprises a mixture of sympathetic and vagal activity. However, in that study there was a significant difference in both systolic and diastolic night BP, with higher levels among TS, even though all participants were normotensive.[7] We also found night systolic and diastolic BP to be elevated among TS. In the present study, we found a defective vagal regulation of heart rate variability, with a dampened response to postural change, which was seen both not only as a changed HF power, but also as a significant difference in CCVHF, a measure of vagal activity where the influence of heart rate has been removed. As a result, we also found a significant difference in the LF:HF ratio, which can be viewed as a measure of sympathovagal balance or tone. We also found that metabolic variables, such as the level of triglycerides and HbA1c, influenced the observed differences in measures of sympathovagal tone, emphasizing that the metabolic state of individuals with TS interlinks with the cardiovascular risk profile.

Age was an important predictor of all the measured variables of heart rate variability, and although TS and controls were not completely matched on age—the TS females being somewhat younger than the controls—heart rate variability was indeed quite abnormal among TS. Since heart rate variability decreases with age, the present findings most likely tend to underestimate our results, as the control group was on average 8 years older than the participating TS. The aetiology behind the defective vagal tone and the sympathovagal balance in TS is not clear. Previously, we have suggested that it may be mechanical in origin and be caused by the in utero changes seen, with the developing lymph channels distension causing harm to the heart and great vessels and in such a manner mechanically inducing congenital heart defects,[2] as well as the autonomous nervous system. The prolonged oestrogen-deficient state that many girls with TS go through before receiving substitution therapy with oestrogen (and progestins) may be harmful, and oestrogen may be necessary for maturation of the autonomic nervous system. Among postmenopausal women, hormone replacement therapy (HRT) has been seen to attenuate heart rate variability,[25] but others have found favourable effects of HRT on heart rate variability.[26]

Hypertension is a widespread concern in the care of TS,[3,6] but may still be unnoticed or insufficiently treated. It is a major concern that the prevalence of hypertension is so high in an unselected group of women with TS despite young age and independent of body weight.[6] This should lead clinicians to monitor BP in all TS at all ages very carefully and initiate treatment when necessary. Taking the grossly increased risk of aortic dilatation and dissection in TS into account,[27,28] treatment of hypertension should be aggressive and sufficient. The aetiology behind hypertension among females with TS may thus be viewed as happening on a backdrop of altered sympathovagal tone, possibly due to congenital abnormalities of the wiring of the parasympathetic and/or the sympathetic nervous system, frequent congenital malformations of the left side of the heart and dilated branching arteries,[29] increased resting norepinephrine levels,[13] while the renin-aldosterone system seems to be normal.[7]

Lipid levels were comparable to controls in the present study, as they are in most studies.[8] However, elevated triglyceride levels have been reported but could be a consequence of hyperinsulinemia and obesity.[30] Central obesity and an increase in visceral fat have been shown to be increased in TS,[31] and even though an association was found to insulin levels in TS, insulin levels in TS did not differ from controls in these studies.

5 | CONCLUSION

Vagal tone and modulation of the sympathovagal balance during alteration in body position are significantly impaired in TS. Night-time diastolic blood pressure was also significantly increased in TS, which can be associated to the development of aortic dilatation.

ACKNOWLEDGEMENTS

Bente Mortensen, Lone Svendsen, Merete Møller, Joan Hansen and Karen Mathiasen are thanked for their expert technical help. Line Gether is thanked for expert secretarial assistance. The study was supported by a grant from the Danish Agency for Science Technology and Innovation (# 271-07-0333) and by an unrestricted grant from Novo Nordisk.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ORCID

Sara Brun https://orcid.org/0000-0002-3708-2949

Agnethe Berglund https://orcid.org/0000-0001-9185-1342
Kristian H. Mortensen https://orcid.org/0000-0002-8986-6067
Britta E. Hjerrild https://orcid.org/0000-0002-1409-0516
Klavs W. Hansen https://orcid.org/0000-0002-7452-2747
Niels H. Andersen https://orcid.org/0000-0002-5394-3016
Claus H. Gravholt https://orcid.org/0000-0001-5924-1720

REFERENCES

1. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*. 2017;177:G1-G70.
2. Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome–integrating cardiology, genetics, and endocrinology. *Endocr Rev*. 2012;33:677-714.
3. Brun S, Cleemann L, Holm K, et al. Five-year randomized study demonstrates blood pressure increases in young women with Turner syndrome regardless of estradiol dose. *Hypertension*. 2019;73:242-248.
4. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Mortality in women with turner syndrome in Great Britain: a national cohort study. *J Clin Endocrinol Metab*. 2008;93:4735-4742.
5. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91:3897-3902.
6. Elsheikh M, Casadei B, Conway GS, Wass JA. Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. *Clin Endocrinol*. 2001;54:69-73.
7. Gravholt CH, Hansen KW, Erlandsen M, Ebbehoj E, Christiansen JS. Nocturnal hypertension and impaired sympathovagal tone in Turner syndrome. *J Hypertens*. 2006;24:353-360.
8. Landin-Wilhelmsen K, Bryman I, Wilhelmsen L. Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. *J Clin Endocrinol Metab*. 2001;86:4166-4170.
9. Manzella D, Carbonella M, Ragno E, Passariello N, Grella R, Paolisso G. Relationship between autonomic cardiac activity, beta-cell function, anthropometrics and metabolic indices in type II diabetics. *Clin Endocrinol*. 2002;57:259-264.
10. Min KB, Min JY, Paek D, Cho SI. The impact of the components of metabolic syndrome on heart rate variability: using the NCEP-ATP III and IDF definitions. *Pacing Clin Electrophysiol*. 2008;31:584-591.
11. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care*. 2003;26:1895-1901.
12. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*. 2003;107:565-570.
13. Zuckerman-Levin N, Zinder O, Greenberg A, Levin M, Jacob G, Hochberg Z. Physiological and catecholamine response to sympathetic stimulation in turner syndrome. *Clin Endocrinol*. 2006;64:410-415.
14. Mortensen KH, Hjerrild BE, Stochholm K, et al. Dilation of the ascending aorta in Turner syndrome – a prospective cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2011;13:24.
15. Mortensen KH, Erlandsen M, Andersen NH, Gravholt CH. Prediction of aortic dilation in Turner syndrome – Enhancing the use of serial cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2013;15:47.
16. Yamamoto Y, Hughson RL. Coarse-graining spectral analysis: new method for studying heart rate variability. *J Appl Physiol*. 1991;71:1143-1150.
17. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. *Cardiovasc Res*. 1996;32:208-216.
18. Hayano J, Sakakibara Y, Yamada A, et al. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol*. 1991;67:199-204.
19. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J*. 1996;17:354-381.
20. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care*. 1985;8:491-498.
21. Heitmann BL. Prediction of body water and fat in adult Danes from measurement of electrical impedance. A validation study. *Int J Obes*. 1990;14:789-802.
22. Gravholt CH, Naeraa RW, Nyholm B, et al. Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. The impact of sex hormone replacement. *Diabetes Care*. 1998;21:1062-1070.
23. Patel VN, Pierce BR, Bodapati RK, Brown DL, Ives DG, Stein PK. Association of Holter-derived heart rate variability parameters with the development of congestive heart failure in the cardiovascular health study. *JACC Heart Fail*. 2017;5:423-431.
24. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ*. 2016;188:E53-63.
25. Christ M, Seyffart K, Wehling M. Attenuation of heart-rate variability in postmenopausal women on progestin-containing hormone replacement therapy. *Lancet*. 1999;353:1939-1940.
26. Farag NH, Nelesen RA, Parry BL, Loredo JS, Dimsdale JE, Mills PJ. Autonomic and cardiovascular function in postmenopausal women: the effects of estrogen versus combination therapy. *Am J Obstet Gynecol*. 2002;186:954-961.
27. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation*. 2007;116:1663-1670.
28. Duijnhouwer AL, Bons LR, Timmers H, et al. Aortic dilatation and outcome in women with Turner syndrome. *Heart*. 2018. https://doi.org/10.1136/heartjnl-2018-313716.
29. Mortensen KH, Gopalan D, Norgaard BL, Andersen NH, Gravholt CH. Multimodality cardiac imaging in Turner syndrome. *Cardiol Young*. 2016;26:831-841.
30. Gravholt CH, Nyholm B, Saltin B, Schmitz O, Christiansen JS. Muscle fiber composition and capillary density in Turner syndrome: evidence of increased muscle fiber size related to insulin resistance. *Diabetes Care*. 2001;24:1668-1673.
31. Ostberg JE, Thomas EL, Hamilton G, Attar MJ, Bell JD, Conway GS. Excess visceral and hepatic adipose tissue in Turner syndrome determined by magnetic resonance imaging: estrogen deficiency associated with hepatic adipose content. *J Clin Endocrinol Metab*. 2005;90:2631-2635.

How to cite this article: Brun S, Berglund A, Mortensen KH, et al. Blood pressure, sympathovagal tone, exercise capacity and metabolic status are linked in Turner syndrome. *Clin Endocrinol (Oxf)*. 2019;91:148–155. https://doi.org/10.1111/cen.13983