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Global longitudinal strain differentiates physiological hypertrophy from maladaptive remodeling

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ABSTRACT

Aims: Differentiation of left ventricular (LV) hypertrophy in healthy athletes from pathological LV hypertrophy in heart disease is often difficult. We explored whether extended echocardiographic measurements such as E/e' and global longitudinal strain (GLS) distinguish physiologic from maladaptive hypertrophy in hypertrophic cardiomyopathy, excessively trained athletes' hearts and normal hearts.

Methods: Seventy-eight professional athletes (cyclists n = 37, soccer players n = 29, handball players n = 21) were compared with patients (n = 88) with pathological LV hypertrophy (hypertrophic obstructive cardiomyopathy (HOCM, n = 17), hypertensive heart disease (HHD, n = 36), severe aortic valve stenosis (AVS, n = 35) and with sedentary healthy individuals as controls (n = 37).

Results: LV ejection fraction (LVEF) was ≥50% in all patients, athletes (median age 26 years, all male) and the controls (97% male, median age 32 years). LV mass index (LVMI) and septal wall thickness was in normal range in controls, but elevated in cyclists and patients with pathological hypertrophy ($p < 0.001$ for both). E/e' was elevated in all patients with maladaptive hypertrophy but normal in controls and athletes ($p < 0.001$ vs. pathological hypertrophy). Furthermore GLS was reduced in patients with pathological hypertrophy compared with athletes and controls (for both $p < 0.001$). In subjects with septal wall thickness >11 mm, GLS (≥−18%) has a specificity of 79% to distinguish between physiological and pathological hypertrophy.

Conclusion: GLS and E/e' are reliable parameters unlike left ventricular mass or LV ejection fraction to distinguish pathological and physiological hypertrophy.

1. Introduction

Maladaptive cardiac remodeling in cardiomyopathy and physiological adaptation to exercise both results in increased ventricular mass index on echocardiography [1,2]. Thus, physiological and maladaptive myocardial hypertrophy are difficult to distinguish by standard echocardiography [3]. Herein, we explored whether extended echocardiographic determination employing the diastolic parameter E/e' and global longitudinal strain can distinguish maladaptive and physiological hypertrophy in cardiomyopathy and following rigorous exercise training, respectively, compared to hearts of non-diseased sedentary individuals. Therefore, we explored myocardial hypertrophy in pressure overload, trained cyclists and normal healthy hearts. As sensitivity analysis, we studied how different forms of pathological hypertrophy such as aortic stenosis, hypertensive heart disease or idiopathic hypertrophic cardiomyopathy compare to other sports disciplines with mixed-training conditions (professional handball players, professional soccer players) and those with hearts of professional cyclists and normal individuals.

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2. Methods

2.1. Study population

From October 2018 to October 2019, a total of 87 professional athletes (cyclists n = 37; soccer players n = 29; handball players n = 21), aged 18 to 45 years were enrolled. The elite-level athletes included herein participated in international and/or top national level tournaments and trained regularly at least 6 times a week with training sessions of at least 90 min per day. All athletes underwent physical examination, resting and exercise 12-lead ECG as well as 2D and Doppler echocardiography. All athletes were subject to routine anti-doping controls. Professional cyclists were part of the professional team KATUSHA ALPECIN and trained between 15 and 25 h per week. Soccer players were employed by RB Leipzig, a soccer club taking part in the Bundesliga, the highest league in German football. Handball players were part of the team SC DHfK Leipzig, also competing in the highest national handball league. Athletes were compared with patients with pathological LV hypertrophy as a result from different hypertrophic heart diseases: hypertrophic obstructive cardiomyopathy (HOCM, n = 17), hypertensive heart disease (HHD, n = 36) and severe aortic valve stenosis (AVS, n = 35). Untrained, healthy subjects (n = 37) served as controls. HOCM is defined by a wall thickness ≥15 mm (and an instantaneous peak Doppler LV outflow tract pressure gradient ≥30 mm Hg at rest or during physiological provocation) in one or more LV myocardial segments unexplained by abnormal loading conditions (e.g., hypertension, valvular, congenital disease) or infiltrative cardiomyopathies [4]. Unexplained left ventricular wall thickness of ≥13 mm was sufficient for diagnosis in relatives of individuals with HCM or those who are genotype positive [4]. Controls performed regular exercise trainings <3 times a week and did not participate in any tournaments. All subjects agreed to take part in the study and provided written informed consent in accordance with the declaration of Helsinki.

2.2. Echocardiography

Echocardiographic examinations were performed by experts using the latest ultrasound technology (GE Vivid E9 or E95 or iQ). Two-dimensional assessment of LV end-diastolic diameter, left atrial size, septal wall thickness, and left ventricular ejection fraction (EF) were performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiac Imaging [5]. Linear internal measurements of the LV were performed in the parasternal long-axis view obtained perpendicular to the LV long axis, and measured at the level of the mitral valve leaflet tips [5]. The current ESC echocardiographic guidelines for cardiac chamber quantification defined the normal range for LV-wall thickness (septal and posterior wall) in women between 6–9 mm and in men between 6–10 mm, as well as a LVMI in women between 43–95 g/m^2 and in men between 49–115 g/m^2 [5]. However, some athletes have small increases in LV wall thickness and LV cavity diameter outside the normal range [6]. LV mass was determined by using the Devereux formula, which is composed of the septal and posterior wall thickness, the LV end-diastolic diameter, and the body surface area derived from 2D-guided M-mode [5]. 2-D and Doppler methods were used for the assessment of LV diastolic function. Early diastolic peak E-wave velocity (PW-E), late diastolic peak A-wave velocity (PW-A), their ratio (E/A) and mitral valve deceleration time were recorded using PW Doppler in the apical four-chamber view [7,8]. In accordance to the guidelines an annular e′ velocity (septal e′ < 7 cm/sec, lateral e′ < 10 cm/sec) and average E/e′ ratio >14 were used as cutoff values for pathological findings [7]. Analyses of 2D strain imaging were performed offline with a commercially available software version (GE Healthcare GmbH, Echopac, Version 203). For speckle-tracking analysis, apical four-chamber, two-chamber and three-chamber-views were acquired in cardiac cycles with the same length and during the same respiratory phase (expiration) [5,9]. Detection of endocardial and epicardial borders was performed semi-automatically. Manual corrections were used to ensure accurate tracking of the endocardial and epicardial borders and the correct segmentation of the LV. Regional strain parameters are reported for each segment in each apical window. The LV was divided into six segments in each apical window. Herein, the longitudinal component of myocardial strain, the GLS, was measured. GLS was derived as the average of longitudinal strain in all 17 myocardial segments. In accordance to the current recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging average GLS values ≥−18% were considered physiological [5]. Assessment of the echocardiographic images was performed by a cardiovascular imaging specialist blinded to the subject's characteristics.

2.3. Statistical analysis

Data management and statistical analyses were performed using SPSS Statistics version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.2.1 (GraphPad Software, La Jolla, CA, USA). Categorical data were presented as numbers (%). Continuous variables were tested for normal distribution using the Shapiro-Wilk test and were expressed as means ± standard deviations (SDs) for normally distributed data or medians and interquartile ranges (IQRs) for non-normally distributed data. For categorical variables, comparisons between- independent groups were performed using Pearson's chi^2 or Fisher's exact test. For continuous variables, between-group differences were tested using a one-way analysis of variance (ANOVA) if data were normally distributed or the Kruskal-Wallis test if data were non-normally distributed. If the null hypothesis was rejected, multiple pairwise comparison tests with Bonferroni adjustment were performed. A two-tailed p-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline characteristics of athletes, patients and controls are summarized in Table 1 A and Table 2. All athletes were male with a median age of 26 (7) years, a median height of 184 (11) cm and median weight of 80 (17) kg. Among professional athletes, handball players showed the highest body surface area (BSA) with 2.27 (0.17) m^2 and cyclists the smallest BSA of 1.93 (0.17) m^2. 36/37 controls were male (97%) with a median age of 32 (17) years and a mean BSA of 1.98 ± 0.19 m^2. Median age of patients with pathological hypertrophy (HOCM (51 (30) years),

Table 1A
Baseline characteristics of all professional athletes.

	Pro cyclists		Pro soccer players		Pro handball players		p-value
Male, n (%)	37 (100)	37	29 (100)	29	21 (100)	21	.
Age, years	29 (7) †‡	37	22 (6) *	29	26 (7) *	21	<0.001
Height, cm	182.8 ± 6.2 ‡	35	182.4 ± 6.6 ‡	29	192.5 ± 7.6 *†	21	<0.001
Weight, kg	73 (12) ‡	35	76 (13) ‡	29	95 (10) *†	21	<0.001
BSA, m^2	1.93 (0.17) ‡	35	1.96 (0.23) ‡	29	2.27 (0.17) *†	21	<0.001

Data were presented as numbers (%), mean ± standard deviation (SD) or medians (interquartile ranges, IQRs). One-way analysis of variance (ANOVA) and the Kruskal-Wallis test were used for between-group comparisons followed by multiple-comparison (post-hoc) test with Bonferroni adjustment: * indicates an adjusted p <0.05 for comparison with pro cyclists, † indicates an adjusted p <0.05 for comparison with pro soccer players, ‡ indicates an adjusted p <0.05 for comparison with pro handball players.
Abbreviations: pro cyclists, professional cyclists; pro handball player, professional handball player; pro soccer player, professional soccer player.

Table 1B
Echocardiographic parameters of all professional athletes.

	Pro cyclists		Pro soccer players		Pro handball players		p-value
Septal wall thickness, mm	13 (2) †‡	37	10 (1) *	29	10 (2) *	21	<0.001
LVEDD, mm	51 (5) †‡	37	55 (4) *	29	57 (3) *	21	<0.001
LVEDD/BSA, mm/m^2	26.7 (2.8)	35	27.0 (2.4) ‡	29	21.0 (2.3) †	21	<0.001
LVEF, %	64.0 ±7.5	37	63.6 ±4.6	29	64.3 ±4.6	21	0.912
LA size, mm	36.7 ±4.6	37	35.8 ±2.5	29	36.6 ±4.7	21	0.624
LA size/BSA, mm/m^2	19.0 ±2.3 ‡	35	18.0 ±1.4 ‡	29	16.2 ±1.8 *†	21	<0.001
LVMI, g/m^2	160.5 (42.0) †‡	36	97.0 (11.0) *	29	89.0 (20.0) *	21	<0.001
PW-E, cm/s	77.1 ±13.2	36	78.2 ±11.5	29	70.1 ±9.6	21	0.044
PW-A, cm/s	46 (14)	36	43 (10)	29	41 (13)	21	0.482
E/A ratio	1.72 ±0.42	36	1.83 ±0.26 ‡	29	1.52 ±0.41 †	21	0.020
Deceleration time, ms	189.3 ±50.3 †	36	157.2 ±32.8 *	29	181.5 ±36.5	21	0.010
E' septal, m/s	12.3 ±1.9 †	31	14.4 ±2.0 *	29	13.7 ±2.1	21	<0.001
E' lateral, m/s	12.9 ±1.1 †‡	7	20.5 ±2.8 *‡	29	17.5 ±3.6 *†	21	<0.001
E/e' ratio	6.5 (1.4) †‡	35	4.5 (0.9) *	29	4.5 (1.0) *	21	<0.001
Strain analyses							
GLS Av, %	−21.0 (2.0) †‡	37	−18.4 (2.3) *	29	−18.4 (1.7) *	21	<0.001
GLS PLAX, %	−21.0 (4.0) †‡	37	−18.8 (2.5) *	29	−18.6 (3.8) *	21	<0.001
GLS 4CH, %	−21.0 (2.0) †‡	37	−17.8 (2.1) *	29	−18.1 (2.4) *	21	<0.001
GLS 2CH, %	−21.0 (3.0) †‡	37	−18.9 (2.6) *	29	−19.2 (2.7) *	21	<0.001

Data were presented as numbers (%), mean ± standard deviation (SD) or medians (interquartile ranges, IQRs). One-way analysis of variance (ANOVA) and the Kruskal-Wallis test were used for between-group comparisons followed by multiple-comparison (post-hoc) test with Bonferroni adjustment: * indicates an adjusted p <0.05 for comparison with pro cyclists, † indicates an adjusted p <0.05 for comparison with pro soccer players, ‡ indicates an adjusted p <0.05 for comparison with pro handball players.
Abbreviations: pro cyclists, professional cyclists; pro handball player, professional handball player; pro soccer player, professional soccer player.

HHD (60 (18) years) and AV stenosis (81 (5) years)) was older compared with athletes and controls ($p < 0.001$). Patients with HHD showed the highest median weight (91 (19) kg) of all patient cohorts with a median height of 172 (10.2) cm (mean BSA of 2.10 ± 0.21 m^2).

3.2. Echocardiographic parameters

Table 1 B and Table 3 show the echocardiographic parameters of the study population. In all 212 subjects included, a preserved LV ejection fraction ≥50% was documented (Fig. 1 A). Septal wall thickness was in normal range in controls, soccer players and handball players, but elevated in cyclists and patients with pathological hypertrophy ($p < 0.001$ for both). LV end-diastolic diameter (LVEDD) was not elevated in any patient cohort and did not correlate with GLS or any type of hypertrophic disorder. LV mass index (LVMI) in cyclists was significantly higher when compared to soccer players and handball players ($p < 0.001$). HOCM patients showed highest LVMI values when compared to HHD and AV stenosis patients. When compared to controls, LVMI was elevated in patients with pathological hypertrophy and in professional cyclists (Fig. 1 B).

In patients with pathological hypertrophy average GLS was reduced when compared to controls and cyclists ($p < 0.001$ for both, Fig. 1 C). Among athletes, normal values for GLS were found regardless of sports discipline, with cyclists showing significantly higher average GLS values than soccer and handball players ($p < 0.001$).

In subjects with septal wall thickness of >11 mm, GLS has a specificity of 79% and a sensitivity of 66% to distinguish between physiological and pathological hypertrophy. Diastolic parameter E/e' was elevated in all patients with maladaptive hypertrophy but normal in controls and athletes ($p < 0.001$ vs. pathological hypertrophy). Athletes showed lower PW-A velocities, with higher E/A ratios as compared to controls and patients with pathological hypertrophy ($p < 0.001$). The combination of findings acquired from echocardiography and resting or exercise 12-lead-ECG did not improve the diagnostic accuracy.

4. Discussion

Echocardiographically assessed diastolic function and average GLS help to differentiate between physiological adaption like in professional cyclists and maladaptive pathological hypertrophy in different hypertrophic myocardial diseases.

4.1. Differentiation between pathological and physiological LVH

Some athletes have small increases in LV wall thickness and LV cavity diameter outside the normal range [8,10]. Physiological hypertrophy adaption in highly trained athletes is associated with increased LVM without fibrotic remodeling [4,8,10]. It seems that borderline hypertrophy as adaption to excessive training (athlete's heart) only develops in distinct sports disciplines that are accompanied with intensive endurance training like cycling, as in our study cyclists had the highest septal wall thickness (13 (2) mm) compared with the other athletes [11]. In addition, we found a significant increase in LVMI among cyclists compared to soccer and handball players. The group of professional cyclists had the smallest body surface area and thickest left ventricular

Table 2
Baseline characteristics.

	Control		HOCM		HHD		Pro cyclists		AV stenosis		p-value
Male, n (%)	36 (97)	37	9 (53)	17	22 (61)	36	37 (100)	37	22 (63)	35	<0.001
Age, years	32 (17) †‡‖	37	51 (30) *§‖	17	60 (18) *§‖	36	29 (7) †‡‖	37	81 (5) *†‡§	35	<0.001
Height, cm	178.7 ± 7.9 †‡‖	37	171.5 ± 9.8 *§	17	172.0 ± 10.2 *§	36	182.8 ± 6.2 †‡‖	35	169.9 ± 8.6 *§	35	<0.001
Weight, kg	80 (16) ‡	37	75 (27) ‡	17	91 (19) *†§‖	36	73 (12) ‡	35	78 (24) ‡	35	<0.001
BSA, m^2	1.98 ± 0.19	37	1.94 ± 0.25	17	2.10 ± 0.21 §‖	36	1.93 ± 0.12 ‡	35	1.91 ± 0.24 ‡	35	<0.001
Diabetes, n (%)	0 (0)	37	1 (6)	17	8 (22)	36	0 (0)	35	9 (26)	35	<0.001
Hypertension, n (%)	0 (0)	37	6 (35)	17	36 (100)	36	0 (0)	35	13 (37)	35	<0.001

Data were presented as mean ± standard deviation (SD) or medians (interquartile ranges, IQRs). One-way analysis of variance (ANOVA) and the Kruskal-Wallis test were used for between-group comparisons followed by multiple-comparison (post-hoc) test with Bonferroni adjustment: * indicates an adjusted p <0.05 for comparison with control, † indicates an adjusted p <0.05 for comparison with HOCM, ‡ indicates an adjusted p <0.05 for comparison with HHD, § indicates an adjusted p <0.05 for comparison with pro cyclists, ‖ indicates an adjusted p <0.05 for comparison with AV stenosis.
Abbreviations: AV, aortic valve; HHD, hypertensive heart disease; HOCM, hypertrophic obstructive cardiomyopathy; pro cyclists, professional cyclists.

Table 3
Echocardiographic data.

	Control		HOCM		HHD		Pro cyclists		AV stenosis		p-value
Septal wall thickness, mm	11 (2) †‡§‖	37	18 (4) *‡§‖	17	13 (2) *†	36	13 (2) *†	37	14 (2) *†	35	<0.001
LVEDD, mm	49 (5) †‡	37	43 (6) *§‖	17	44.5 (36) *§	36	51 (5) †‡	37	48 (10) †	35	<0.001
LVEDD/BSA, mm/m^2	24.4 (3.7) †‡	37	22.3 (3.1) *§‖	17	22.0 (17.8) *§‖	36	26.7 (2.8) †‡	35	25.1 (4.8) †‡	35	<0.001
LVEF, %	61 (4) ‖	37	61 (5) ‖	17	62.5 (9) ‖	36	64 (10) ‖	37	57 (10) *†‡§	35	<0.001
LA size, mm	34.7 ± 5.3 †‡‖	37	41.5 ± 5.6 *	17	44.6 ± 7.9 *§	36	36.7 ± 4.6 ‡‖	37	41.8 ± 5.5 *§	35	<0.001
LA size/BSA, mm/m^2	17.5 ± 2.2 †‡‖	37	21.8 ± 4.1 *§	17	21.2 ± 3.5 *§	36	19.0 ± 2.3 †‡‖	35	22.2 ± 3.5 *§	35	0.002
LVMI, g/m^2	89 (31) †‡§‖	37	159 (33) *‡	17	125 (31) *†§	36	160.5 (42) *‡‖	36	137 (62) *§	35	<0.001
PW-E, cm/s	72 (21)	37	74 (34)	17	73 (27)	16	76 (20)	36	81 (36)	35	0.249
PW-A, cm/s	57 (10) †§‖	37	87 (45) *§	17	74.5 (18) §	8	46 (14) *†‡‖	36	109 (61) *§	27	<0.001
E/A ratio	1.2 (0.5) †‡§‖	37	0.7 (0.4) *§	17	0.85 (0.4) *§	33	1.6 (0.6) *†‡‖	36	0.7 (0.3) *§	26	<0.001
Deceleration time, ms	190 (55) ‡	37	216 (127)	17	279 (72) *§‖	33	190.5 (76) ‡	36	186 (165) ‡	35	<0.001
E' septal, m/s	10 (3) †‡‖	37	4 (2) *§	17	6 (3) *§	34	12 (3) †‡‖	31	5 (1) *§	35	<0.001
E' lateral, m/s	13 (5) †‡‖	37	8 (4) *§	11	7 (3) *§	34	13 (2) †‡‖	7	6 (2) *§	35	<0.001
E/e' ratio	6.8 (2.2) †‡‖	37	11.4 (15.4) *§	11	9.3 (4.0) *§‖	33	6.5 (1.4) †‡‖	35	14.9 (9.1) *†§	35	<0.001
Strain analyses											
GLS Av, %	−19.0 (3.0) ‡§‖	37	−15.0 (6.5) §	17	−13.8 (5.7) *§	36	−21.0 (2.0) *†‡‖	36	−16.0 (7.0) *§	35	<0.001
GLS PLAX, %	−18.0 (5.0) ‡§	37	−15.0 (6.0) §	17	−14.0 (9.0) *§	36	−21.0 (4.0) *†‡‖	36	−15.0 (8.0) §	35	<0.001
GLS 4CH, %	−18.0 (3.0) ‡§	37	−17.0 (4.0) §	17	−14.0 (6.5) *§	36	−21.0 (2.0) *†‡‖	36	−16.0 (7.0) §	35	<0.001
GLS 2CH, %	−20.0 (4.0) †,‡‖	37	−14.0 (4.0) * §	17	−15.0 (9.5) * §	36	−21.0 (3.0) †‡‖	36	−17.0 (6.0) *§	35	<0.001

Data were presented as mean ± standard deviation (SD) or medians (interquartile ranges, IQRs). One-way analysis of variance (ANOVA) and the Kruskal-Wallis test were used for between-group comparisons followed by multiple-comparison (post-hoc) test with Bonferroni adjustment: * indicates an adjusted $p < 0.05$ for comparison with control, † indicates an adjusted $p < 0.05$ for comparison with HOCM, ‡ indicates an adjusted $p < 0.05$ for comparison with HHD, § indicates an adjusted $p < 0.05$ for comparison with pro cyclists, ‖ indicates an adjusted $p < 0.05$ for comparison with AV stenosis.
Abbreviations: AV, aortic valve; HHD, hypertensive heart disease; HOCM, hypertrophic obstructive cardiomyopathy; pro cyclists, professional cyclists.

septum compared with the other athletes and controls. Elevated wall thickness and LVEDD can indicate heart disease. In our study that focused on myocardial hypertrophy, LVEDD did not correlate with a specific disease or hypertrophy in athletes.

4.2. Diastolic function

Our data on athletes indicate "normal"/physiological diastolic values in line with data from the literature, in which normal diastolic values were found in Olympic athletes [12–14]. In our cohorts, only the professional cyclists presented with hypertrophic or borderline hypertrophic hearts. Echocardiographic parameters evaluation diastolic function showed no deviations from normal in cyclists in contrast to patients with pathological LVH, who showed impaired diastolic function. We did not observe specific differences in diastolic function between patients with HOCM, HHD and AV stenosis. The evaluation of diastolic function can be regarded as diagnostic tool in distinguishing physiological from pathological LV hypertrophy.

4.3. Speckle-tracking

Speckle-tracking echocardiography allows quantification of myocardial deformation by analyzing standard B-mode images and is mainly used for functional assessment of the LV [15]. In contrast to the biplane EF, strain echocardiography allows a more sensitive detection of functional disorders with lower interobserver variability [16]. Several components of the contractile deformation can be distinguished: i) longitudinal shortening, ii) circumferential shortening (the radius of the ventricle decreases in cross-section) and iii) radial thickening [17]. Average GLS represents the best-validated strain parameter, which has been established in various pathologies such as coronary heart disease, heart failure, or HCM [18,19]. Reduced GLS has been associated with poor prognosis and increased risk of adverse cardiovascular events, independent of other clinical and echocardiographic risk factors [9,20]. With the echocardiography technologies used in this study (GE Healthcare), a GLS < -16 % is considered as pathologic and a GLS ≥ -18 % as normal. Because GLS varies with age, gender and LV load, the range between −16% and −18% is considered borderline or slightly impaired [5]. GLS analysis measures the mobility of the longitudinally arranged subendocardial myocardial fibers of the left and right ventricles [21]. It has been shown that GLS is reduced in patients with HCM [22]. Our findings are in agreement with this and maladaptive LVH in patients with HOCM, HHD and AV stenosis was associated with a significant reduction of GLS compared with controls. As athletes exhibit adaptive physiological hypertrophy, the differentiation between maladaptive and adaptive hypertrophy can be challenging, especially with a septal wall thickness in the "grey zone" (IVSd 12–15 mm). The Maron's criteria recommend the evaluation based on family history, ECG, gender and functional capacity in HCM [6,8]. There are only few studies on GLS in athletes [11,23–25] and there have been no reference values proposed for the definition of an athlete's heart. Most of these studies included one single sport discipline and often used different software tools with individual ranges to evaluate GLS [21,26,27]. This study, is the first to compare GLS in different professional sports (cycling, soccer, or handball) with various exercise burdens and training focus (excessively trained endurance training vs. ball sport) to controls and patients with different forms of hypertrophic heart disease. In all athletes, the median GLS was in normal ranges (−19 (4) %). The investigated game sports including a ball herein are comparable to Olympic athletes [23] (−18.1 (2.2) %), grouped into skill, power, mixed, and endurance disciplines, or professional NBA athletes (−18.5 (2.5)%) [25]. Particularly the cyclists had a median GLS above normal ranges (−21.0 (3.5) %) which was higher than the GLS value in the other sports disciplines and the control group. Our data generated in professional cyclists are in line with top-level rowers [11]. In parallel to diastolic function evaluation, GLS easily discerns physiological cardiac hypertrophy in athletes from pathological changes. GLS seems especially suited for this task since GLS values were highest in cyclists who on the other hand showed the most pronounced hypertrophy with increased septal wall thickness and LVMI. This also raises the interesting question of whether "above normal" values could be evaluated to assess cardiac fitness in extreme athletes.

5. Limitations

Group sizes vary, which is related to the different group sizes of the individual sport teams. Also, in this study only male individuals were explored and the data cannot be extrapolated to female athletes, since we were not able to obtain data from female athletes subjected to similar exercise schedules. In our study, only patients with echocardiographically clear etiological findings were included as a control group.

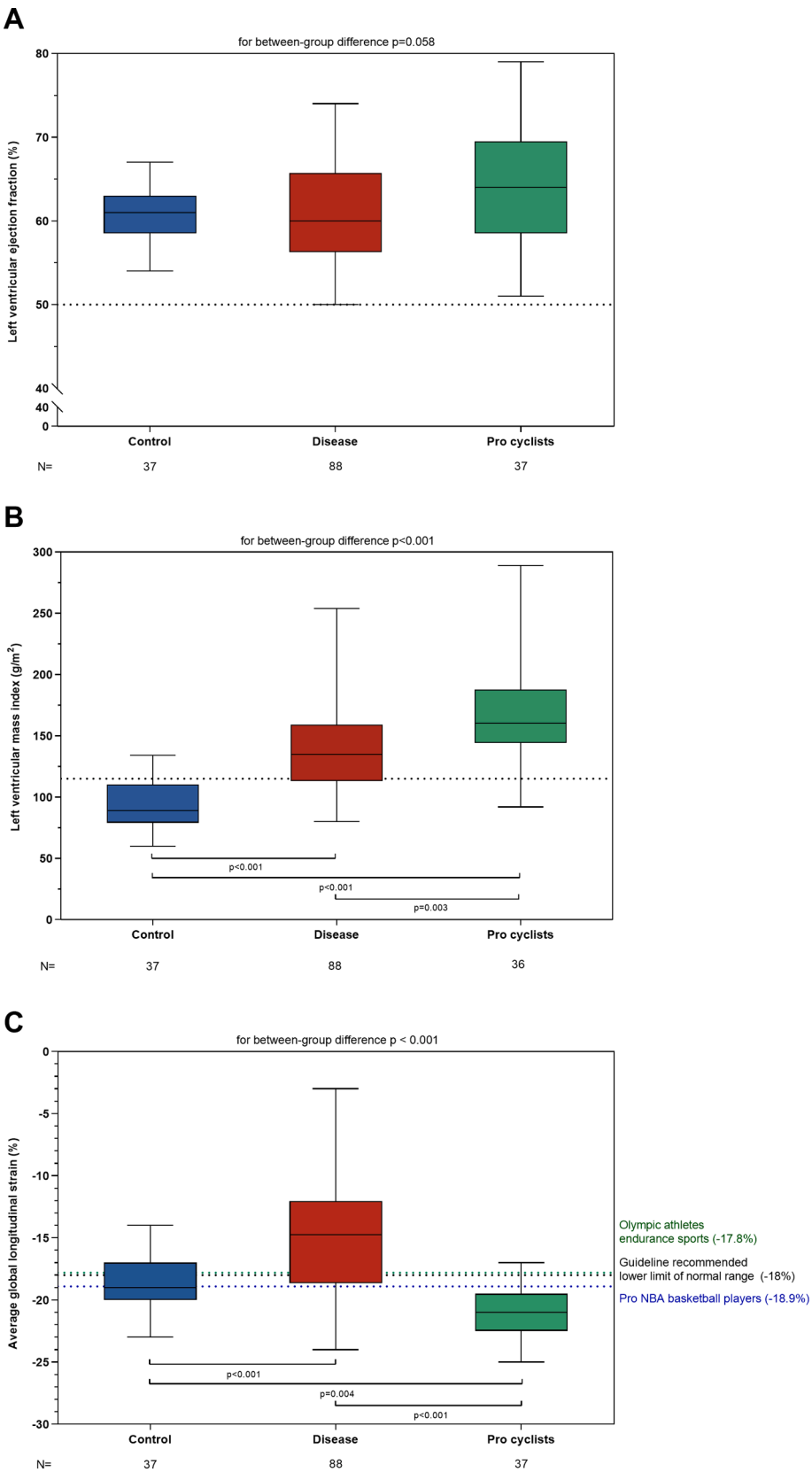

Fig. 1. Min to Max: the whiskers go down to the smallest value and up to the largest. (A) Left ventricle ejection fraction (LVEF), (B) left ventricular mass index (LVMI) and (C) average global longitudinal strain (GLS): professional cyclists, disease (patients with hypertrophic obstructive cardiomyopathy (HOCM), hypertensive heart disease (HHD), severe aortic stenosis (AVS)), and healthy controls. The black dotted lines indicate the limits recommended by the guidelines (LVEF $\geq$ 50%, LVMI (in men) = 115 g/m^2, GLS $\geq$ −18%) [5]. The green dotted line indicates the average GLS (−17.8%) in Olympic athletes in endurance sports [23] and the blue dotted line indicates the average GLS (−18.9%) in professional NBA basketball players [25]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

However, it would be interesting to also evaluate patients with borderline LV hypertrophy compared to athletes. This would be an interesting thesis for a further evaluation.

6. Conclusion

Differentiation of LV hypertrophy in healthy athletes from pathological LV hypertrophy in heart disease is often difficult. Neither the LV

ejection fraction nor the LVMI can distinguish physiological from pathological hypertrophy. The diastolic parameter E/e' was elevated in all patients with maladaptive hypertrophy but normal in controls and athletes. Furthermore, GLS was reduced in patients with pathological hypertrophy compared with athletes and controls. Therefore, assessment of diastolic function and average GLS help to differentiate between athletes' hearts and pathologic left ventricular hypertrophy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L. L. received speaker honoraria from Medtronic and ReCor Medical, outside the submitted work. M.B. reports support from Abbott, Amgen, Astra-Zeneca, Bayer, Boehringer-Ingelheim, Medtronic, Novartis, Recor, Servier, and Vifor outside the submitted work. All other authors have declared no conflict of interest. S.E. received speakers or consultant honorarium and/or travel support from Medtronic, Recor, Bayer, Daiichi Sankyo, Böhringer Ingelheim, Novartis, AstraZeneca, Akcea Therapeutics and Bristol-Myers Squibb-Pfizer.

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Author contributions

Y.B., S.E., F.M. and M.B. contributed to conceptualization of the research project; data curation and formal analysis of the data were performed by Y.B., S.K., O.S., C.U., R.P.M., P.H., U.L., S.S., A.H. and L.L.; Y.B., S.K., M.B. and S.E. wrote the original draft of the manuscript; F.M., O.S., C.U., R.P.M., P.H., U.L., S.S. and A.H. reviewed and edited the manuscript.

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