Magnetic resonance imaging of myocardial injury and ventricular torsion after marathon running

Henner HANSSEN∗†1, Alexandra KEITHAHN‡1, Gernot HERTEL∗, Verena DREXEL∗, Heiko STERN§, Tibor SCHUSTER∥, Dan LORANG∗, Ambros J. BEER‡, Arno SCHMIDT-TRUCKSASS†, Thomas NICKEL¶, Michael WEIS¶, Rene BOTNAR∗∗, Markus SCHWAIGER‡ and Martin HALLE∗

∗Department of Prevention and Sports Medicine, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany, †Division of Sports Medicine, Institute of Exercise and Health Sciences, Medical Faculty, University of Basel, Basel, Switzerland, ‡Department of Nuclear Medicine, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany, §Deutsches Herzcentrum München, Clinic of Pediatric Cardiology and Congenital Heart Disease, Munich, Germany, ¶Institute for Medical Statistics and Epidemiology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany, ∥Department of Cardiology, Campus Großhadern, Ludwig-Maximilians-Universität, Munich, Germany, and **Rayne Institute, Division of Imaging Science, St Thomas’ Hospital, King’s College, London, U.K.

ABSTRACT
Recent reports provide indirect evidence of myocardial injury and ventricular dysfunction after prolonged exercise. However, existing data is conflicting and lacks direct verification of functional myocardial alterations by CMR [cardiac MR (magnetic resonance)]. The present study sought to examine structural myocardial damage and modification of LV (left ventricular) wall motion by CMR imaging directly after a marathon. Analysis of cTnT (cardiac troponin T) and NT-proBNP (N-terminal pro-brain natriuretic peptide) serum levels, echocardiography [pulsed-wave and TD (tissue Doppler)] and CMR were performed before and after amateur marathon races in 28 healthy males aged 41 ± 5 years. CMR included LGE (late gadolinium enhancement) and myocardial tagging to assess myocardial injury and ventricular motion patterns. Echocardiography indicated alterations of diastolic filling [decrease in E/A (early transmitral diastolic filling velocity/late transmitral diastolic filling velocity) ratio and E’ (tissue Doppler early transmitral diastolic filling velocity)] postmarathon. All participants had a significant increase in NT-proBNP and/or cTnT levels. However, we found no evidence of LV LGE. MR tagging demonstrated unaltered radial shortening, circumferential and longitudinal strain. Myocardial rotation analysis, however, revealed an increase of maximal torsion by 18.3 % (13.1 ± 3.8 to 15.5 ± 3.6°; P = 0.002) and maximal torsion velocity by 35 % (6.8 ± 1.6 to 9.2 ± 2.5° · s−1; P < 0.001). Apical rotation velocity during diastolic filling was increased by 1.23 ± 0.33° · s−1 after marathon (P < 0.001) in a multivariate analysis adjusted for heart rate, whereas peak untwist rate showed no relevant changes. Although marathon running leads to a transient increase of cardiac biomarkers, no detectable myocardial necrosis was observed as evidenced by LGE MRI (MR imaging). Endurance exercise induces an augmented systolic wringing motion of the myocardium and increased diastolic filling velocities. The stress of marathon running seems to be better described as a burden of myocardial overstimulation rather than cardiac injury.

Key words: cardiac biomarker, endurance sport, magnetic resonance imaging, myocardial tagging, tissue Doppler imaging.

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; A, late transmitral diastolic filling velocity; A’, tissue Doppler late transmitral diastolic filling velocity; CI, confidence interval; CS, circumferential; cTnT, cardiac troponin T; E, early transmitral diastolic filling velocity; E’, tissue Doppler early transmitral diastolic filling velocity; GEE, generalized estimation equation; IQR, interquartile range; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, magnetic resonance; CMR, cardiac MR; MRI, MR imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; PWD, pulsed-wave Doppler; RS, radial shortening; TD, tissue Doppler; TEDD3/kg, total LV end-diastolic volume per kg of body weight; TFE, turbo field echo.

1 These authors contributed equally to the study.

Correspondence: Dr Henner Hanssen (email hennerhanssen@hotmail.com).
INTRODUCTION

The number of recreational marathon runners, including overweight and obese individuals, is constantly rising [1]. Regular physical exercise is widely advocated due to its capability to delay atherosclerosis and reduce the incidence of cardiovascular disease [2–5] and overall mortality [6,7]. Nevertheless, vigorous exertional exercise can acutely and transiently increase the risk of myocardial infarction and sudden cardiac death in susceptible individuals [8,9]. The paradox of exercise describes the conundrum of vigorous exertion triggering sudden death from cardiac causes on the one hand and habitual exercise diminishing this risk on the other.

Extensive exercise, such as marathon running, has been shown to induce biochemical evidence of myocardial injury and LV (left ventricular) diastolic dysfunction [10]. Whether the elevation of cTnT (cardiac troponin T) after a marathon is due to myocardial necrosis, or simply reflects an increased permeability of cardiac enzymes from the cytoplasm, is unclear [11,12]. A general prevalence of subclinical myocardial injury of 12% in older marathon runners, independent of acute exercise, has previously been assessed by LGE (late gadolinium enhancement) [13]. In contrast, two more recent MRI [MR (magnetic resonance) imaging] studies did not detect any myocardial damage by LGE in runners immediately after a marathon race [14,15].

For analysis of the extent of cardiac injury, LGE MRI is now increasingly accepted as the most accurate diagnostic imaging tool [16]. In addition, MRI motion pattern analysis of radial shortening, circumferential and longitudinal strain as well as torsional deformation by myocardial tagging is one of the most accurate modalities for imaging LV function [17–19]. The LV wringing motion of the heart is a key element for regulating LV systolic and diastolic mechanics. Taken in conjunction, these MRI techniques allow a precise clinical approach to the question addressed.

In the present study, we sought to shed light on the conflicting data of LGE MRI detectable myocardial damage after marathon. No study, to date, has performed cardiac MRI motion pattern analysis immediately after a marathon to assess the acute effects of marathon running on myocardial function and integrity. MRI tagging represents an innovative methodological approach to non-invasively assess systolic torsional deformation and diastolic untwisting and filling postmarathon with high spatial and temporal resolution.

MATERIALS AND METHODS

Study design and screening

Male amateur marathon runners were recruited by a study appeal in a local newspaper and by written invitations sent to local running clubs. In order to rule out any gender-specific influences on myocardial motion pattern, only male marathon runners were recruited. The study complies with the Declaration of Helsinki and was approved by the university hospital’s Ethics Committee. All athletes gave written informed consent.

In 2007, three separate marathon events in the direct vicinity of the hospital were organized to optimize post-race timing and enable cardiovascular imaging in all subjects. To achieve this, the individual participants started half an hour apart with the fastest starting first. Ten marathon runners were scheduled to take part in each marathon, adding up to a total of 30 participants. Two runners dropped out due to musculoskeletal injuries shortly before the start of the marathon events. To minimize volume depletion, liberal oral intake of fluid was encouraged during and after the marathon.

Prior to the marathon, all athletes received CMR (cardiac MR), echocardiography, ECG analysis and blood sampling within 5 days before the race. After the marathon, echocardiography as well as ECG analysis and blood sampling were performed immediately postmarathon. CMR, including LGE and myocardial tagging, was performed 1 h after cessation of the race. Follow-up screening of biochemical markers and echocardiography were performed the next day.

Inclusion and exclusion criteria

A total of 200 runners replied to the initial study appeal. Male marathon runners were eligible if aged 30–60 years with a recent history of at least one marathon. Exclusion criteria consisted of known coronary or structural heart disease, Type 1 diabetes, drug treatment for Type 2 diabetes or hypertension, active smoking, renal dysfunction, chronic inflammatory, musculoskeletal disease or claustrophobia.

Biochemical markers

Blood was collected into EDTA and serum separator tubes and processed immediately. Quantitative measurement of cTnT (third generation; Roche Diagnostics) was performed on a Roche Elecsys 1010 platform. The 99th percentile for normal subjects is 0.01 ng/ml. The cut-off point providing 10% coefficient of variation is 0.03 ng/ml, which represents the conventional upper limit of normal for this assay [20]. NT-proBNP (N-terminal pro-brain natriuretic peptide) levels were measured with an electrochemiluminescence sandwich immunoassay (Elecsys ProBNP; Roche Diagnostics), with the Roche 2010 system. In individuals <75 years of age, the upper limit of normal is considered to be 125 pg/ml.

Echocardiography

All studies were performed using a commercially available echocardiography device equipped with a 2.5-MHz probe and digital storage capacity (Philips iE32
Figure 1  Late enhancement imaging and myocardial tagging sequences
(a) Inversion recovery sequence in the short-axis, long-axis and four-chamber view for complete heart coverage. (b) The tagging sequences consist of two sets of images with horizontally and vertically modulated stripes acquired in one breath-hold. The quantification of the software-acquired grid deformation allows an exact and objective assessment of global wall motion.

MR examination protocol
All examinations were performed on a 1.5-T MRI scanner (ACS NT; Philips Medical Systems), equipped with a five-element cardiac coil used for signal reception. The MRI protocol included ECG-triggered, breath-hold SSFP (steady-state free precession) (2DFFE) cine sequences on which inversion recovery and tagging sequences were planned.

After injection of a gadolinium-based contrast medium (0.2 mmol/kg of body weight; Magnevist), LGE imaging was performed using a 3D (three-dimensional) inversion recovery sequence in two long-axis (two- and four-chamber) and one short-axis view for complete heart coverage, as previously described [25] (Figure 1a). Scans for delayed enhancement were performed with a breath-hold, ECG-triggered 3D fast gradient echo [TFE (turbo field echo)] inversion recovery sequence with echo planar readout. Parameters included echo time 3.3 ms, recovery time 5.4 ms, EPI factor 11, slice thickness 5 mm, spatial resolution 1.2 mm × 1.2 mm², flip angle 15°, acquisition time 284 ms, prepulse delay 225–300 ms. The inversion delay (TI) was individually determined using a Look-Locker sequence in a midventricular short-axis view.

For tagging, ECG-triggered breath-hold CSPAMM (complementary spatial modulation of magnetization)-based sequences were performed in three short-axis views: apex, midventricular and base. Imaging parameters included segmented k-space, multishot FFE-EPI (TFE echo-planar) sequences: EPI factor 11, flip angle 30°, two averages, slice thickness 8 mm, 20 heart phases, heart phase interval 30 ms. The tagging sequence generates two sets of images with horizontally and vertically modulated

System; Philips Healthcare). Interobserver variability was excluded, since analysis was performed by the same experienced investigator in all cases. Standard measurements were performed according to the American Society of Echocardiography guidelines [21]. Owing to the extensive postrace screening, echocardiographic imaging was limited to measurements of LV systolic and diastolic function. The study was performed in 2D (two-dimensional) and colour TD (tissue Doppler) imaging modes. All TD images were obtained at a frame rate of at least 60 frames/s. 2D measurements included LV end-diastolic and end-systolic volumes. Systolic ejection fraction was calculated using Simpson’s rule (biplane). Cardiac size was determined by assessing TEDD³/kg (total LV end-diastolic volume per kg of body weight), as previously described in athletes [22]. Pulsed annular Doppler and colour TD were used to determine regional and global diastolic function [23,24]. Mitral inflow velocities E (early transmirtal diastolic filling velocity) and A (late transmirtal diastolic filling velocity) and colour TD measurements of septal mitral annulus velocities E’ (tissue Doppler early transmirtal diastolic filling velocity) and A’ (tissue Doppler late transmirtal diastolic filling velocity) were performed in the apical four-chamber view.
lines, acquired in one single breath-hold (Figure 1b). The quantification of grid deformation after image multiplication allows an exact and objective assessment of regional and global wall motion [26,27]. A temporal resolution of 30 ms allows assessment of rapid cardiac motion components, such as diastolic untwisting and filling.

Image analysis

Late enhancement imaging

All data sets for the assessment of LGE of the left and right ventricle were viewed on Totoku monitors (ME 203L, Totoku). The transmural extend and pattern were evaluated based on the 17-segment model of the American Heart Association guidelines [28]. LGE was recorded as present only when detectable in two orthogonal planes. All scans were interpreted by two independent experienced investigators.

Tagging

After multiplication of the two images to obtain the grid, analysis of the apical, midventricular and base short-axis slices were performed with semiautomatic software (Tag Track version 1.7.5 Gyro Tools), which allows tracing of the intersection points of the tag lines in each phase image. Epi- and endo-cardial borders of the left ventricle were defined manually on an end-diastolic image and automatically copied and adapted to all subsequent heart phases. End systole is determined by searching for the smallest inner cavity lumen in the time series of images. The MRI analysis procedures for calculation of RS (radial shortening), CS (circumferential) and LS (longitudinal strain) as well as myocardial torsion have been described elsewhere[18,19,26,29,30]. Briefly, RS is defined as the relative shortening of the distance between a mid-myocardial point and the calculated centre of the left ventricle and is expressed as a percentage of radial end-diastolic distance (mean ± S.D.). CS was measured as the decrease of the circumferential distance expressed as a percentage of the end-diastolic distance [95 % CI (confidence interval)]. Mean RS and CS were calculated using 72 mid-myocardial points. LS was measured in the long-axis view as a fractional change of the longitudinal length, also expressed as a percentage of end-diastolic distance.

Torsion is defined to be the difference of averaged apical and basal rotation as measured in the myocardium. Rotation is the apical movement of each mid-myocardial point around the centre of gravity of the left ventricle, expressed in degrees (◦). As viewed from the apex, counterclockwise rotation was defined as a positive angle, and clockwise rotation as a negative angle. Torsion velocity is calculated as the first derivation of the rotation curve (◦· s⁻¹). Isovolumic backrotation (untwisting) has been shown to be a sensitive parameter for the description of diastolic relaxation and filling [31]. Therefore the rotation velocity and its peak untwist velocity during diastole were calculated as described previously [29].

Statistical analysis

Sample size consideration

Increased myocardial torsion has been demonstrated in 13 patients with pressure overload hypertrophy (14.1 ± 6.4°) compared with healthy controls (8.0 ± 2.1°), using the same image acquisition and analysis technique [32]. The burden of marathon running leads to a transient increase in myocardial pressure load due to a constant rise of systemic blood pressure. On the basis of an expected average S.D. of 4°, a cohort of 28 healthy participants had 80 % power to detect changes in myocardial torsion premarathon compared with postmarathon of ≥3° at a two-sided level of significance of 0.05.

Data analysis

This was performed using SPSS software version 16.0. To describe the distribution of quantitative data, arithmetic mean and S.D. or median and IQR (interquartile range) (from the 25th to 75th percentile) were reported. The paired Student’s t test was used to assess changes in normally distributed parameters. Assumption of normal distribution of data was verified by using descriptive methods (skewness, outliers and distribution plots) and inferential statistics (the Shapiro–Wilk test). In case of considerable violation of normal assumption, the Wilcoxon-signed–rank test was used for non-normally distributed parameters to compare quantitative measurements within the same subjects at two distinct time points. ANOVA was used to compare means between more than two independent samples. A GEE (generalized estimation equation) model approach was used to evaluate frequently measured parameters per individual. The GEE model reflects the structure of repeated measurement data and takes correlation within subjects (autocorrelation) into account. All statistical tests were conducted two-sided and a P value <0.05 was considered to indicate statistical significance.

RESULTS

Baseline parameters

Two of the initially recruited athletes dropped out during the training programme due to respiratory tract infections and musculoskeletal complaints. Successful participants included 28 male runners with an average age of 41 ± 5 (range, 30–60) years. LGE imaging and echocardiography were performed in all 28 runners pre- and post-marathon. The mean training mileage was 43 ± 17 km/week in the 10 weeks before the marathon, and the median (range) finish time was 245 ± 55 (176–335) min. Within 30 min
Table 1  Vital parameters and echocardiography pre- and post-marathon
Values are means ± S.D. or medians (95% CI).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Premarathon (n = 28)</th>
<th>Postmarathon (n = 28)</th>
<th>Change (pre to post)</th>
<th>P value (pre to follow-up)</th>
<th>Follow-up (n = 28)</th>
<th>Median change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>57 ± 7</td>
<td>86 ± 13</td>
<td>28 ± 13</td>
<td>&lt;0.001</td>
<td>58 ± 10</td>
<td>0.92 (−2.58 to 4.42)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132 ± 13</td>
<td>121 ± 12</td>
<td>−11 ± 11</td>
<td>&lt;0.001</td>
<td>122 ± 8</td>
<td>10 (5 to 14)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86 ± 8</td>
<td>74 ± 7</td>
<td>−12 ± 7</td>
<td>&lt;0.001</td>
<td>79 ± 4</td>
<td>7 (3 to 9)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65 ± 4</td>
<td>67 ± 5</td>
<td>1 ± 6</td>
<td>0.280</td>
<td>65 ± 5</td>
<td>0.14 (−2.01 to 2.3)</td>
</tr>
<tr>
<td>LV end-diastolic volume (cm³)</td>
<td>120 ± 25</td>
<td>113 ± 27</td>
<td>−7 ± 26</td>
<td>0.142</td>
<td>123 ± 28</td>
<td>3.54 (−2.95 to 10.02)</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>74 ± 14</td>
<td>66 ± 14</td>
<td>−7 ± 18</td>
<td>0.054</td>
<td>81 ± 14</td>
<td>6.63 (0.54 to 12.72)</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>56 ± 13</td>
<td>72 ± 12</td>
<td>17 ± 15</td>
<td>&lt;0.001</td>
<td>55 ± 16</td>
<td>−1.00 (−6.45 to 4.45)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.4 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>−0.5 ± 0.3</td>
<td>&lt;0.001</td>
<td>1.6 ± 0.3</td>
<td>0.17 (0.09 to 0.26)</td>
</tr>
<tr>
<td>Septal E′ (cm/s)</td>
<td>10 ± 1</td>
<td>8 ± 2</td>
<td>−2 ± 2</td>
<td>0.001</td>
<td>9 ± 2</td>
<td>−0.14 (−0.73 to 0.44)</td>
</tr>
<tr>
<td>Septal A′ (cm/s)</td>
<td>10 ± 2</td>
<td>12 ± 3</td>
<td>2 ± 3</td>
<td>0.001</td>
<td>9 ± 2</td>
<td>−0.57 (−1.24 to 0.1)</td>
</tr>
<tr>
<td>E/E′ ratio</td>
<td>8.3 ± 1.6</td>
<td>8.4 ± 3.4</td>
<td>−0.1 ± 3.1</td>
<td>0.871</td>
<td>8.7 ± 1.6</td>
<td>0.34 (−0.13 to 0.8)</td>
</tr>
</tbody>
</table>

after the marathon, heart rate was still increased (28 ± 13 beats/min) and systolic blood pressure was decreased (−11 ± 11 mmHg) (Table 1). ECG analysis postmarathon revealed no signs of ischaemia in any of the athletes. No runner required medical attention.

Biochemical markers
cTnT
At baseline, serum cTnT levels were <0.01 ng/ml in all participants. The median (IQR) postrace cTnT value was 0.02 (<0.003 to 0.02) ng/ml (P = 0.001 pre- compared with post-marathon) with a postrace maximum of 0.04 ng/ml (<0.01 ng/ml in 43%, ≥0.01 ng/ml in 50% and ≥0.03 ng/ml in 7% of cases). On follow-up, only one participant had a cTnT level above the normal range of <0.01 ng/ml (Figure 2a).

NT-proBNP
NT-proBNP concentrations increased during the marathon from a baseline median (IQR) value of 24 (18 to 35) pg/ml to 113 (78 to 163) pg/ml postmarathon (P ≤ 0.001). The postrace range was between 24 and 260 pg/ml. Overall, 39% of participants had levels of NT-proBNP above the upper limit (≥125 pg/ml). On follow-up, NT-proBNP levels decreased, but were not yet within the baseline range (Figure 2b). No significant correlation between NT-proBNP or cTnT serum levels postmarathon and the individual training mileage prior to the marathon or the finishing time was found.

Echocardiography
Baseline characteristics of the echocardiographic indices were within the expected range of amateur marathon runners, with a slightly increased mean septal diameter of 12 ± 1 mm. Mean TEDD was 11.2 ± 2.5 ml/kg of body weight. LV dimensions, volumes and ejection fraction remained unchanged after the marathon (Table 1). Although heart rates were still increased at the time of examination postmarathon, no fusion of E and A, either by transmitral Doppler or pulsed-annular Doppler, was observed. Postrace echocardiographic examinations showed an altered E/A ratio. The decrease in E/A ratio (mean change, −0.5 ± 0.3, P ≤ 0.001) was attributed to a...
reduction in $E$ of $7 \pm 18 \text{ cm} \cdot \text{s}^{-1}$ and an increase in $A$ of $17 \pm 15 \text{ cm} \cdot \text{s}^{-1}$ ($P = 0.05$ and $P \leq 0.001$ respectively).

A similar pattern was assessed by septal TD-derived annular velocities. $E'$ decreased from $10 \pm 1 \text{ cm} \cdot \text{s}^{-1}$ to $8 \pm 2 \text{ cm} \cdot \text{s}^{-1}$, $A'$ increased from $10 \pm 2 \text{ cm} \cdot \text{s}^{-1}$ to $12 \pm 3 \text{ cm} \cdot \text{s}^{-1}$ postmarathon. TD imaging revealed no significant changes in $E/E'$. The end-diastolic volume, a preload parameter of the heart, did not change significantly after the marathon. Diastolic indices were fully recovered 1 day postmarathon (Table 1).

**Cardiovascular MRI**

All subjects completed the CMR examination without complications. The imaging time for cardiac tissue characterization and regional wall motion analysis with LGE imaging and myocardial tagging was below 40 min. All images were adequate for this evaluation.

**LGE**

Late enhancement imaging was applied in 28 individuals premarathon and within 90 min postmarathon. Myocardial LGE showed no contrast medium accumulation indicative of structural myocardial damage in any of the participants, neither before nor immediately after the marathon.

**Myocardial tagging**

Radial shortening, circumferential and longitudinal strain

No significant changes in maximal RS were measured pre- compared with post-marathon, neither at the apex nor at the base. Maximal RS at the apex was reached in phase 12 and was found to be $76 \pm 4.2\%$ of the radial end-diastolic distance premarathon and $77 \pm 4.1\%$ postmarathon. At the base, maximal RS was reached in phase 11 premarathon and in phase 10 postmarathon, indicating a slightly faster contraction sequence at the base after the marathon (Figure 3). Time course analysis of the radial movement included all phases. GEE regression analysis also revealed no significant changes in RS after the marathon.

The analysis of CS depicted similar results compared with RS and revealed no significant changes postmarathon. Maximal CS at the apex was $-22.8\%$ (95\% CI, $-24.3$ to $-21.3\%$) decrease of circumferential end-diastolic distance premarathon and $-22.2\%$ (95\% CI, $-23.7$ to $-20.7\%$) postmarathon. At the base, maximal CS was $-19.7\%$ (95\% CI, $-20.7$ to $-18.7\%$) before and $-19.2\%$ (95\% CI, $-20.6$ to $-17.8\%$) after the marathon, with a similar slight phase shift at the base compared with RS. Moreover, longitudinal strain did not significantly change after the marathon ($86 \pm 3.4\%$ of the longitudinal end-diastolic length premarathon compared with $86 \pm 2.7\%$ postmarathon).

**Figure 3** Radial shortening MRI

Pre- and post-marathon analysis of radial shortening at the apex (a) and the base (b). Heart phases on the x-axis describe the time course of contraction and relaxation. Each heart phase constitutes 30 ms. Radial shortening on the y-axis describes the relative shortening of the distance between a mid-myocardial point and the calculated centre of the left ventricle, expressed as a percentage of the end-diastolic distance. Bands represent means with interpolated pointwise 95\% CI bounds across the phases. ▲, premarathon; ●, postmarathon (grey after-image).

**Torsion and diastolic untwisting**

Maximal LV torsion increased by 18.3\% postmarathon, from $13.1 \pm 3.8^\circ$ to a torsion angle of $15.5 \pm 3.6^\circ$ after the marathon ($P = 0.002$) (Figure 4a). Maximal torsion was reached in phase 11 pre- as well as post-marathon. The increase of torsional deformation was confirmed in a time course analysis by means of a GEE model ($P = 0.001$) and proved to be heart rate-independent in an adjusted regression analysis.

Maximal torsion velocity increased significantly by 35\%, with $6.8 \pm 1.6 \cdot \text{s}^{-1}$ before the marathon and $9.2 \pm 2.5 \cdot \text{s}^{-1}$ after the marathon ($P < 0.001$). However, the increase of torsion velocity postmarathon was not statistically significant ($P = 0.19$) applying a time course analysis with simultaneous consideration of heart rate.

During isovolumic relaxation, a rapid apical clockwise untwisting proceeds diastolic filling of the LV as described previously [31]. The mean peak diastolic untwisting
velocity at the apex was slightly lower postmarathon, but the difference was not significant (mean difference: $0.82^\circ \pm 0.64^\circ$, $P = 0.21$) (Figure 4b). The time to peak untwist was reached in phase 14 in both cases. The peak untwist rate was not significantly correlated to changes in diastolic filling as assessed by echocardiography.

However, diastolic ventricular filling was accompanied by changes in apical rotation velocity. Before the marathon, rotation velocity after peak untwist declined rapidly during diastolic filling (phase 14–20). After the marathon, rotation velocity after peak untwist was higher and declined gradually during diastolic filling, reaching premarathon levels in end diastole (phase 20) (Figure 4b). The difference in apical rotation velocity during diastolic filling premarathon compared with postmarathon proved to be significant (mean absolute increase by $1.23 \pm 0.33^\circ \cdot \text{s}^{-1}$; $P < 0.001$) in a time course analysis by means of a GEE model, where heart rate was simultaneously considered as an adjustment variable.

**DISCUSSION**

The present study has examined whether the elevation of cardiac biomarkers and ventricular alterations after prolonged exertional exercise represent sustainable myocardial damage and dysfunction as evidenced directly by LGE MRI and MR tagging after marathon. To date, conflicting data exists whether or not the elevation of cardiac biomarkers after marathon represents indirect proof of detectable myocyte cell death. In a relatively large cohort, this study, for the first time, analysed the effects of an acute bout of prolonged endurance exercise on myocardial motion patterns by MRI tagging.

LGE MRI has become the preferred method for assessing the extent of myocardial injury in ischaemic and non-ischaemic heart disease [16]. With an in-plane spatial resolution of 1–2 mm, regions of myocardial necrosis can be accurately detected and quantified [16,33]. In our study, LGE MRI in marathon runners did not detect any traumatic structural damage of the myocardium in the presence of increased cTnT and NT-proBNP levels 1 h after a marathon. From our results and two previous MRI studies [14,15], we can infer that marathon running does not induce MRI detectable myocardial necrosis in healthy subjects without cardiovascular risk factors.

Our findings seem to contradict a previous study of LGE imaging in marathon runners performed independently of acute endurance exercise [13]. The study demonstrated a general prevalence of myocardial injury of 12 % as assessed by LGE. However, the examined cohort was much older ($57.2 \pm 5.7$ years), and 56.5 % of the marathon runners had a history of smoking or were current smokers. On the basis of our findings of a negative LGE examination before and after marathon, there seems to be sufficient evidence that the exercise-induced increase of cardiac biomarkers does not indicate myocyte death but may represent an enhanced membrane permeability and cytoplasmic release of myocytes. It is also possible, however, that mild diffuse necrosis causes homogeneous myocardial microinjury below the detection level of LGE.

In order to substantiate the functional myocardial burden after endurance exercise, systolic and diastolic function by means of echocardiography, using PWD (pulsed-wave Doppler) as well as colour TD imaging were analysed. PWD detected alterations of diastolic filling with a significant decrease in the $E/A$ ratio after the marathon. However, PWD is sensitive to changes in volume load, and the $E/A$ ratio alone does not sufficiently assess diastolic dysfunction.

In contrast, TD imaging is not load-dependent, and changes in $E'$ and $E/E'$ are established markers of diastolic dysfunction [34]. In our study, we found a significant decrease of $E'$ to a borderline value of $8 \pm 2$ cm $\cdot$ s$^{-1}$ postmarathon, indicating a volume load-independent alteration of diastolic filling. On the other
hand, TDI did not show significant changes in $E/E'$. These echocardiographic results confirm that marathon running induces moderate alterations of diastolic filling, as previously described [10,14], but not manifest diastolic dysfunction as defined by Nagueh et al. [34]. Echocardiography revealed an unchanged LVEF (left ventricular ejection fraction), a conventional parameter of systolic ventricular function, after marathon. This has been confirmed by a recent cardiac MRI study, which did not detect any differences in LVEF and volumes premarathon compared with postmarathon [15].

MR tagging is an alternative and very accurate modality for the assessment of ventricular function and allows the additional analysis of basoapical torsional deformation of the myocardium [30]. Similar to our echocardiographic finding of an unchanged LVEF, MRI tagging analysis of radial shortening as well as circumferential and longitudinal strain showed no impairment. However, motion pattern analysis revealed an increase in LV torsion (‘wringing’) and maximal torsion velocity in a heart rate-independent manner directly after the marathon. In response to prolonged exercise, the myocardium seems to improve cardiac output performance by an increased wringing motion rather than augmenting other contraction properties. Increased systolic torsion and torsion velocity may represent compensatory mechanisms to preserve cardiac performance during prolonged physical stress.

During isovolumic relaxation, a rapid apical clockwise untwisting proceeds diastolic filling of the LV. Although no significant changes in mean peak diastolic untwisting velocity at the apex were observed, ventricular diastolic filling was accompanied by changes in myocardial motility. Higher rotation velocities in mid-diastole are likely to limit diastolic filling and indicate a reduction in myocardial relaxation time. The altered pattern of MRI diastolic wall motion may resemble the echocardiographic alterations of diastolic filling after marathon.

Our findings of an impaired LV diastolic filling and increased myocardial wringing motion were independent of training status, LV mass and dimensions as well as body weight. Furthermore, no significant correlation was found between the increase of cardiac biomarkers postmarathon and the individual training mileage prior to the marathon or the finishing time. Neilan et al. [10] reported that athletes with less training are more likely to present with an exercise-induced elevation of cardiac enzymes, which could not be confirmed by a recent meta-analysis by Shave et al. [35].

Factors that potentially influence systolic LV output performance are increased preload and afterload conditions. However, volume and pressure loading have been shown to have negligible effects on LV torsion [36]. The amount of torsion at rest seems to be dependent on an inotropic stimulation of catecholamines. Therefore a bulge of inotropic stimulation following excessive endurance exercise is likely to cause the increase of myocardial torsion in marathon runners. Interestingly, torsional deformation has been reported to be more sensitive to inotropic stimulation than conventional indexes of LV systolic performance [36], which supports our findings.

Exercise-induced sympathetic overstimulation may also explain the increased rotation velocity and reduced relaxation time during diastolic filling. A stunned myocardium, for example, due to perfusion injury, would be characterized by a prolonged relaxation period as described previously in patients with coronary artery disease [37]. Therefore, the physical stress of marathon running seems to be better described as a burden of myocardial overstimulation rather than cardiac injury.

Whether the detected functional myocardial burden of vigorous exertion may hold the potential to trigger acute non-ischaemic myocardial failure and arrhythmias in susceptible individuals remains to be elucidated. The paradox of exercise remains unsolved, but the data presented help to further place the risk of marathon running into perspective.

Limitations

Although marathon running does not induce verifiable myocardial necrosis as confirmed by a negative LE MRI examination, mild diffuse myocardial injury cannot fully be excluded. To rule out a delayed appearance of reversible cardiac injury within days or weeks after the marathon, a longer term follow-up using LGE MRI would be warranted. Our study protocol focused on the assessment of LV wall motion abnormalities. Right ventricular function has previously been shown to be impaired after prolonged exercise, which has been attributed to alterations of pulmonary haemodynamics [10,14]. Whether alterations of torsional deformation after prolonged exercise also appear in the right ventricle, remains to be shown.

AUTHOR CONTRIBUTION

Henner Hanssen was responsible for the conception, design, implementation and lead through, data analysis and interpretation and drafting of the manuscript. Alexandra Keithahn was responsible for the conception, cMRI implementation, data analysis and interpretation. Gernot Hertel was in charge of the cMRI implementation, data analysis and interpretation. Verena Drexel was in charge of the data analysis and implementation of marathon events. Heiko Stern gave expert advice and was responsible for the interpretation of MR myocardial tagging and data analysis. Tibor Schuster was responsible for the data analysis.

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analysis and interpretation and statistics. Dan Lorang gave expert advice on sports science and was responsible for the implementation of marathon events. Ambros Beer was responsible for the data analysis of LGE MRI. Arno Schmidt-Trucksäss was in charge of the design, revision and gave the final approval. Thomas Nickel was responsible for the conception, data interpretation of echocardiography and revision. Michael Weiss gave expert advice on cardiac biomarkers and was in charge of revising the manuscript. Rene Botnar was responsible for data analysis, gave expert advice and was in charge of the interpretation of LGE MRI. Markus Schwaiger was in charge of the data analysis and final approval. Martin Halle was responsible for the conception, design, revision of the manuscript and final approval.

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