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ARTICLE

Systolic and Diastolic Strain Measurements Show Left Ventricular Dysfunction in Women with Turner Syndrome

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ABSTRACT

Aim: This study aimed to describe the systolic left ventricular global longitudinal strain (LvGLS) and left ventricular peak early diastolic strain rate (Sre) in adult women with Turner syndrome (TS) and to determine its relationship with exercise capacity and clinical parameters. **Methods:** In this cross-sectional cohort study, consecutively included adult TS women underwent an electrocardiogram, transthoracic echocardiogram (TTE) and cardiopulmonary exercise test (CPET) on the same day. LvGLS and Sre were measured using 2D speckle tracking analysis (STE) and compared with age-matched healthy female controls. **Results:** Ninety-four adult women (age 36 ± 13 years) with TS and 32 healthy age-matched female controls were included. Women with TS had a significantly impaired/reduced systolic LvGLS ($-17.82 \pm 2.98\%$ *vs.* $-21.80 \pm 1.85\%$, $p < 0.001$) and Sre (0.98 ± 0.32 s-1 *vs.* 1.27 ± 0.19 s-1, $p > 0.001$), compared to healthy female controls. Furthermore, TS women had reduced diastolic function as measured by conventional echocardiographic parameters: A higher A-wave ($p < 0.001$), lower E/A-ratio ($p = 0.001$), longer deceleration time ($p = 0.006$), and a higher E/E'-ratio ($p < 0.001$). Women with TS also had a significantly reduced maximal workload ($p = 0.033$), reduced oxygen uptake ($p < 0.001$) and a reduced maximal heart rate ($p < 0.001$) during exercise. Multivariable linear regression analysis revealed that Age, karyotype and QT-duration were significantly associated with Sre, but not with LvGLS, in the TS population. **Conclusion:** Systolic and diastolic strain and exercise capacity were significantly reduced in TS women compared to healthy women. No correlation between strain itself and exercise capacity could be demonstrated, but correlations with conventional TTE parameters and baseline characteristics were found.

KEYWORDS

Turnersyndrome; speckletracking echocardiography; strain; exercise capacity

1 Introduction

Turner syndrome (TS) is caused by a partial or complete loss of the X chromosome and affects approximately 1 in 2000 live-born girls [1]. Besides the classical features, such as short stature and gonadal dysgenesis, these women have an increased risk of cardiovascular disease which is an important

cause of morbidity and mortality among TS patients [1,2]. Common congenital heart defects are bicuspid aortic valve (BAV; 25%–39%) [3,4], coarctation of the aorta (CoA; 12%–16%) [3], and partial abnormal pulmonary venous return (PAPVR; 18%–25%) [5,6]. These congenital heart defects may affect left ventricular (LV) function [7]. However, TS has also been associated with increased LV mass and reduced LV dysfunction independent of congenital heart disease [8–10]. The etiology of this predominantly sub-clinical LV impairment that exists in absence of hypertension or poor metabolic control remains enigmatic [8,9]. To date there is very little data on left ventricular global longitudinal strain (LV GLS) and LV diastolic strain rate (Sre) in adult women with Turner syndrome. And studies that did examine left ventricular function in TS patients were often done using conventional echocardiography [9,11]. Where conventional echocardiography may not be able to detect early sub-clinical LV dysfunction and children may not have developed dysfunction yet. Therefore, this study uses deformation measurements by 2D speckle-tracking echocardiography (STE) which may offer advantages, such as angle independency, over conventional echocardiographic markers for diastolic dysfunction [12–14]. Moreover, the myocardial deformation parameters as LvGLS and Sre have not yet been comprehensively described in adult women with TS. Furthermore, the effect of sub-clinical LV dysfunction on exercise capacity has not yet been described in a TS population, whereas this effect is well-studied in non-TS cohorts [15,16]. While these effects may be clinically relevant, especially in a population that often struggles with unexplained fatigue [17]. Therefore, the aims of this study are threefold; firstly, to comprehensively describe systolic (LvGLS) and diastolic LV function (Sre) using STE and compare it to age and gender matched controls. Secondly, to determine exercise capacity in women with TS. Finally, we aim to investigate possible relation between left ventricular function and exercise parameters.

2 Methods

2.1 Study Population and Design

In this multi-center, cross-sectional study 94 consecutive adult women with genetically proven TS were included from October 2014 to April 2016. All patients underwent a physical examination, transthoracic echocardiogram (TTE), electrocardiogram (ECG) and a cardio pulmonary exercise test (CPET) on a bike ergometer on the same day. Electronic patient records were used to collect medical history. A total of 32 age-matched healthy women were selected from a cohort study consisting of 155 healthy volunteers to serve as control group. All healthy controls were free from a history of systemic disease, cardiovascular disease, renal dysfunction or cardiac medication use. Details of this control cohort have been described previously [7]. Hypertension was defined as the prescription of antihypertensive medication or an elevated blood pressure (systolic >140 mmHg and/or diastolic blood pressure >90 mmHg). Hypercholesterolemia and diabetes were defined as the requirement for treatment. Body surface area was determined using the DuBois formula [18]. This study was approved by the medical ethical committee of the Erasmus Medical Center. Written informed consent was obtained from all participants.

2.2 Echocardiography

2.2.1 Imaging Acquisition

Two-dimensional greyscale images were obtained by two experienced sonographers using the ultrasound system iE33 (Philips Medical Systems, Best, The Netherlands) equipped with a S5-1 transducer (1-MHz to 5-MHz, frequency transmitted 1.7 MHz, frequency received 3.4 MHz). A minimum framerate of 60 Hz is obtained to optimize the speckle tracking echocardiograph. Digital images are stored in QLAB workstation (Philips Medical Systems) for further analysis.

2.2.2 Image Analysis

Dimensional and functional measurements were done according to the recommendations for cardiac chamber quantification in adults [19]. The mitral- and aortic valve regurgitation were visually graded as

none, mild, moderate or severe. Ejection fraction was visually graded as reduced, mildly reduced or good. Left ventricular strain analysis using STE was done by Allard T. van den Hoven and Sultan Yilmazer, blinded to patient specific information. 2D-speckle tracking analysis was done using Tomtec Imaging Systems (2D Cardiac Performance Analysis). Feasibility was assessed by both observers, in case of insufficient imaging quality patients were excluded from further analysis. The peak systolic LV GLS, defined as the maximum strain value during the ejection, was calculated from the apical four-, three- and two-chamber views according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [19]. Also, LV global longitudinal early diastolic strain rate (Sre) was assessed as the maximum strain rate during early diastole. Sre was calculated for each apical chamber view by averaging the segmental Sre values. The myocardial contours, both end diastolic and end-systolic, are drawn automatically by the software. Contours were checked during the full cardiac cycle and manually adjusted if necessary.

2.2.3 Electrocardiogram and Cardiopulmonary Exercise Test

Participants underwent a 12-lead standard resting electrocardiogram (ECG) and a symptom-limited cardiopulmonary bike exercise test (CPET) including a breath-by-breath analysis. The diastolic and systolic blood pressure was measured at rest, and at maximal exertion. All parameters are determined according to the ATS/ACCP guidelines [20]. Individual standardized reference value are calculated according to the CPET-protocol used in our center using the formula for women: $((2 \times \text{length} -2.37 \times \text{age} -73) \times 1.01 + 16,6) \times 0.8$. A workload or VO2max lower than 85% of the predicted value is considered as reduced exercise capacity. The reference group did not complete a bike ergometry as this was a retrospective cohort and this was not included in the protocol at the time of inclusion

2.3 Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) when normally distributed, and as median and IQR in case of a non-normal distribution. Categorical variables are expressed in frequencies and percentages. Differences between two groups are compared by using the Student unpaired *T*-test when normally distributed and the Mann-Whitney U test in case of a non-normal distribution. Furthermore, differences between two measurements in a group were compared by using the paired *T*-test. Correlation analysis is performed by Pearson or Spearman correlation test, as appropriate. Univariable linear regression analysis and subsequent stepwise multivariable linear regression analysis ($p < 0.10$) was performed to identify patient characteristics that are significantly associated with LV function and exercise capacity. In case of collinearity of variables, we entered the variable with the strongest correlation with the outcome into the multivariate linear regression analysis. A *p*-value of <0.05 is considered statistically significant. The inter-observer variability was analyzed by using the Bland-Altman analysis. The limits of agreement between two observers were defined as the mean of the differences ±1.96 SD. The coefficient of variation (COV) was calculated as the ratio of the standard deviation of the mean difference to the mean of the two measurements. All statistical analyses were performed with the Statistical Package for Social Sciences, Version 21.0 (SPSS, Chicago, Illinois).

3 Results

3.1 Characteristics of the Study Population

Ninety-four adult women with TS (mean age 36 ± 13 years, all female) were included. The control group consisted of 32 healthy women (mean age 37 ± 6 years). Forty-four women had a monosomy X, 14 had a mosaicism, other karyotypes included isochromosome (n = 14), polyploidy (n = 5), ring chromosome (n = 3), deletion (n = 3), derivative (n = 2).

Of these women, 41 (44%) were known with structural heart disease, such as BAV (n = 27), PAPVR (n = 13), CoA (n = 9), persistent left vena cava superior (n = 4), arteria lusoria (n = 3), persistent ductus

arteriosus (n = 2), persistent foramen ovale (n = 3), hypoplastic aortic arch (n = 1), aortic stenosis (n = 1), pulmonary atresia (n = 1), incomplete double aortic arch (n = 1) or tetralogy of Fallot (n = 1). Baseline characteristics for TS patients and healthy controls are shown in Tab. 1. There was no difference in baseline characteristics between TS women with and without structural heart disease. Moreover, eight TS women (9%) had underwent aortic intervention at moment of inclusion including: Coarctation repair (n = 6), coarctation repair and a graft replacement of the aortic root (n = 1), and coronary artery bypass grafting (n = 1). Furthermore, seven patients (7%) had underwent valve intervention. There were 23 (24%) TS women using cardiovascular medication: Statin (n = 8), angiotensin ll receptor blockers (n = 6), beta-blockers (n = 8) or angiotensin converting enzyme inhibitors (n = 7).

Table 1: Baseline characteristics

	Total TS (n = 94)	Healthy controls (n = 32)	p-value*
Baseline			
Age, years	36 ± 13	37 ± 6	0.674
Height, cm	155 ± 8	169 ± 6	**<0.001**
Weight, kg	62.9 ± 15.1	66.1 ± 9.8	0.171
BSA, m^2	1.61 ± 0.20	1.76 ± 0.13	**<0.001**
BMI, kg/m^2	26 ± 5.5	23 ± 3.3	**0.001**
SBP, mmHg	126 ± 15	118 ± 9	**<0.001**
DBP, mmHg	81 ± 12	75 ± 8	**0.001**
Hypertension	19 (20)	NA	
Hypercholesterolemia	10 (11)	NA	
Diabetes	4 (4)	NA	
HRT	94 (100)	NA	
Exercise		Completeness n (%)	
Workload, % of predicted	95 ± 23		92 (100)
Workload, watt	124 ± 39		92 (100)
Heart rate			
HR, % of predicted	89 ± 9		92 (100)
Heart rate, beats/min	163 ± 23		92 (100)
O_2 pulse, ml/min/beat	9.31 ± 2.00		90 (98)
Blood pressure			
SBP, mmHg	155 ± 22		92 (100)
DBP, mmHg	80 ± 14		92 (100)
Ventilation			
VO_2, ml/min	1555 ± 384		91 (99)
VO_2, % of predicted	89 ± 16		91 (99)
VO_2, ml/min/kg	25.16 ± 6.10		91 (99)
VCO_2, ml/min	1819 ± 500		90 (98)
V'E, l/min	58.5 ± 16.6		91 (99)
V'E, l/min/kg	0.96 ± 0.29		91 (99)
$PETO_2$, kPa	15.7 ± 0.9		91 (99)
$EqCO_2$	30.2 ± 4.6		90 (98)
EqO_2	35.4 ± 7.5		90 (98)
Peak RER	2.2 ± 0.1		91 (99)

Note: Continuous data are presented as 'mean ± SD' and categorical data as 'n = (%)'. BSA: Body Surface Area, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HRT: Homone Replacement Therapy, BAV: Bicuspid Aortic Valve, NA: Not Applicable, *: significance of the difference between patients with all Turner syndrome patients and healthy controls. Measurements at maximal exertion. HR: Heartrate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, VO_2: O_2 Consumption, VCO_2: CO_2 Production, V'E: Minute Volume, $PETO_2$: End Tidal Tension of Oxygen, $EqCO_2$: Ventilatory Equivalent for CO_2, EqO_2: Ventilatory Equivalent for O_2, RER: Respiratory Equivalent Ratio.

3.2 Systolic and Diastolic Myocardial Deformation Measurements

Twelve TS patients (13%) and one healthy control (3%) had to be excluded from strain analysis in advance because of poor imaging quality. Women with TS had a significantly impaired systolic LvGLS (−17.82% ± 2.98% *vs*. −21.80% ± 1.85%, $p < 0.001$; Fig. 1A) and diastolic Sre (0.98 ± 0.32 s-1 *vs*. 1.27 ± 0.19 s-1, $p > 0.001$; Fig. 1B) compared to healthy female controls. Furthermore, 28 TS women (30%) had a systolic LvGLS below normal (<17% [19]). When compared with the lower limit of normal for their age group (<0.89 s-1, [21]), 35 TS patients (37%) had a low Sre value. The intra-observer variability analysis showed low mean differences and good correlation for systolic LvGLS (0.31% ± 1.36, Pearson's R: 0.885, *p*-value<0.001, Appendix A: Supplementary Fig. 1) and Sre (−0.07 s-1 ± 0.19, Pearson's R: 0.817, *p*-value<0.001, Appendix A: Supplementary Fig. 1).
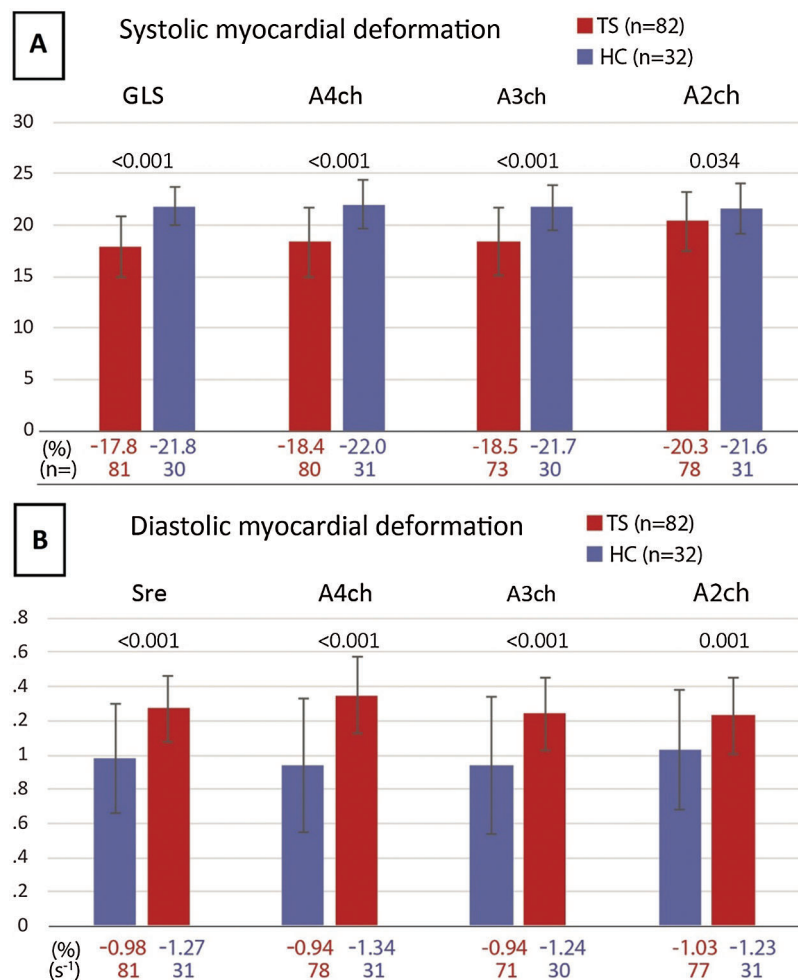
Figure 1: A) Systolic myocardial deformation B) Diastolic myocardial deformation
Note: TS: turner syndrome, HS Healthy controls, Sre: strain rate, A4ch: apical four chamber, A3ch: apical three chamber, A2ch: apical two chamber

3.3 Conventional Echocardiography

Echocardiographic measurements are shown in Tab. 2. All functional LV parameters, LV chamber function, E-wave, and E'-wave were significantly different in TS patients compared with healthy women. The absolute LV dimensions were not significantly different; however, when corrected for BSA, LV was

significantly larger in TS women, both in end-diastole (LVEDd: 28 mm/m^2 ± 3.6 *vs*. 26 mm/m^2 ± 2.6, $p = 0.002$) and in end-systole (LVEDs: 18 mm/m^2 ± 3.2 *vs*. 16 mm/m^2 ± 2.4, $p = 0.002$). TS women may have higher BMI than their non-TS peers, which may influence their BSA. Therefore, we also examined LV dimension corrected for height, where the same statistically significant difference was observed (LVEDd per meter: 29 mm/m ± 2.9 *vs*. 27 mm/m ± 2.1, $p = 0.002$) and in end-systole (LVEDs: 18 mm/m ± 3.2 *vs*. 16.5 mm/m ± 2.4, $p = 0.001$).

Table 2: Conventional echocardiographic parameters

	Turner Syndrome n = 94 n (%)	Completeness n (%)	Healthy controls n = 32 n (%)	Completeness n (%)	*p*-value
Left ventricular function					
LVEF, %	53 ± 10	84 (89)	62 ± 5	31 (97)	**<0.001**
E-wave, m/s	0.84 ± 0.21	90 (96)	0.81 ± 0.18	31 (97)	0.503
A-wave, m/s	0.66 ± 0.23	89 (95)	0.45 ± 0.12	31 (97)	**<0.001**
E/A-ratio	1.40 ± 0.55	89 (95)	1.95 ± 0.79	31 (97)	**0.001**
DET, ms	199 ± 53	88 (94)	177 ± 27	31 (97)	**0.006**
E'-wave, cm/s	10.1 ± 3.6	84 (89)	10.7 ± 2.0	30 (94)	0.968
E/e'-ratio	9.7 ± 4.0	84 (89)	7.5 ± 1.7	30 (94)	**<0.001**
Left sided dimensions					
LVEDd, mm	44.6 ± 4.6	93 (99)	45.6 ± 3.5	32 (100)	0.240
LVEDd per BSA, mm/m^2	27.9 ± 3.6	93 (99)	26.1 ± 2.6	32 (100)	**0.002**
LVEDs, mm	28.6 ± 4.6	93 (99)	27.9 ± 4.0	32 (100)	0.446
LVEDs per BSA, mm/m^2	17.9 ± 3.2	93 (99)	15.9 ± 2.4	32 (100)	**0.002**
Valvular heart disease					
MV regurgitation					
None	78 (83)	94 (100)	NA	–	–
Mild	16 (17)				
Moderate	0 (0)				
AV regurgitation					
None	71 (76)	94 (100)	NA	–	–
Mild	22 (23)				
Moderate	1 (1)				

Note: *LVEF:* Left Ventricular Ejection Fraction, *BSA:* Body Surface Area, *E-wave:* Mitral Flow E Velocity, *A-wave:* Mitral Valve A velocity, *E/A-Ratio:* Mitral Flow E Velocity/A Velocity, *DET:* Deceleration Time, *E'-Wave:* Early Diastolic Annular Myocardial Velocity (septal), *E/E'-ratio* Mitral Flow E Velocity/Early Diastolic Annular Myocardial Velocity, *LVEDd:* Left Ventricular Dimension At End-diastole, *LVEDs:* Left Ventricular Dimension at End-systole, *MV Regurgitation:* Mitral Valve Regurgitation, *AV Regurgitation:* Aortic Valve Regurgitation, *NA:* Not Applicable.

3.4 Electrocardiography

Women with TS had significantly higher resting heart rate (77 bpm ± 13) compared to healthy controls (60 bpm ± 8, $p < 0.001$). Also, conduction times differed between groups: The PR-duration was shorter (137 ms ± 25 and 148 ms ± 24, $p = 0.029$), and QTc-duration was longer (420 ms ± 31 and 395 ms ± 14,

$p < 0.001$) in women with TS compared to healthy women. None of the patients had signs of LV hypertrophy on the electrocardiogram and all TS patients, except one, were in sinus rhythm (n = 92, 99%).

3.5 Cardio Pulmonary Exercise Test

Cardiopulmonary exercise testing was performed in 92 (98%) patients and exercise parameters are shown in Tab. 1. Thirty-two TS women (35%) had a reduced workload and 33 women (36%) had a reduced VO2max (<85%). Moreover, TS women had a significantly reduced maximal heart rate ($p < 0.001$), reduced oxygen uptake ($p < 0.001$) and a reduced maximal workload ($p = 0.033$) when compared with individual standardized reference values. Moreover, exercise capacity did not differ between women with and without cardiac defects (94% *vs.* 96% of predicted, $p = 0.752$).

3.6 Associations of Systolic and Diastolic Myocardial Deformation Parameters

The results of the regression analysis are presented in Tab. 3. In line with previous higher age was significantly associated with reduced Sre, and longer QTc times with a higher Sre. Also karyotype remained significantly associated with Sre (β-coefficient: 0.005, p-value <0.001; R2 = 0.445). For LvGLS no significant associations were found with baseline characteristics (Tab. 3).

Table 3: Linear regression analysis

Baseline characteristics	Univariable regression				Multivariable regression			
	Left ventricular diastolic strain rate (SRe)							
	β-coefficient	95% CI		p-value	β-coefficient	95% CI		p-value
		Lower limit	Upper limit			Lower limit	Upper limit	
Age, years	–0,009	–0,014	-0,004	**<0.001**	–0.01	–0,14	–0,005	**<0.001**
BMI, kg/m²	–0,005	–0,019	0,008	0.445				
Heart rate, beats/min	0,001	–0,004	0,007	0.632				
DBP, mmHg	0,004	–0,002	0,010	0.169				
SBP, mmHg	0,001	–0,004	0,006	0.610				
Karyotype*	0,142	–0,007	0,291	**0.061**	0.130	0,009	0,250	**0.035**
QT$_c$-duration, ms	0.004	0,002	0,007	**<0.001**	0.005	0,003	0,007	**<0.001**
PR-interval duration, ms	–0,001	–0,004	0,002	0.534				
	Left ventricular global longitudinal strain (LV GLS)							
Age, years	0.024	–0.025	0.074	0.335				
BMI, kg/m²	0.064	–0.063	0.192	0.316				
Heart rate, beats/min	0.025	–0.028	0.079	0.342				
DBP, mmHg	–0.049	–0.103	0.005	**0.074**				
SBP, mmHg	0.013	–0.032	0.058	0.567				
Karyotype*	0.145	–1.623	1.333	0.845				
QT$_c$-duration, ms	0.014	–0.036	0.007	0.193				
PR-interval duration, ms	0.013	–0.012	0.038	0.315				

Note: Regression analysis. *HR*: Heartrate, *SBP*: Systolic Blood Pressure, *DBP*: Diastolic Blood Pressure, * karyotype was dichotomized; monosomy (0) *vs.* other Type (1), e.g., mosaic, NS: Not Significant.

Although it was not the main objective of our study, we did compare patients with and without cardiovascular disease. We did test for a possible difference in patients with or without structural heart disease. However, no such influence could be found for the main outcome measurements such as strain or exercise capacity. Moreover, some minor differences were observed that may point in the direction of minor diastolic dysfunction in the patient group with cardiac disease. A higher a-wave was observed in

(0.7 *vs*. 0.6 m/s, *p* = 0.019), a lower e'-wave (9 *vs*. 11 cm/s, *p* = 0.031). Patients with cardiac disease also had a larger 'LVED/BSA' both in systole and diastole (28.9 *vs*. 27.2, *p* = 0.19 and 18.6 and 17.3 *p* = 0.49). However, this was largely explained by them having a lower BSA (1.56 *vs*. 1.65; *p* = 0.02).

4 Discussion

This study demonstrates significantly lower myocardial deformation parameters (LvGLS and Sre) in women with TS Furthermore. Furthermore, TS women showed reduced conventional diastolic parameters, significantly different conduction times and a lower exercise capacity. Age, karyoptype and QTc-duration were significantly associated with Sre but not with LvGLS in the TS population. We did observe impaired diastolic function on conventional echocardiography compared to the healthy controls, mainly: lower A-wave and E/A-ratio, shorter DET, and higher E/e'-ratio.

4.1 LV Myocardial Deformation in Women with TS

Although LV myocardial deformation measurement using STE is superior to tissue Doppler imaging (TDI), [22,23] earlier studies have already described a higher A-wave and subsequently a lower E/A-ratio compared to healthy female subjects [8–11]. Our study supports these findings and adds a prolonged deceleration time and higher E/e'-ratio compared to healthy women.

Hypertension is an important risk factor for LV diastolic dysfunction and aortic dilatation. In line with previous studies [24–27], we found an elevated diastolic and systolic blood pressure in women with TS. Therefore, vigilant surveillance of not only systolic but also diastolic blood pressure in TS patients is important as described earlier [25]. We hypothesized that this difference in blood pressure may explain the difference in myocardial deformation parameters between TS and healthy controls. However, our current study shows no significant effect of blood pressure on the myocardial deformation parameters. This finding is in line with earlier studies that have shown that the changes in LV function seem to occur irrespective of hypertension or metabolic control in women with TS [9,10].

An alternative explanation could lie in the increased prevalence of congenital heart disease in this population. Some congenital heart defects such as CoA and BAV are known to cause a reduced LvGLS, [7,28] both of which occur frequently in women with TS. Unfortunately, our study was not designed to and further studies are therefore needed to definitively confirm such a relation in TS women.

A third potential explanation could be offered by the decreased aortic distensibility that is described in women with TS [29–32]. Vascular stiffening reduces compliance and increases arterial pressure which augments overall vascular resistance. Subsequently the LV would have to compensate for this pressure overload by increasing myocardial wall thickness, leading to reduced diastolic compliance or even increased end-diastolic volume. However, to our knowledge no longitudinal studies have been conducted that investigate a possible relation between diastolic function and aortic elasticity in women with TS. We found an indication of increased LV size when corrected for BSA or height in the TS population and a decreased exercise capacity. This could resemble the impaired diastolic reserve seen in HF with preserved ejection fraction (HFpEF) which leads to LV end-diastolic pressure (EDP) resulting in exercise intolerance [33]. However, a follow-up study would be needed to investigate if this holds any relation to the aortic distensibility.

Although hypertension, congenital heart disease and vascular compliance may all contribute to the observed LV dysfunction in women with TS, a common underlying cause could be assumed in TS. Recently, TS women were found to have increased cortisol levels [34]. Several aspects of the TS phenotype may well fit a 'hypercortisolism theory'. Like in patients with Cushing syndrome, long term exposure to increased levels of cortisol could lead to increased prevalence of left ventricular (LV) hypertrophy, higher frequency of concentric remodeling, and subsequent LV systolic and diastolic dysfunction, and left atrial systolic dysfunction, as well as increased regional LV wall thickness [35–38].

Possibly the electrophysiological changes [39], increased pulse wave velocity [40] and metabolic syndrome [37,41] also fit such an explanation. Also, the higher resting heart rate could fit in this hypothesis.

4.2 Limitations

The main limitation is the small sample size of the study, although this is one of the largest most comprehensive studies to date. Another shortcoming may be the lack of data on the coronary arteries of these patients. This study cannot fully discern the possible influence of the presence of structural heart disease on the cardiac function. We show that no significant difference on the main outcome parameter were found. However, since this was not the primary objective of this study, we suggest future studies to expand upon our current effort. A possible inclusion bias is unlikely as patients were consecutively included into this study. A possible source of bias is the time and effort taken by the study. This may cause only less affected patients to participate. As more severely affected patients may already be intensively monitored. Where less affected individuals may be tempted by a very comprehensive check-up. In this current study we have no information on the behavioral aspects of the deficit in exercise capacity. Future studies should therefore for example include a questionnaire to determine baseline activity levels of TS women.

5 Conclusion

Systolic LvGLS and Sre were both significantly lower in TS women compared to healthy females and exercise capacity was found to be reduced in TS women. Reduced LVGLS and Sre were not associated with exercise capacity, but correlation with conventional TTE parameters and baseline characteristics were observed.

Data Sharing: Data is available upon reasonable request.

**Conflicts of Interest:** The authors report no relationships that could be construed as a conflict of interest.

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Appendix A
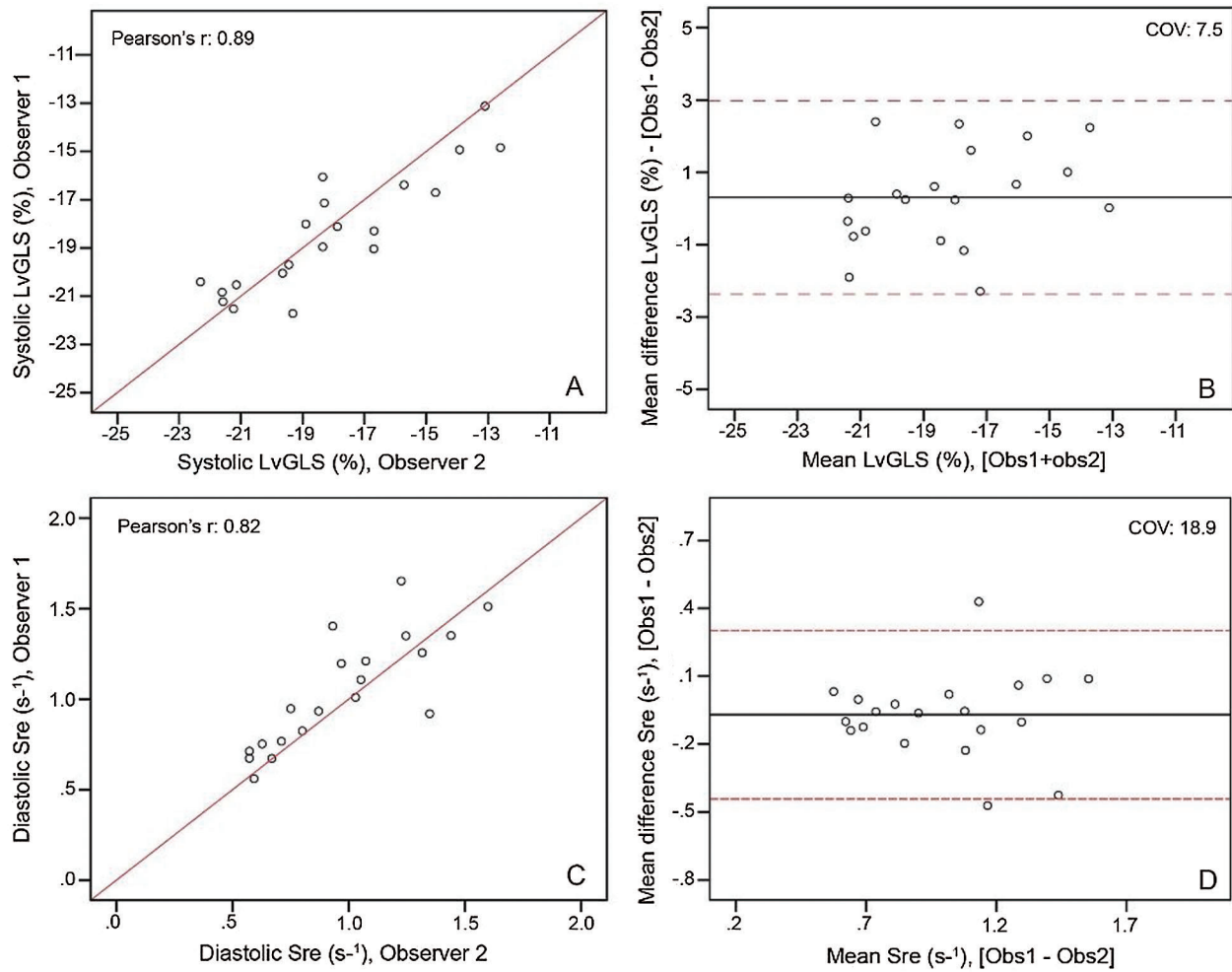
Supplementary Figure 1: Inter observer analysis as linear regression (left) and Blandt-altman plots (right) for systolic LvGLS (top) and diastolic Sre (bottom).

Note: COV: Coefficient of Variation, LvGLS: Systolic Left Ventricular Global Longitudinal Strain, Sre: Left Ventricular Peak Early Diastolic Strain Rate.