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Enhanced aortic stiffness in adolescents with chronic disease is associated with decreased left ventricular global longitudinal strain

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ABSTRACT

Background: The recent *Cardiovascular Disease in Adolescents with Chronic Disease* (CDACD) study showed enhanced aortic stiffness and wall thickness in adolescents with various chronic disorders. Enhanced aortic stiffness can increase left ventricular (LV) afterload and trigger a cascade of adverse arterioventricular interaction. Here, we investigate the relation between aortic changes and LV function in the CDACD study participants.
Methods: This cross-sectional study included 114 adolescents 12–18 years old with cystic fibrosis (CF, n = 24), corrected coarctation of the aorta (CoA, n = 25), juvenile idiopathic arthritis (JIA, n = 20), obesity (n = 20), and healthy controls (n = 25). Aortic pulse wave velocity (PWV), which reflects aortic stiffness, and aortic wall thickness (AWT) were assessed with cardiovascular magnetic resonance imaging (CMR). Echocardiography was employed to study conventional markers of LV function, as well as LV global longitudinal strain (LVGLS), which is an established (pre)clinical marker of LV dysfunction.
Results: First, aortic PWV and AWT were increased in all chronic disease groups, compared to controls. Second, in adolescents with CoA, JIA, and obesity, echocardiography showed a decreased LVGLS, while LV dimensions and conventional LV function markers were similar to controls. Third, multivariable linear regression identified aortic PWV as the most important determinant of their decreased LVGLS (standardized β −0.522, $p < 0.001$).
Conclusions: The decreased LVGLS in several adolescent chronic disease groups was associated with enhanced aortic PWV, which might reflect adverse arterioventricular interaction. Whether the decreased LVGLS in the chronic disease groups could negatively impact their long-term cardiovascular outcomes requires further study.

Abbreviations: ASD, atrial septal defect; AWT, aortic wall thickness; CDACD, 'cardiovascular disease in adolescents with chronic disease' study; CF, cystic fibrosis; CMR, cardiovascular magnetic resonance imaging; CoA, corrected coarctation of the aorta; JIA, juvenile idiopathic arthritis; LV, left ventricle; LVEF, LV ejection fraction; LVFS, LV fractional shortening; LVGLS, LV global longitudinal strain; PWV, pulse wave velocity.

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1. Introduction

Children with chronic disease are frequently exposed to systemic inflammation, metabolic derangements, and hypertension, which can induce arterial changes [1]. The 'Cardiovascular Disease in Adolescents with Chronic Disease' (CDACD) study recently demonstrated a higher aortic wall thickness (AWT) and aortic pulse wave velocity (PWV), the latter of which reflects aortic wall stiffness, in adolescents with various chronic disorders, compared to controls [2]. The CDACD population included various chronic disease-associated risk factors for arterial changes, including metabolic risk factors in cystic fibrosis (CF) and obesity, inflammatory risk factors in juvenile idiopathic arthritis (JIA), and hypertension in corrected coarctation of the aorta (CoA). These chronic disease-associated risk factors may not only affect the aortic wall, but could have secondary effects on cardiovascular function. Aortic abnormalities, and particularly enhanced aortic stiffness, can increase left ventricular (LV) afterload by a reduced arterial Windkessel effect, and trigger a cascade of adverse arterioventricular interaction [3]. In the classical cascade, increased LV afterload leads to compensatory LV hypertrophy, and subsequently to diastolic filling abnormalities, systolic LV dysfunction and overt heart failure [4]. We hypothesized that the increased aortic stiffness and wall thickness in adolescents with chronic disease could induce adverse arterioventricular interaction. Therefore, we investigated whether the aortic changes observed in the CDACD study coincide with changes in LV dimensions and function. Next to conventional echocardiographic markers of LV function, we have studied LV global longitudinal strain (LVGLS), which is an established preclinical marker of LV systolic dysfunction [5]. Over the last few years, LVGLS has emerged as a strong predictor of cardiovascular events, with superior prognostic value in several cardiac diseases including heart failure and acute myocardial infarction, compared to conventional markers such as LV ejection fraction [6]. Our study is the first to investigate the association between early aortic abnormalities and LV function in adolescents with various chronic disorders.

2. Methods

2.1. Study design and population

In the cross-sectional CDACD study, 114 adolescents aged 12–18 were prospectively enrolled between April 2017 and June 2019, as recently published [2]. The study population included patients with metabolic, inflammatory, and hemodynamic disorders: cystic fibrosis (CF, n = 24), corrected coarctation of the aorta (CoA, n = 25), rheumatoid factor negative polyarticular or extended oligoarticular juvenile idiopathic arthritis (JIA, n = 20), obesity (n = 20), and as a control group healthy adolescents with a corrected atrial septal defect (ASD), who showed normal cardiac dimensions and functions during follow-up (n = 25). Obesity was defined as a body mass index > 30 kg/m2 projected to the age of 18 years, according to the international Obesity Task Force [7]. Exclusion criteria for all participants were acute illness, mental retardation, pregnancy, or contraindications for MRI with gadolinium-based contrast agents. Ethical approval was obtained from the institutional Medical Research Ethics Committee (protocol number 16–589), and the study complied with the Declaration of Helsinki. Written informed consent was obtained from all participants and if applicable also of their parents/guardians.

2.2. Clinical measurements

Waist and hip circumference were measured following established clinical standards [2]. Blood pressure was measured three times at the right arm after 10 min rest while seated. The lowest measurement of three readings was used.

2.3. Echocardiography

Echocardiographic examinations were performed on a GE Vivid E95 ultrasound system (General Electric Healthcare, Wauwatosa, Wisconsin, USA), using established clinical protocols including two-dimensional (2D) imaging, pulsed-wave Doppler velocities and tissue Doppler imaging (TDI) [8]. All data were analyzed offline by a blinded observer, using commercially available software ('EchoPAC' version 203, General Electric, Milwaukee, Wisconsin, USA). 2D-imaging of the parasternal short axis view was used to measure LV dimensions, LV ejection fraction (LVEF) as assessed with the Teichholz method, and LV fractional shortening (LVFS) [8]. LV dimensions were converted to Z-scores based on body surface area (BSA), and were expressed as LV end-diastolic (LVEDd) and LV end-systolic (LVESd) diameter, interventricular septum thickness (IVSd) and LV posterior wall thickness (LVPWd) at end-diastole. Reference values for the obese group are not available, so that Z-scores for the obese adolescents could not be calculated.(9) LVEF, LVFS, TDI peak systolic mitral annular velocity (TDI S') and LVGLS were calculated for assessment of global systolic LV function. Grey-scale images in the apical two-, three-, and four-chamber views were acquired for myocardial strain analysis with speckle tracking and analyzed for LVGLS. Speckle tracking analysis was performed using EchoPAC software as previously reported [10]. Briefly, the endocardial border was manually traced, and aortic valve closure was used for timing of end-systole. Tracking was automatically performed and the endocardial border was manually retraced if needed. LVGLS analysis was accepted when the software and visual inspection indicated adequate tracking. LVGLS was calculated by averaging the peak longitudinal strain in the two-, three- and four-chamber views. LVGLS values were excluded if one of these views had insufficient quality. Due to strict quality control, LVGLS could be calculated for 70 out of 114 cases (12 ASD, 19 CF, 19 CoA, 14 JIA, and 6 obese). LVGLS reflects longitudinal myocardial shortening of the LV during systole and is traditionally expressed as a negative value (e.g. −20 %). However, we use absolute (positive) values for LVGLS (e.g. 20 %), as interpreting changes in negative percentages can be challenging. Values closer to zero (e.g. 10 %) are indicative of impaired LVGLS and are referred to as 'decreased LVGLS' throughout the paper. For assessment of diastolic LV function, mitral valve (MV) inflow velocities were analyzed using pulsed-wave Doppler early (E) and late (A) peak velocity measurements to calculate the MV E/A ratio [8].

2.4. Cardiovascular magnetic resonance imaging (CMR)

CMR was performed on a Philips 3.0 Tesla CMR system, as reported previously [2]. In short, aortic PWV was assessed using 2D velocity-encoded CMR. Two through-plane phase contrast acquisitions were obtained at the levels of the ascending aorta and in the abdominal aorta. Velocity mapping was performed using Mass software (Medis, Leiden), and subsequent calculation of the aortic PWV was performed using in-house developed and validated Matlab software. The thoracic and abdominal wall were imaged using a three-dimensional (3D) T1-weighted black blood VISTA sequence. Analysis was performed by manual tracing of the inner and outer contours of the vessel wall with 0.6 mm increments and 1.2 mm slice thickness, analyzing 1 out of 5 slices using VesselMass software (Medis, Leiden), according to a previously established protocol [2].

2.5. Statistical analysis

In case of normally distributed variables, mean and standard deviation were reported and groups were compared against controls using independent *t* tests. In case of non-normality, median and interquartile range were shown and groups were compared against controls using Mann-Whitney U tests. Benjamini & Hochberg's correction for false discovery was applied to correct for multiple testing when appropriate. To study correlations between the aortic parameters (PWV and AWT)

Table 1
Clinical characteristics and arterial measurements.

	Controls	CF	CoA	JIA	Obesity	N[a]
N (m/f)	25 (3/22)	24 (13/11)**	25 (17/8)***	20 (6/14)	20 (8/12)*	114
Age (years)	14.32 (12.66–17.02)	15.92 (14.18–17.29)	14.55 (12.73–16.46)	16.10 (13.82–16.95)	14.61 (12.99–16.72)	114
Height (m)	1.68 (1.55–1.70)	1.70 (1.62–1.74)*	1.71 (1.58–1.77)	1.68 (1.61–1.76)	1.67 (1.62–1.72)	114
Weight (kg)	51.7 (40.9–65.8)	54.6 (50.3–60.0)	57.2 (45.7–66.2)	57.7 (48.4–63.9)	89.4 (83.0–97.4)***	114
BMI (SD)	−0.15 ± 0.99	−0.36 ± 0.93	0.19 ± 1.26	0.07 ± 1.06	3.23 ± 0.33***	114
Waist-to-hip ratio	0.76 (0.73–0.79)	0.84 (0.78–0.89)**	0.81 (0.77–0.85)*	0.79 (0.73–0.83)	0.91 (0.83–0.96)***	114
Hemodynamic						
HR (bpm)	69.83 ± 6.72	77.29 ± 12.05*	68.76 ± 11.32	71.20 ± 12.18	74.45 ± 12.35	114
SBP (mmHg)	114.28 ± 11.44	115.63 ± 11.35	122.20 ± 11.62*	114.45 ± 11.66	122.50 ± 9.76*	114
SBP percentile	62.00 (28.50–90.00)	55.5 (39.25–83.75)	91.00 (62.00–96.00)*	66.50 (22.50–85.00)	84.50 (77.75–92.50)	114
DBP (mmHg)	64.00 (60.00–67.00)	65.00 (61.50–67.75)	66.00 (63.00–70.00)	66.00 (65.00–70.75)	65.50 (63.50–68.50)	114
DBP percentile	46.08 ± 26.11	45.38 ± 23.78	51.12 ± 20.20	54.25 ± 18.11	50.50 ± 20.17	114
Aortic parameters						
Aortic pulse wave velocity (m/s)	3.74 ± 0.28	4.10 ± 0.50**	4.11 ± 0.58*	4.10 ± 0.46**	4.01 ± 0.31**	101
Aortic wall thickness (mm)	1.83 (1.70–1.95)	1.97 (1.85–2.10)**	1.95 (1.83–2.11)*	1.99 (1.86–2.06)*	2.00 (1.93–2.11)**	104

Mean ± standard deviation or median (lower quartile-upper quartile) were reported. All chronic disease groups were compared with healthy ASD controls. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [a]Total number analyzed. Abbreviations: controls: healthy adolescents with a corrected atrial septal defect; CF: cystic fibrosis; CoA: corrected coarctation of the aorta; JIA: juvenile idiopathic arthritis; bpm: beats per minute; BMI (SD): body mass index standard deviation from the age- and sex matched population mean; SBP: systolic blood pressure; SBP percentile: systolic blood pressure percentile based on the age-, sex-, and height matched population; DBP: diastolic blood pressure; DBP percentile: diastolic blood pressure percentile based on the age-, sex-, and height matched population.

Table 2
Cardiac dimensions and function measurements.

	Controls	CF	CoA	JIA	Obesity	N[b]
Left ventricular dimensions						
LVEDd (mm)	47.38 ± 4.84	48.45 ± 4.64	47.51 ± 3.70	46.96 ± 3.94	49.02 ± 2.64	114
LVEDd Z-score	0.27 ± 0.59	0.42 ± 0.64	0.05 ± 0.97	−0.01 ± 0.73	*a*	94
LVESd (mm)	31.30 (27.05–34.30)	31.05 (29.00–33.88)	28.30 (25.60–33.00)	31.05 (26.33–34.13)	31.40 (29.40–34.10)	114
LVESd Z-score	0.44 ± 0.82	0.72 ± 0.67	−0.16 ± 0.98	0.36 ± 0.94	*a*	94
IVSd (mm)	6.60 (6.15–7.40)	6.90 (6.05–7.40)	7.30 (6.80–8.65)	6.25 (5.65–6.70)	7.55 (6.93–8.75)*	114
IVSd Z-score	−0.40 ± 0.59	−0.46 ± 0.67	−0.01 ± 0.77	−0.72 ± 0.73	*a*	94
LVPWd (mm)	6.76 ± 1.17	7.24 ± 0.92	7.57 ± 1.57	7.03 ± 1.10	7.80 ± 1.24*	114
LVPWd Z-score	−0.06 ± 0.67	0.24 ± 0.57	0.34 ± 0.70	0.00 ± 0.79	*a*	94
Left ventricular function						
LVEF (%)	65.20 ± 5.62	64.27 ± 4.49	69.00 ± 6.00	65.03 ± 5.92	64.76 ± 5.35	114
LVFS (%)	35.92 ± 4.00	35.34 ± 3.05	38.90 ± 4.61	35.85 ± 4.36	35.65 ± 4.20	114
TDI S' (cm/s)	9.41 (8.34–11.57)	10.04 (9.11–11.77)	8.39 (7.37–9.93)	10.21 (8.75–12.04)	11.66 (10.27–13.06)*	113
LVGLS (%)	20.00 ± 1.82	18.93 ± 1.53	17.75 ± 2.12*	18.11 ± 1.91*	18.00 ± 1.11*	70
MV E/A ratio	2.00 (1.82–2.38)	1.82 (1.46–2.40)	1.97 (1.67–2.76)	1.97 (1.66–2.61)	1.99 (1.73–2.42)	114

Mean ± standard deviation or median (lower quartile-upper quartile) were reported. All chronic disease groups were compared with healthy ASD controls. Analyses were corrected for multiple testing. *$p < 0.05$. [a] Z-scores for obese adolescents are not available. [b] Total number of patients available for analysis (missing cases due to strict quality control). Abbreviations: controls: healthy adolescents with a corrected atrial septal defect; CF: cystic fibrosis; CoA: corrected coarctation of the aorta; JIA: juvenile idiopathic arthritis; LVEDd: left ventricular end diastolic diameter; LVESd: left ventricular end systolic diameter; IVSd: interventricular septum thickness at end-diastole; LVPWd: left ventricular posterior wall thickness at end-diastole; LVEF: left ventricular ejection fraction; LVFS: left ventricular fractional shortening; TDI S': tissue doppler imaging of the peak systolic mitral annular velocity; LVGLS: left ventricular global longitudinal strain; MV E/A ratio: mitral valve early (E) over late (A) peak velocity.

and cardiac function (LVFS, LVEF, TDI S', LVGLS and MV E/A ratio), normally- or non-normally distributed parameters were assessed using Pearson's- or Spearman's correlation coefficients, respectively. For multivariable linear regression analysis, determinants were tested for normality and for multicollinearity by calculation of the Variance Inflation Factors. Relevant determinants were identified using backwards selection. The number of patients analyzed for a particular analysis is presented in the tables and figures. Statistical analysis was performed using IBM SPSS statistics 26. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

All groups showed similar subject numbers, with a higher number of girls in the control group, compared to the cystic fibrosis, corrected coarctation, and obesity groups (Table 1). Adolescents with cystic fibrosis, corrected coarctation, and obesity showed a higher waist-to-hip ratio (WHR) than controls, which is associated with visceral adipose tissue accumulation (Table 1) [11]. Adolescents with juvenile idiopathic arthritis were generally in remission, with similar clinical characteristics as the healthy controls (Table 1). Corrected coarctation and obese adolescents showed an elevation of their systolic blood pressure (SBP),

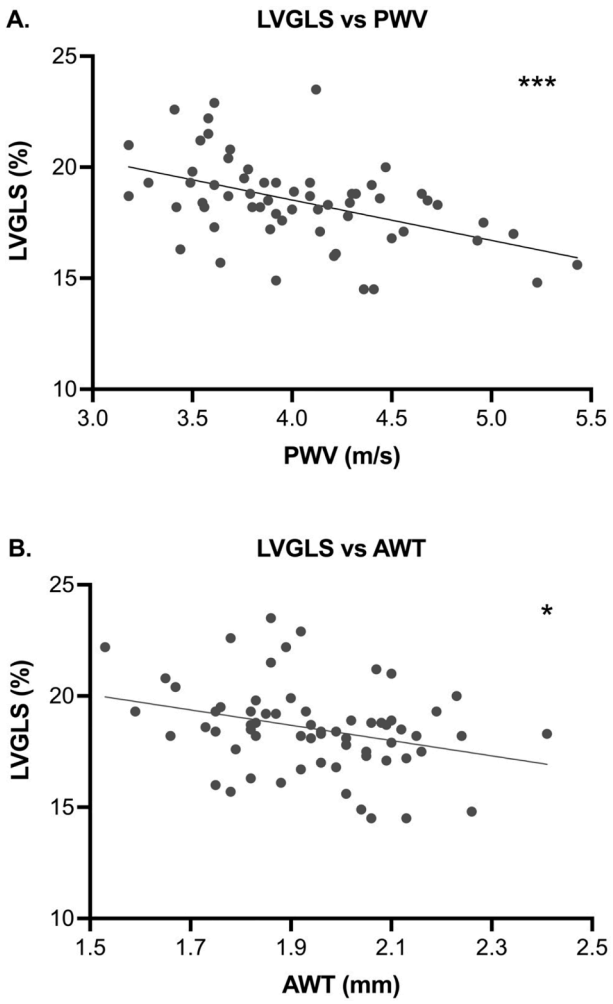

Fig. 1. Bivariate correlation analysis between left ventricular global longitudinal strain (LVGLS) and aortic measurements: A) LVGLS showed a negative correlation with aortic pulse wave velocity (PWV) (Spearman's rho = -0.479, p = 0.0001) (n = 61) and B) LVLGS showed a negative correlation with aortic wall thickness (AWT) (Pearson's r = −0.307, p = 0.014) (n = 64). *p < 0.05, ***p < 0.001.

compared to controls. Altogether, obese adolescents exhibited a characteristic phenotype including a higher weight and body mass index (BMI) (Table 1). As recently demonstrated in the CDACD study, aortic PWV and AWT were higher in all adolescent chronic disease groups when compared to controls (Table 1) [2].

3.2. Cardiac left ventricular dimensions and function

All groups showed LV dimensions within normal ranges, with Z-scores < 1, except for the obese adolescents for whom indexation by Z-scores could not be performed due to a lack of available reference values (Table 2) [9] .The thicker interventricular septum and LV posterior wall in obese adolescents may reflect a higher LV mass. With respect to systolic LV function, conventional markers including LV ejection fraction, LV fractional shortening and peak systolic mitral annular velocity (TDI S'), were preserved in all chronic disease groups (Table 2). In contrast, LVGLS was significantly decreased in CoA, JIA, and obese adolescents compared to the ASD controls (Table 2). Regarding diastolic LV function, mitral valve early over late peak velocity (MV E/A) ratio was preserved in all chronic disease groups (Table 2).

Table 3
Multivariable linear regression to identify determinants of left ventricular global longitudinal strain (LVGLS).

LV global longitudinal strain (LVGLS)			$R^2 = 0.40$	N = 59
	Standardized β	Unstandardized β (CI)	P-value	
Age (years)	0.245	0.258 (−0.019–0.535)	0.067	
SBP (mmHg)	−0.247	−0.040 (−0.077–−0.002)	0.039*	
Height (cm)	−0.315	−0.065 (−0.115–−0.014)	0.013*	
Aortic PWV (m/s)	−0.522	−2.027 (−2.932–−1.123)	<0.001***	

Variables were selected using backwards selection. Variables added for selection: age, sex, height, BMI (SD), SBP (mmHg), DBP (mmHg), AWT, PWV. Abbreviations: CI: confidence interval; LV: left ventricular; BMI (SD): body mass index standard deviation from the age- and sex matched population mean; SBP: systolic blood pressure; DBP: diastolic blood pressure; AWT: aortic wall thickness; PWV: pulse wave velocity. *p < 0.05, ***p < 0.001. N = Total number analyzed.

3.3. Arterioventricular interaction

To assess whether the decreased LVGLS in several chronic disease groups was associated with aortic abnormalities, bivariate and multivariable analyses were performed. Bivariate correlation analysis showed a negative correlation between aortic PWV and LVGLS (Spearman's rho = -0.479, p = 0.0001, Fig. 1A). AWT was also inversely correlated with LVGLS (Pearson's r = -0.307, p = 0.014, Fig. 1B). Multivariable linear regression analysis showed that aortic PWV, rather than AWT, was a significant determinant of the decreased LVGLS (β −0.522, p < 0.001, Table 3) next to height (β −0.315, p = 0.013) and SBP (β −0.247, p = 0.039). The inverse correlation of aortic PWV with LVGLS coincided with a positive correlation of aortic PWV and conventional function markers, including LVEF (Spearman's rho = 0.237, p = 0.017) and LVFS (Spearman's rho = 0.248, p = 0.012) (Fig. 2A and 2B). No correlation was observed between PWV, and TDI S' and the MV E/A ratio (Fig. 2C and 2D). Furthermore, we did not observe a correlation between aortic measurements and IVSd Z-score or LVPWd Z-score (supplemental Fig. 1).

4. Discussion

The CDACD study is the first to investigate the relationship between aortic stiffness and cardiac function in adolescents with various chronic disorders, employing CMR and echocardiography. Here, we would like to discuss two key findings. First, LVGLS is a preclinical marker of LV dysfunction, and was significantly decreased in CoA, JIA and obese adolescents, compared to controls. Second, enhanced aortic PWV, which reflects aortic stiffness, was identified as a key determinant of the decreased LVGLS in adolescents with chronic disease.

While global LV function by conventional echocardiography was preserved in all chronic disease groups, myocardial strain expressed by LVGLS was significantly decreased in CoA, JIA, and obese adolescents. These results are consistent with earlier studies, indicating preclinical LV dysfunction in CoA, JIA, and obese adolescents [12–14]. A previous study also showed a decreased LVGLS in CF adolescents after adjustment for lung function, suggesting subtle alterations in cardiac function in young CF patients as well [15]. We observed a similar trend of decreased LVGLS in CF patients, compared to the control group. The decreased LVGLS in adolescents with a chronic disease may have clinical implications, as LVLGS is a strong predictor of heart failure and other adverse cardiovascular outcomes in adults [6,16,17]. Whether the decreased LVGLS in the adolescent chronic disease groups negatively impacts their long-term cardiovascular outcomes remains to be determined, and

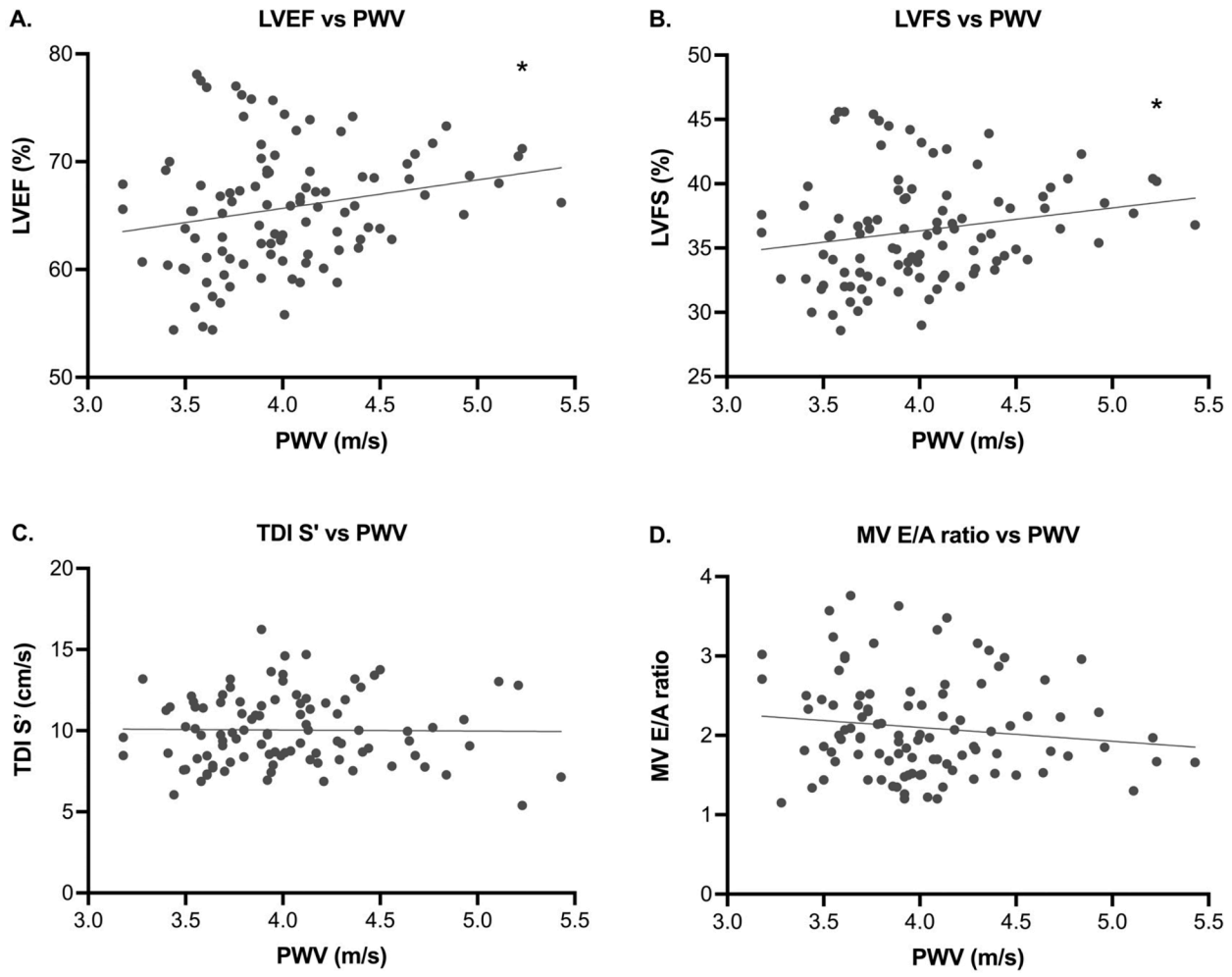

Fig. 2. Bivariate correlation analysis between conventional left ventricular (LV) function markers and aortic pulse wave velocity (PWV): A) LV ejection fraction (LVEF) showed a positive correlation with PWV (Spearman's rho = 0.237, p = 0.017) (n = 101), B) LV fractional shortening (LVFS) showed a positive correlation with PWV (Spearman's rho = 0.248, p = 0.012) (n = 101), C) Tissue doppler imaging peak systolic velocity (TDI S') (n = 100) and D) Mitral valve (MV) E/A ratio (n = 101) showed no significant correlation with PWV (Spearman's rho = 0.037, p = 0.711 and Spearman's rho = -0.119, p = 0.237). *p < 0.05.

requires further study.

The decreased LVGLS in most adolescent disease groups was associated with increased aortic stiffness as measured by a higher aortic PWV. In earlier studies in children with and without chronic disease, a higher aortic PWV was associated with dyslipidemia, obesity and chronic disease, and was adversely associated with cardiac function and cardiorespiratory fitness [2,18–23]. In adults, aortic PWV is the gold standard for assessing aortic stiffness, and a strong predictor of atherosclerotic disease and cardiovascular events, independent of established cardiovascular risk factors [24–27]. The observed association between aortic PWV and LVGLS might reflect adverse arterioventricular interaction in adolescents with chronic disease. This relationship has previously been shown in adults with rheumatoid arthritis, and the impact of aortic stiffness on LV dysfunction was established in large cohort studies [28,29]. Our study is yet one of the first showing the association between aortic stiffness and decreased LVGLS in adolescents with several chronic disorders, encompassing a variety of metabolic, inflammatory, and hemodynamic risk factors. Adverse arterioventricular interaction has previously been suggested in CoA and obese adolescents [30,31]. In young CF and JIA patients however, this study is the first to show adverse correlation between aortic PWV and LVGLS. Prior studies revealed preclinical LV dysfunction in CF and JIA adolescent but did not investigate the association with aortic stiffness [13,15].

In the classical cascade of adverse arterioventricular interaction, a higher LV afterload causes augmentation of LV wall stress, which stimulates the development of LV hypertrophy to maintain normal LV wall stress levels. LV hypertrophy subsequently increases myocardial stiffness and this may, in combination with abnormal myocardial relaxation, result in diastolic LV filling abnormalities. Ultimately, diastolic LV dysfunction and/or systolic LV dysfunction may develop [3,4]. LV hypertrophy was not observed in our study population, but the decreased LVGLS in CoA, JIA and obese adolescents may suggest a preclinical stage of LV dysfunction. In preclinical stages of LV dysfunction, the arrangement of the myocardial fibers preserves systolic LV function, which is a result of the contraction of longitudinal myocardial fibers in the subendocardial region, oblique myocardial fibers in the subepicardium, and a layer of circumferential myocardial fibers in between (midmyocardial orientation). LVGLS assesses systolic shortening of the longitudinal myocardial fibers in the subendocardial region [32]. A higher LV afterload and augmentation of LV wall stress will first reduce LVGLS, as subendocardial located fibers are most vulnerable to increased LV wall stress. The midmyocardial and subepicardial myocardial fibers remain relatively unaffected in the early stages of myocardial disease. Upon further augmentation of LV wall stress, increased circumferential strain can even compensate for the decreased LVGLS to preserve LV systolic performance, leading to compensatory LV hypertrophy [32,33]. The positive correlation between aortic PWV, and LVEF and LVFS in our study could be explained by similar compensatory mechanisms to preserve LV function. Taken together, the decreased LVGLS in absence of LV hypertrophy in adolescents with chronic disease

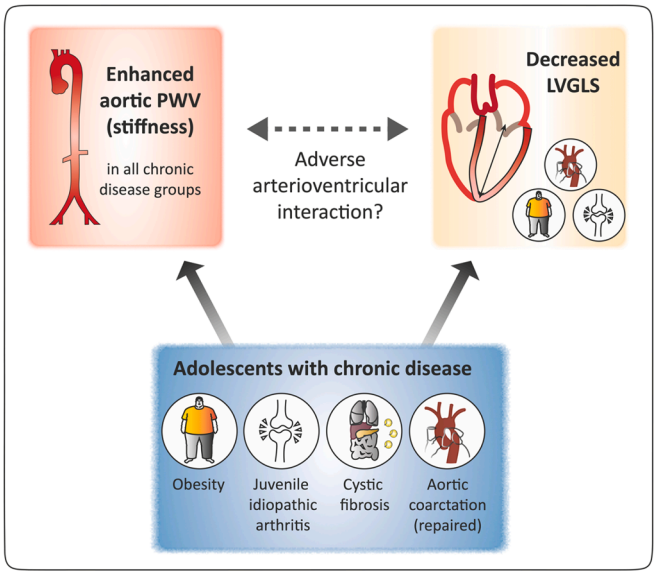

Fig. 3. Graphical abstract. Adolescents with various chronic diseases showed enhanced aortic stiffness and a decreased left ventricular (LV) global longitudinal strain (LVGLS), which is a preclinical marker of LV dysfunction. The decreased LVGLS in several adolescent chronic disease groups is associated with enhanced aortic stiffness, which might reflect adverse arterioventricular interaction. Abbreviations: CDACD: Cardiovascular Disease in Adolescents with Chronic Disease study; LVGLS: left ventricular global longitudinal strain; and PWV: pulse wave velocity.

may reflect a preclinical stage of LV dysfunction. As mentioned earlier, the impact on long-term cardiovascular outcomes remains to be determined, and requires further study.

Our study has several limitations. First, the cross-sectional design of the study enables identification of associations and determinants, but precludes causality studies. In other words, the observed adverse association between aortic stiffness and decreased LVGLS is no proof of a causal relationship. A causal role for adverse arterioventricular interaction in this association is merely speculative. Second, the number of patients per group is relatively small, which limits group-to-group comparisons. Our study may be underpowered to identify differences between the disease groups. Third, there were small sex and age differences between groups, partly explained by disease epidemiology. ASD is more common in females, and CoA is more common in males, for example [34]. Earlier studies showed that aortic PWV and LVGLS measurements are similar for boys and girls [27,35]. With respect to age differences however, slightly higher aortic PWV has been reported in older adolescents, compared to younger children [27]. As a consequence, the higher mean age in the CF and JIA group (15.92 and 16.10 years compared to 14.32 years in the control group) could induce a small positive bias towards a higher aortic PWV in the CF and JIA group. Fourth, our study included adolescents with corrected ASD as controls. We included ASD controls because they underwent medical treatment and follow-up just like the disease groups, but without any known long-term arterial effects. The ASD controls underwent elective surgery early in life and had normal cardiac dimensions and function during follow-up. Previous studies on the long-term outcome after ASD repair showed that these children are not at risk for early arterial changes or atherosclerosis [36]. Nonetheless, an additional control group of healthy peers could have strengthened our findings. Fifth, some echocardiographic measurements could not be provided for all study participants due to impaired echo windows in some adolescents, particularly adolescents with obesity, and due to strict quality control for the LVGLS analysis. The lower number of available measurements impacts statistical power. In addition, we were not able to perform myocardial work analysis with our GE ultrasound system since the necessary pre-echocardiographic blood pressure measurements in the study were not performed at time of the echocardiographic examination. Finally, studies in adults have established LVGLS and aortic PWV as predictors of future cardiovascular events and all-cause mortality [6,24]. Their predictive value in adolescents may be different. Longitudinal studies are needed to assess the predictive value of aortic PWV and LVGLS during adolescence for cardiovascular health later in life.

In conclusion, the CDACD study showed a decreased LVGLS in several adolescent chronic disease groups. Whether the decreased LVGLS in the adolescent chronic disease groups negatively impacts their long-term cardiovascular outcomes remains to be determined, and requires further study. The decreased LVGLS is associated with enhanced aortic stiffness in adolescent chronic disease groups, which might reflect adverse arterioventricular interaction (Fig. 3). Altogether, our findings substantiate the emerging call for tailored cardiovascular follow-up and prevention programs in children with chronic disease, to study whether atherosclerotic disease and LV dysfunction later in life can be prevented [37].

CRediT authorship contribution statement

Victor A. Verpalen: Writing – original draft, Investigation, Formal analysis, Data curation. **Francesca A. Ververs:** Writing – review & editing, Investigation, Data curation. **Martijn Slieker:** Writing – review & editing, Methodology. **Roos Nuboer:** Writing – review & editing, Data curation. **Joost F. Swart:** . **Cornelis K. van der Ent:** . **Zina Fejzic:** Writing – review & editing. **Jos J.M. Westenberg:** . **Tim Leiner:** Writing – review & editing, Validation, Conceptualization. **Heynric B. Grotenhuis:** Writing – review & editing, Methodology, Conceptualization. **Henk S. Schipper:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No author had any financial interest in the subject matter discussed in the submitted manuscript. No conflict of interest needs to be disclosed. All authors state that this study complies with the Declaration of Helsinki.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101385.

References

[1] S.D. de Ferranti, J. Steinberger, R. Ameduri, A. Baker, H. Gooding, A.S. Kelly, et al., Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association, Circulation 139 (13) (2019 March 26) e603–e634.
[2] F.A. Ververs, A.L.M. Eikendal, D. Kofink, R. Nuboer, J.J.M. Westenberg, G. T. Hovenkamp, et al., Preclinical aortic atherosclerosis in adolescents with chronic disease, J. Am. Heart Assoc. 11 (14) (2022 July 19) e024675.
[3] C.Y. Shim, Arterial-cardiac interaction: the concept and implications, J Cardiovasc Ultrasound 19 (2) (2011 June 01) 62–66.
[4] L. Mandinov, F.R. Eberli, C. Seiler, O.M. Hess, Diastolic heart failure, Cardiovasc. Res. 45 (4) (2000 March 01) 813–825.
[5] E. Potter, T.H. Marwick, Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to

ejection fraction, J. Am. Coll. Cardiol. Img. 11 (2 Pt 1) (2018 February 01) 260–274.
[6] K. Kalam, P. Otahal, T.H. Marwick, Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction, Heart 100 (21) (2014 November 01) 1673–1680.
[7] T.J. Cole, K.M. Flegal, D. Nicholls, A.A. Jackson, Body mass index cut offs to define thinness in children and adolescents: international survey, BMJ 335 (7612) (2007 July 28) 194.
[8] L.A.L.L. Lopez, S.D. Colan, P.C. Frommelt, G.J. Ensing, K. Kendall, A.K. Younoszai, et al., Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the pediatric measurements writing Group of the American Society of echocardiography pediatric and congenital heart disease council, J. Am. Soc. Echocardiogr. 23 (5) (2010 May 01) 465–467.
[9] L. Lopez, S. Colan, M. Stylianou, S. Granger, F. Trachtenberg, P. Frommelt, et al., Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: the pediatric heart network Normal echocardiogram database, Circ. Cardiovasc. Imaging 10 (11) (2017 November 01) e006979.
[10] F. Dallaire, C. Slorach, T. Bradley, W. Hui, T. Sarkola, M.K. Friedberg, et al., Pediatric reference values and Z score equations for left ventricular systolic strain measured by two-dimensional speckle-tracking echocardiography, J. Am. Soc. Echocardiogr. 29 (8) (2016 August 01) 786–793.e8.
[11] M.P. Bellissimo, I. Zhang, E.A. Ivie, P.H. Tran, V. Tangpricha, W.R. Hunt, et al., Visceral adipose tissue is associated with poor diet quality and higher fasting glucose in adults with cystic fibrosis, J. Cyst. Fibros. 18 (3) (2019 May 01) 430–435.
[12] H. Jashari, K. Lannering, P. Ibrahimi, D. Djekic, M. Mellander, A. Rydberg, et al., Persistent reduced myocardial deformation in neonates after CoA repair, Int. J. Cardiol. 15 (221) (2016 October) 886–891.
[13] A.F. AbdelMassih, A. Salem, S. Arabi, L. Malak, H. Marzouk, Intensity of inflammation as the most important predictor of myocardial involvement in JIA. a 3D echocardiographic study, Acta Reumatol. Port. 44 (4) (2019 December 01) 296–302.
[14] J.A.A. Barbosa, C.C.C. Mota, A.C. Simoes E Silva, M.D.C.P. Nunes, M.M. Barbosa, Assessing pre-clinical ventricular dysfunction in obese children and adolescents: the value of speckle tracking imaging, Eur Heart J Cardiovasc Imaging 14 (9) (2013 September 01) 882–889.
[15] J.B. Eising, C.K. van der Ent, A.J. Teske, M.M. Vanderschuren, C.S.P.M. Uiterwaal, F.J. Meijboom, Young patients with cystic fibrosis demonstrate subtle alterations of the cardiovascular system, J. Cyst. Fibros. 17 (5) (2018 September 01) 643–649.
[16] T.M. Koelling, G.W. Dec, L.C. Ginns, M.J. Semigran, Left ventricular diastolic function in patients with advanced cystic fibrosis, Chest 123 (5) (2003 May 01) 1488–1494.
[17] P. Blomstrand, P. Sjoblom, M. Nilsson, M. Wijkman, M. Engvall, T. Lanne, et al., Overweight and obesity impair left ventricular systolic function as measured by left ventricular ejection fraction and global longitudinal strain, Cardiovasc. Diabetol. 17 (1) (2018 August 14) 113.
[18] A. Hacker, B. Reiner, R. Oberhoffer, A. Hager, P. Ewert, J. Muller, Increased arterial stiffness in children with congenital heart disease, Eur. J. Prev. Cardiol. 25 (1) (2018 January 01) 103–109.
[19] A.O. Agbaje, J.P. Zachariah, T. Tuomainen, Arterial stiffness but not carotid intima-media thickness progression precedes premature structural and functional cardiac damage in youth: a 7-year temporal and mediation longitudinal study, Atherosclerosis 01 (380) (2023 September) 117197.
[20] C. Saner, T.T. Laitinen, J. Nuotio, S.J. Arnup, B.E. Harcourt, S. Bekkering, et al., Modest decrease in severity of obesity in adolescence associates with low arterial stiffness, Atherosclerosis 01 (335) (2021 October) 23–30.
[21] U. Fernberg, M. Fernstrom, A. Hurtig-Wennlof, Arterial stiffness is associated to cardiorespiratory fitness and body mass index in young Swedish adults: the lifestyle, biomarkers, and atherosclerosis study, Eur. J. Prev. Cardiol. 24 (17) (2017 November 01) 1809–1818.
[22] E.A. Haapala, K. Lankhorst, J. de Groot, M. Zwinkels, O. Verschuren, H. Wittink, et al., The associations of cardiorespiratory fitness, adiposity and sports participation with arterial stiffness in youth with chronic diseases or physical disabilities, Eur. J. Prev. Cardiol. 24 (10) (2017 July 01) 1102–1111.
[23] A.O. Agbaje, D.M. Lloyd-Jones, C.G. Magnussen, T. Tuomainen, Cumulative dyslipidemia with arterial stiffness and carotid IMT progression in asymptomatic adolescents: a simulated intervention longitudinal study using temporal inverse allocation model, Atherosclerosis 01 (364) (2023 January) 39–48.
[24] C. Vlachopoulos, K. Aznaouridis, C. Stefanadis, Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis, J. Am. Coll. Cardiol. 55 (13) (2010 March 30) 1318–1327.
[25] E.K. Laakkonen, J.E. Karppinen, S. Lehti, E. Lee, E. Pesonen, H. Juppi, et al., Associations of sex hormones and hormonal status with arterial stiffness in a female sample from reproductive years to menopause, Front Endocrinol (Lausanne) 30 (12) (2021 November) 765916.
[26] P. Mone, U. Kansakar, F. Varzideh, E. Boccalone, A. Lombardi, A. Pansini, et al., Epidemiology of obstructive sleep apnea: what is the contribution of hypertension and arterial stiffness? J. Clin. Hypertens. (Greenwich) 24 (4) (2022 April 01) 395–397.
[27] D. Bia, Y. Zocalo, Physiological age- and sex-related profiles for local (aortic) and regional (carotid-femoral, carotid-radial) pulse wave velocity and center-to-periphery stiffness gradient, with and without blood pressure adjustments: reference intervals and agreement between methods in healthy subjects (3–84 years), J Cardiovasc Dev Dis 8 (1) (2021 January 12) 3, https://doi.org/10.3390/jcdd8010003.
[28] A. Ilter, A. Kiris, M. Karkucak, M. Sahin, O.F. Serdar, Y. Ugan, Arterial stiffness is associated with left ventricular dysfunction in patients with rheumatoid arthritis, Clin. Rheumatol. 35 (11) (2016 November 01) 2663–2668.
[29] V. Bell, E.L. McCabe, M.G. Larson, J. Rong, A.A. Merz, E. Osypiuk, et al., Relations between aortic stiffness and left ventricular mechanical function in the community, J. Am. Heart Assoc. 6 (1) (2017 January 09) e004903.
[30] Q. Shang, S. Sarikouch, S. Patel, A. Schuster, M. Steinmetz, P. Ou, et al., Assessment of ventriculo-vascular properties in repaired coarctation using cardiac magnetic resonance-derived aortic, left atrial and left ventricular strain, Eur. Radiol. 27 (1) (2017 January 01) 167–177.
[31] L.P. Koopman, B.W. McCrindle, C. Slorach, N. Chahal, W. Hui, T. Sarkola, et al., Interaction between myocardial and vascular changes in obese children: a pilot study, J. Am. Soc. Echocardiogr. 25 (4) (2012 April 01) 401–410.e1.
[32] S.A. Luis, J. Chan, P.A. Pellikka, Echocardiographic assessment of left ventricular systolic function: an overview of contemporary techniques. Including speckle-tracking echocardiography, Mayo Clin. Proc. 94 (1) (2019 January 01) 125–138.
[33] H. Geyer, G. Caracciolo, H. Abe, S. Wilansky, S. Carerj, F. Gentile, et al., Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications, J. Am. Soc. Echocardiogr. 23 (4) (2010 April 01) 351–355.
[34] P. Engelfriet, B.J.M. Mulder, Gender differences in adult congenital heart disease, Neth. Heart J. 17 (11) (2009 November 01) 414–417.
[35] P.T. Levy, A. Machefsky, A.A. Sanchez, M.D. Patel, S. Rogal, S. Fowler, et al., Reference ranges of left ventricular strain measures by two-dimensional speckle-tracking echocardiography in children: a systematic review and meta-analysis, J. Am. Soc. Echocardiogr. 29 (3) (2016 March 01) 209–225.e6.
[36] Z. Karunanithi, C. Nyboe, V.E. Hjortdal, Long-term risk of atrial fibrillation and stroke in patients with atrial septal defect diagnosed in childhood, Am. J. Cardiol. 119 (3) (2017 February 01) 461–465.
[37] H.S. Schipper, S. de Ferranti, Atherosclerotic cardiovascular risk as an emerging priority in pediatrics, Pediatrics 150 (5) (2022 November 01) e2022057956, https://doi.org/10.1542/peds.2022-057956.