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Left Ventricular Untwisting in Athlete's Heart: Key Role in Early Diastolic Filling?

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Key words

- echocardiography
- speckle tracking
- untwist
- MRI
- athlete's heart

Abstract

Untwisting contributes to left ventricular filling through suction generation. We sought to investigate diastolic function and untwisting dynamics in different forms of left ventricular hypertrophy: in athlete's heart and hypertrophic cardiomyopathy. Elite athletes in kayaking, canoeing and rowing (n=28), patients with hypertrophic cardiomyopathy (HCM, n=15) and healthy sedentary volunteers (n=13) were compared. Left ventricular volumes, wall thickness-to-volume ratio were assessed by cardiac MRI. Following conventional and tissue Doppler measurements, untwist and untwist rate were determined by speckle tracking echocardiography. Wall thickness-to-volume ratio describing remodelling was significantly

higher in HCM, but similar in athletes and controls (athlete vs. HCM vs. control: 0.107 ± 0.019 vs. 0.271 ± 0.091 vs. 0.104 ± 0.012 mm \times m 2 /ml, mean \pm SD, $p < 0.001$). Mitral lateral annulus e' velocity referred to diastolic dysfunction in HCM (15.3 ± 3.6 vs. 7.9 ± 3.3 vs. 15.0 ± 3.0 cm/s, $p < 0.01$). At time point of mitral valve opening, untwist and untwist rate were significantly different: the highest values were measured in athletes, while the lowest were found in HCM (untwist: 51.3 ± 19.1 vs. 11.6 ± 10.4 vs. 35.9 ± 16.3 %; untwist rate: -32.5 ± 13.0 vs. -10.6 ± 10.8 vs. -23.0 ± 7.7 °/s, $p < 0.05$). Untwisting correlated with E/A, e' and E/e'. Athlete's heart is characterized by increased untwist and untwist rate, which can aid diastolic function. Evaluation of untwisting dynamics may help to distinguish pathological hypertrophy.

Introduction

The athlete's heart can be characterized by altered left ventricular (LV) dimensions, increased relative wall thickness, mass and myocardial hypertrophy [20]. Although increased LV mass has adverse effect on diastolic function in various disorders, the LV filling of athletes remains unaffected [9,22]. Early diastolic filling of the left ventricle is the consequence of the pressure gradient between the left heart chambers and strongly depends on the relaxation of the ventricle [16]. This flow constitutes the majority of left ventricular filling, and becomes even more relevant at higher heart rates during exercise [1]. LV twist motion induced by apical counterclockwise and basal clockwise rotation in systole aids ventricular ejection, while early diastolic untwist generates suction and facilitates diastolic filling [26]. Rotational mechanics of the ventricle constitutes the base of systolic-diastolic coupling. Timing and absolute value of peak twist is a determinant of untwisting. Nevertheless, untwisting is influenced not just by systolic twist, but by many

other factors [27]. The evaluation of twist and ensuing untwist provides valuable information on the systolic and diastolic function of the left ventricle in numerous diseases [18].

The complex ventricular deformation including systolic twisting and early diastolic untwisting can be accurately quantified by 2-dimensional speckle tracking echocardiography (2D STE) [12]. Speckles are natural acoustic markers of the myocardium that occur as small, hypo- or hyperechoic areas on the standard grayscale B-mode images. Frame-by-frame tracking of the relatively constant and unique speckle pattern is implemented by a suitable algorithm and several deformation parameters of the region of interest can be obtained with dedicated software [2].

Hypertrophic cardiomyopathy (HCM) has been reported the most frequent cause of sudden cardiac death of young elite athletes in the United States [13]. Although several echocardiographic methods are available for detecting possible HCM and confirming the diagnosis thereof, the utility of new techniques in the differentiation between

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this potentially life-threatening pathology and athlete's heart in case of myocardial hypertrophy would perhaps be beneficial [20].

Aim of the Study

Our purposes were to characterize the timing and rate of untwisting in elite athletes compared to HCM patients and healthy volunteers, and to investigate whether untwisting measured by 2D speckle tracking echocardiography could differentiate between physiologic and pathologic hypertrophy.

Methods

Study population

28 elite athletes (EA) in flatwater kayaking, canoeing or rowing, all capped in the Hungarian National Team including numerous European-, World- and Olympic champions, were enrolled. All athletes were examined in the in-season training phase of their preparation. A total of 15 patients with hypertrophic cardiomyopathy (all with sigmoid septal curvature regarding the pattern of hypertrophy [30]) and 13 healthy, sedentary volunteers as normal controls (NC) were included. Exclusion criteria were: medical history or present symptoms of coronary heart disease, hypertension, diabetes mellitus, any other cardiomyopathy, significant valvular disease and any relevant form of cardiac arrhythmias. Standard transthoracic echocardiography, 2D STE and cardiac MRI of each subject were performed in the Heart Center of Semmelweis University. The research was conducted ethically according to international standards [8], the protocol was approved by the National Committee for Science and Research Ethics (TUKÉB), and written informed consent was obtained from all participants prior to the study.

Echocardiography

Following a standard transthoracic echocardiographic examination, parasternal short axis loops of 3 consecutive heart cycles were recorded (Philips iE33, S5-1 probe, Philips Healthcare, Best, The Netherlands) using optimal frame rate (72 ± 6 frames per second) and adequate adjustment of focus position, depth and sector size. To measure the basal and apical rotation of the left ventricle, proper LV cross sections at the mitral valve level and at the apex (just proximal to the level, where systolic luminal obliteration could be observed) were obtained. Subsequent 2D speckle tracking analysis of digitally saved ultrasound data was performed using the Philips QLab CMQ software (v8.1). Following semi-automated detection of the left ventricular epi- and endocardial borders, precise region of interest was adjusted manually, then bulk rotation values throughout the cardiac cycle were calculated and averaged over the 3 recorded cycles. As a result of the complex, helical structure of the myocardium, the base of the left ventricle rotates in clockwise, the apex in counterclockwise direction during contraction. By convention, apical counterclockwise rotation resulted in positive, basal clockwise rotation in negative degrees. The net difference between these 2 motions is defined as twist [14]. In order to correct for the differences in heart rates, timing of the LV twisting events was expressed as a percentage of the duration of systole or diastole. Untwist and untwist rate values were calculated from the following formulas [29]:

$$\text{untwist (\%)} = \left(\frac{\text{twist}_{\text{peak}} - \text{twist}_x}{\text{twist}_{\text{peak}}} \right) \times 100$$

$$\text{untwist rate (}^\circ/\text{s)} = \frac{\text{twist}_x - \text{twist}_{\text{peak}}}{t_x - t_{\text{peak}}}$$

where "twist_{peak}" is the peak systolic twist occurring in "t_{peak}" time and "twist_x" is the twist angle at a certain "t_x" time point of the cardiac cycle. Time points of aortic valve closure (AVC), mitral valve opening (MVO) and peak E velocity were determined using pulsed wave Doppler recordings of mitral inflow and the LV outflow tract.

Cardiac MRI

For the accurate measurement of left ventricular function, hypertrophy and remodelling, gold standard cardiac MRI was also performed in all study subjects using a 1.5 Tesla system (Achieva, Philips Healthcare, Best, The Netherlands). For contrast enhancement, gadolinium was administered intravenously in EA and HCM groups. Breath holding at end expiration was required for each image acquisition to eliminate respiratory motion artefacts. After scout images were obtained, steady-state free-precession breath-hold (bSSFP) cine images were performed in 4-chamber, 3-chamber and 2-chamber long-axis planes and sequential 8mm short-axis slices (flip angle 60°, 0-mm gap) from the atrioventricular ring to the apex. Left ventricular volumes, ejection fraction (EF), maximal end-diastolic wall thickness (MWT) and mass were quantified using manual planimetry of end-diastolic and end-systolic short-axis bSSFP cine images with MASS 7.1 analysis software (Magnetic Resonance Analytical Software System, Medis Medical Imaging Software, Leiden, The Netherlands). Left ventricular end-diastolic-, end-systolic volumes and mass were indexed to body surface area (EDVi, ESVi, LVMI respectively) using the Mosteller formula [15].

Statistical analysis

For data administration and for statistical analysis we used Office 2010 Excel (Microsoft, Redmond, USA.), STATISTICA v8.0 (StatSoft Inc., Tulsa, USA.) software. Polynomial interpolation of corresponding rotation curves was done by Lagrange method. Normal distribution was assessed by Shapiro-Wilk test. Depending on normality, comparison among study groups was done either by one-way ANOVA followed by Tukey post-hoc test, or Kruskal-Wallis ANOVA followed by Mann-Whitney U test. Correlations were calculated using Spearman rank-correlation test. Data are presented as mean \pm SD and for non-normally distributed data as median (interquartile range). P-values less than 0.05 were considered to be statistically significant.

Results

The basic demographic and hemodynamic characteristics of the study population are shown in **Table 1**. All the 3 groups are age-matched. In the HCM group women were also included. Appropriate beta-blocker medication was used in all HCM patients, 2 patients were on calcium-channel blocker and 2 patients were on angiotensin-converting enzyme inhibitor therapy as well. The heart rate values of control subjects were significantly higher than elite athletes and HCM patients, while the EA and HCM group did not differ significantly.

Table 1 Basic demographic, hemodynamic characteristics of the study population, and parameters measured by cardiac MRI or conventional echocardiography.

	EA (n=28)	HCM (n=15)	NC (n=13)	ANOVA p
age (years)	26±8	33±14	30±5	0.107
male, n (%)	28 (100)	10 (66)	13 (100)	
BSA (m ²)	2.0±0.1	2.0±0.2	2.0±0.1	0.484
SBP (mmHg)	139±10	132±23	137±12	0.477
DBP (mmHg)	74±11 [§]	77±10	85±10*	0.036
HR (bpm)	60±9 [§]	68±11 [§]	80±10* [#]	<0.001
	cardiac MRI			
MWT (mm)	12 (1) ^{#§}	25 (7.75) ^{*§}	10.5 (1) ^{*#}	<0.001
LVMi (g/m ²)	89.7 (14.1) ^{#§}	116.9 (54.3) ^{*§}	70.4 (7.4) ^{*#}	<0.001
ESVi (ml/m ²)	50.3±9.7 ^{#§}	32.1±7.7*	38.1±8.2*	<0.001
EDVi (ml/m ²)	119.1±15.0 ^{#§}	90.0±16.3*	97.5±11.3*	<0.001
MWT-to-EDVi ratio (mm×m ² /ml)	0.107±0.019 [#]	0.271±0.091 ^{*§}	0.104±0.012 [#]	<0.001
EF (%)	57.9±4.5 [#]	65.7±6.3*	61.2±5.1	<0.001
	conventional echocardiography			
IVS (mm)	13 (2) [#]	28.5 (10) ^{*§}	12 (1.5) [#]	<0.001
PW (mm)	12 (2.75) ^{#§}	15 (2) ^{*§}	10 (1) ^{*#}	<0.001
IVRT (sec)	0.07 (0.02)	0.07 (0.015)	0.07 (0.02)	0.965
E (cm/sec)	92.0±18.3	92.4±19.9	80.5±5.0	0.153
A (cm/sec)	45 (8) [#]	58.5 (19.5)*	46 (18)	0.002
E/A	1.9 (0.6) ^{#§}	1.5 (0.3)*	1.5 (0.3)*	<0.001
DT (sec)	0.188±0.043	0.190±0.063	0.204±0.039	0.638
e' (cm/s)	15.3±3.6 [#]	7.9±3.3 ^{*§}	15.0±3.0 [#]	<0.001
E/e'	6.0 (1.3) [#]	11.4 (6.2) ^{*§}	5.4 (1.5) [#]	<0.001

Normally distributed data are presented as mean±SD, non-normally distributed as median (IQR). *p<0.05 vs. EA, #p<0.05 vs. HCM, §p<0.05 vs. NC; A: mitral inflow velocity during atrial contraction, BSA: body surface area, DBP: diastolic blood pressure, DT: deceleration time, E: early diastolic mitral inflow velocity, e': mitral lateral annulus early diastolic velocity, EA: elite athletes, EDVi: end-diastolic volume index, EF: ejection fraction, ESVi: end-systolic volume index, IVRT: isovolumic relaxation time, IVS: interventricular septum thickness, HCM: hypertrophic cardiomyopathy, HR: heart rate, LVMi: left ventricular mass index, MWT: maximal end-diastolic wall thickness, NC: normal controls, PW: left ventricular posterior wall thickness, SBP: systolic blood pressure

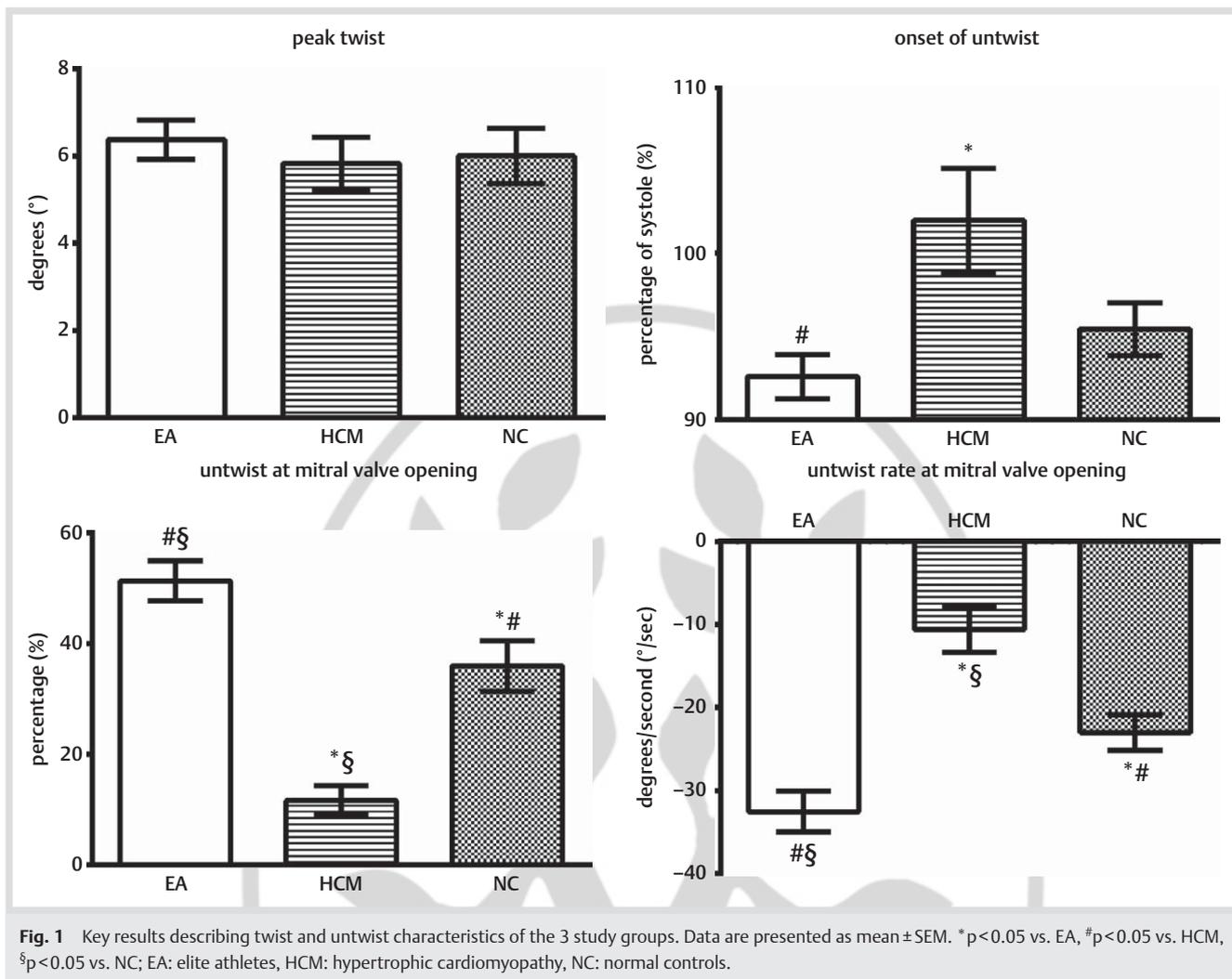
Table 2 Rotational, twisting and untwisting characteristics of the study groups.

	EA (n=28)	HCM (n=15)	NC (n=13)	ANOVA p
peak apical rotation (°)	4.3 (2.5)	3.2 (2.1)	4.4 (2.4)	0.235
time to peak apical rotation (% of systole)	95.8 (20.1)	95.4 (34.3)	94.5 (6.0)	0.856
peak basal rotation (°)	-2.7±1.2	-3.2±1.8	-2.1±1.0	0.112
time to peak basal rotation (% of systole)	91.0 (16.8)	95.4 (14.8)	98.2 (21.1)	0.229
untwist at aortic valve closure (%)	4.2 (10.5) [#]	-0.2 (3.7) ^{*§}	3.3 (6.8) [#]	0.003
untwist rate at aortic valve closure (°/sec)	-12.2±8.8 [#]	-0.4±6.1*	-7.4±9.3	<0.001
untwist at time of peak E velocity (%)	67.8±17.4 [#]	51.8±20.6*	60.2±15.8	0.025
untwist rate at time of peak E velocity (°/sec)	-25.9 (12.5)	-23.3 (9.6)	-20.5 (6.6)	0.401
time to 90% untwist (% of diastole)	70.5 (35.4)	69.3 (26.7)	60.5 (46.5)	0.651

Normally distributed data are presented as mean±SD, non-normally distributed as median (IQR). *p<0.05 vs. EA, #p<0.05 vs. HCM, §p<0.05 vs. NC; EA: elite athletes, HCM: hypertrophic cardiomyopathy, NC: normal controls

Significantly increased MWT and LVMi were measured in the EA group compared to controls. However, the left ventricular hypertrophy of HCM patients were more severe (Table 1). ESVi and EDVi values were increased in athletes, but were similar in the HCM and NC groups. Maximal end-diastolic wall thickness-to-end-diastolic volume index ratio was significantly increased in the HCM group and could differentiate the pathological hypertrophy of HCM from the other normal groups. Ejection fraction was found to be lower in athletes compared to HCM patients. The standard 2-dimensional echocardiographic parameters are summarized in Table 1. E/A ratio describing diastolic left ventricular filling pattern was significantly increased in athletes. The values of pulsed wave tissue Doppler-derived mitral lateral annular e' velocity referred to the impaired diastolic function of HCM patients, but were normal and similar in both EA and NC study groups. In line with this, E/e' values were elevated in HCM compared to the other groups, indicating increased left ventricular filling pressures (Table 1).

Left ventricular rotational parameters measured by 2D STE and the calculated LV twist and untwist are summarized in Table 2 and Fig. 1. In our study groups, no differences could be observed in either maximal systolic basal and apical rotation or in their timing. Twist values were also similar. Peak twist occurred after the aortic valve closure exclusively in HCM, meaning that the onset of untwist was significantly delayed in HCM patients compared to elite athletes. Furthermore, at the time point of mitral valve opening remarkable difference could be observed among the 3 study groups regarding untwist and untwist rate (Fig. 1). Elite athletes showed increased LV untwist motion compared to both NC and HCM. At the time point of mitral inflow peak E velocity, only the difference between athletes and HCM remained significant, said difference finally disappearing in mid-diastole. Untwist and untwist rate at mitral valve opening significantly correlated with E/A ($\rho=0.41$ and $\rho=-0.54$), e' ($\rho=0.47$ and $\rho=-0.63$),



E/e' ($\rho = -0.43$ and $\rho = 0.43$), $ESVi$ ($\rho = 0.63$ and $\rho = -0.37$), and $EDVi$ ($\rho = 0.57$ and $\rho = -0.53$, respectively, all $p < 0.05$).

Discussion

Our capped athletes in flatwater kayaking, canoeing and rowing represent a unique study population with combined, volume- and pressure overload training. As expected from the combined endurance and strength training nature of these sport disciplines, cardiac MRI certified a marked enlargement of the left ventricle and an increased myocardial mass in the athletes group [13]. Because different types of cardiomyopathies, such as HCM or dilated cardiomyopathy may produce similar phenotypes of cardiac remodelling, the differentiation between pathologic and physiologic alterations is of great clinical importance. The conventionally used MRI derived parameter of left ventricular wall thickness-to-volume ratio has the capability to identify pathological hypertrophy, but it does not differentiate between athletes and normal controls, which was confirmed by our results as well [21]. There are conflicting data in the literature whether 2D STE derived myocardial deformation parameters of athletes are increased, normal or even decreased during resting conditions [4,6,24]. The type of conditioning, the intensity and phase of the training, and genetic factors may all influence deformation profiles. Our study population is homogeneous in terms of these factors.

We found no difference in either peak systolic twist, or the onset of untwist between the EA and NC groups. Peak twist values did not differ in HCM patients either, but this group exhibited a marked delay in the onset of untwist (○ Fig. 2). Reduction of early diastolic untwist and untwist rate was also observed in HCM with the deterioration of diastolic function measured by conventional Doppler echocardiography. Untwist and untwist rate at mitral valve opening showed significant correlation with traditional echo parameters of diastolic function, thereby demonstrating clear diastolic impairment in the HCM group. Optimal early diastolic inflow is the major contributor to diastolic filling, especially during intense exercise, when higher heart rates result in a considerable shortening of the duration of diastole [25]. In our EA population untwist and untwist rate measured at mitral valve opening were significantly increased compared not only to HCM patients, but also to NCs.

Although the echocardiographic morphology of left ventricular hypertrophy can be similar in athlete's heart and in some forms of HCM, numerous histological aberrations are responsible for the systolic and diastolic dysfunction in HCM. Beside myocardial disarray and fibrosis, which are indicative of pathological hypertrophy, alterations in sarcomeric proteins can elucidate the impaired relaxation leading to diastolic dysfunction [10,11]. The importance of twisting motion is extensively investigated, and the relationship between the degree and timing of untwisting and diastolic dysfunction in HCM has also been evaluated

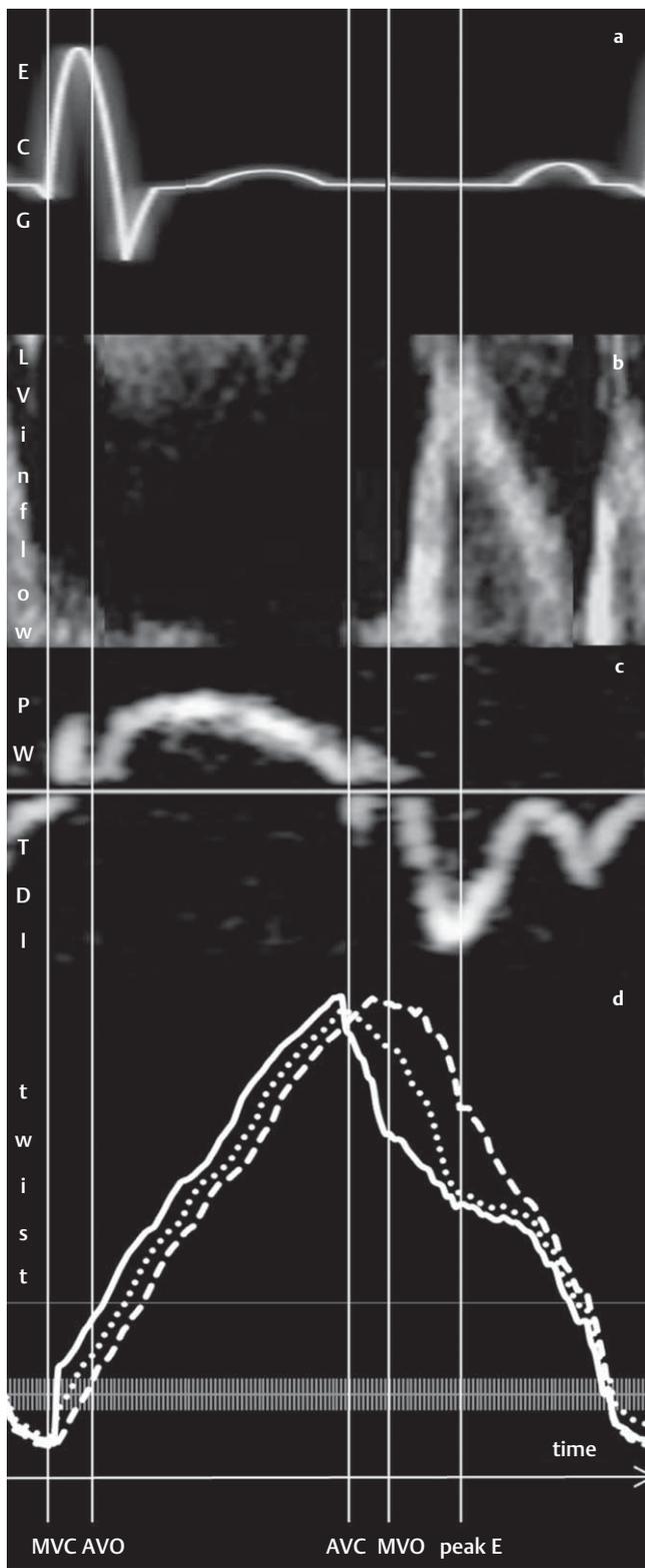


Fig. 2 Schematic illustration of the left ventricular (LV) systolic twisting and diastolic untwisting throughout the cardiac cycle. **a** ECG; **b** pulsed-wave Doppler mitral inflow velocities; **c** mitral lateral annular velocities assessed by pulsed-wave tissue Doppler imaging (PW TDI); **d** twist degrees representing our results: peak twist values were similar in our 3 study groups, but in patients with hypertrophic cardiomyopathy (HCM; dashed line) the onset of untwist was significantly delayed compared to elite athletes (continuous line). Untwist at MVO in elite athletes was increased compared both to HCM patients and normal controls (dotted line). MVC: mitral valve closure, AVO: aortic valve opening, AVC: aortic valve closure, MVO: mitral valve opening.

[7, 19]. In a recent study, Urbano Moral et al. demonstrated that reduced untwist at mitral valve opening is a useful parameter for distinguishing between HCM patients and control subjects [29]. Our study supports these observations. Similar findings were also published in hypertension-induced left ventricular hypertrophy [28]. Beyond this, we also demonstrated, that untwisting is significantly increased at mitral valve opening in elite athletes. The timing and rate of untwisting is a strong predictor of intra-ventricular pressure decay and diastolic suction, as shown in an animal model [17]. In a human experiment using invasive measurements as well, Burns and colleagues concluded that untwisting is an essential component of early filling, but not later events of diastole, which concurs with our results [3].

The early and rapid untwisting of athletes may play a key role in their enhanced ventricular relaxation and diastolic function. Since peak systolic twist values were similar in our 3 study groups, we conclude that the enhancement of diastolic untwisting is determined by intrinsic properties of the myocardium. While the explanation of this phenomenon may be found in the structural and electrical remodelling occurring in athletes, the exact processes remain to be clarified [23]. Geometry of the chambers adapted to combined power-endurance training could also propitiously influence fibre orientation, untwisting, and finally diastolic function, as it can be inferred from the correlation between chamber dimensions and functional parameters.

Limitations

An obvious limitation of our study is the number of cases, which was restricted by the selection of a homogeneous group of world-class elite athletes. Ethnic uniformity can also be conceived as a limitation, since differentiating between morphologically mild HCM and athlete's heart in blacks would appear to be a major clinical problem [5]. Recruiting more HCM patients with wall thickness comparable to athlete's heart could represent an actual differential diagnostic issue. Furthermore, women were also included in the HCM group. However, we investigated these patients as a reference to a conventional issue in sports medicine, since decreased untwisting in HCM is a well established phenomenon.

Conclusions

Untwisting to facilitate early diastolic filling is supernormal in combined power-endurance athletes. Evaluation of untwisting mechanics by speckle tracking echocardiography can deepen our understanding of physiological adaptation to intense exercise and may help to distinguish between physiological and pathological hypertrophy and remodelling.

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