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Exercise-induced ST-segment deviations and cardiac arrhythmias in leisure endurance athletes during a marathon race: Results of the Berlin Beat of Running study

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Short title: ECG changes during a marathon race

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Abstract

Introduction The "Berlin Beat of Running" study focused on ECG-monitoring during strenuous exercise. *Methods and Results* Experienced marathon runners wore a portable electrocardiogram (ECG) recorder during a marathon race, and underwent blood tests 2-3 days prior, directly after and 1-2 days afterwards. Overall, 108 athletes (median 48 years (IQR 45-53), 24% female) completed the marathon in 249±43 min. Blinded ECG-analysis revealed abnormal findings during the marathon in 18 (16.8%) athletes. Ten (9.3%) athletes had at least one episode of non-sustained ventricular tachycardia, one of whom had atrial fibrillation; eight (7.5%) individuals showed transient ST-segment deviations. Abnormal ECG-findings were associated with finishing time (OR 1.70 per 30 minutes [95%CI 1.18-2.43]) and advanced age (OR 1.15 per year [95%CI 1.05-1.27]); sex and cardiovascular risk profile had no impact. Directly after the race, high-sensitive troponin T was elevated in 18 (16.7%) athletes and associated with ST-segment deviation (OR 11.0 [95%CI 2.35-51.7]) and a longer marathon finishing time (OR 1.5 per 30 minutes [95%CI 1.03-2.07]), while age, sex and cardiovascular risk profile had no impact.

Conclusion ECG-monitoring during a marathon is feasible. Abnormal ECG-findings were present in every sixth athlete. Exercise-induced transient ST-segment deviations were associated with elevated hsTnT values.

Trial registration: clinicaltrials.gov NCT01428778.

Keywords: Marathon – ECG – magnetic resonance imaging – arrhythmia – troponin

Strengths and limitations of this study

- An electrocardiogram was recorded during a marathon race in 108 athletes.
- Serial blood testing was performed prior, directly after and 1-2 days after the race and included high-sensitive troponin.
- Cardiac MRI was done in a subset of participants with abnormal findings but echocardiography would have allowed for further conclusions.

Introduction

Regular physical exercise has many health benefits: Improving blood pressure control, insulin sensitivity and lipid profiles, it reduces overall mortality and disability [7] and the number of cardiovascular events [25,29]. Moreover, regular physical exercise also reduces the risk of certain cancers [33] and the number of mood disorders [5]. However, highly strenuous physical exercise may have a negative impact on cardiovascular health [22]. While marathon running has become a popular sport, cardiac arrest is rare but occurs in about 1:100,000 marathon runners, most commonly in those with hypertrophic cardiomyopathy or atherosclerotic coronary disease [21]. Available data on incidence of myocardial infarction after running a marathon is limited to case reports [3], but elevated levels of troponin – a sensitive biomarker of cardiac injury – were reported in a relevant subset of asymptomatic marathon runners [9,11,24]. Other potentially harmful effects of strenuous exercise, like right ventricular dysplasia and ventricular arrhythmia, have also been reported for triathletes and other ultra-endurance athletes [18,19,26]. Moreover, a meta-analysis of mostly retrospective and small case-control series as well as a recent cohort study indicated that intense endurance sport increases the long-term risk of atrial fibrillation [2,4]. The EHRA consortium has recently updated its recommendations regarding abnormal ventricular arrhythmias in endurance athletes and stated that a non-sustained ventricular tachycardia (nsVT) requires diagnostic evaluation for latent hypertrophic cardiomyopathy or ischemic heart disease, especially if these occur under physical exercise [27]. However, there are very few publications regarding cardiac arrhythmias occurring during endurance sport so far [1,12,15,23].

Herewith, we report the results of the "Berlin Beat of Running" study, demonstrating feasibility of continuous ECG-monitoring in 108 leisure endurance athletes during a marathon race. We focus on the frequency of cardiac arrhythmias and ST-segment deviations.

Methods

Study design

The "Berlin Beat of Running" study is a prospective, observational, investigator-initiated study. The study design has been published in detail [17]. In short, all pre-registered participants were informed by the organizers of the marathon about the study, and they contacted the study personnel if they were interested. Participants aged 35-60 years with at least 2 marathon runs within the last 5 years and an average training of 40 km running per week were enrolled after giving written informed consent. Exclusion criteria included known cardiac disease or arrhythmia, prior stroke, tumor or infectious disease, severe liver or kidney disease, hyperthyroidism, pregnancy or lactation. Continuous ECG recording (using the CardioMem® CM 4000 provided by GETEMED AG, Teltow, Germany) was started in 109 study patients at up to 74 hours before the 38th BMW BERLIN MARATHON and continued throughout the entire race and for up to 58 hours afterwards. Laboratory assessment including hsTnT measurement with chemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany; cut-off 0.012 µg/l) was performed at up to 74 hours before, within 30 minutes post-race, and for up to 58 hours after the race. The study protocol is in accordance with the Helsinki declaration and was approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin (EA4/042/11).

MRI analysis

A cardiac MRI after the race was offered to all study participants with either ST-segment deviation or hsTNT elevation. 3T MRI (Magnetom Tim Trio; Siemens AG, Erlangen, Germany) was performed using a phased array receiver coil during breath-holds gated to the electrocardiogram (Body Matrix-coil #TATS; Siemens AG). Cine images of 3 long-axis and 14-18 short-axis views (slices of 4 mm) were created using a steady state free precision

technique [6]. Eight minutes after i.v. administration of 10-12 ml Gadovist® (Bayer Schering Pharma AG, Berlin, Germany) at a concentration of 1 mmol/ml, these views were repeated using a short inversion recovery sequence and continuously adjusting the inversion time [28].

ECG analysis

ECG monitoring was performed using the two-channel portable ECG recorder (CardioMem® CM 4000; GETEMED AG, Teltow, Germany). The cardiologists (AT, AW, WH), who analyzed the ECG data, were blinded for demographic, clinical or laboratory data. As there are no published recommendations on interpretation of a Holter-ECG in athletes, we took into consideration recommendations available for interpreting a 12-lead ECG in athletes (Drezner et al. 2013) as well as recent EHRA guidelines on ventricular arrhythmias [27]. In line with this, we defined an abnormal ECG as presence of ST-segment deviation under physical exercise or arrhythmias. The ST-segment was considered abnormal in the 2-lead ECG if horizontal or down-sloping occurred over the 60 ms after the J-junction (80 ms if the heart rate was <120 beats/min) [16]. Episodes lasting more than 30 seconds preceded and followed by regular ECG recording were also considered abnormal. Drezner et al. defined atrial arrhythmias as atrio-ventricular (AV) block grade IIb or III, atrial fibrillation or supraventricular tachycardia (SVT) [8]. Ventricular arrhythmias were defined as nsVT of at least three premature ventricular complexes (PVC) and a heart rate of ≥100 beats per minute [8,27].

Statistical analysis

In accordance with the sample size calculation, we planned to include 110 participants into the study [17]. For categorical data, absolute and relative frequencies were calculated using SPSS statistics 22. In the case of continuous variables with nearly normal distribution, we

used the arithmetic mean, standard deviation, minimal and maximal values, otherwise median, quartiles, minimal and maximal values. The *Chi* quadrat test was used to compare proportions for dichotomous outcomes between independent groups or to test independency of two dichotomous variables within a population. Outcomes in an ordinal scale or continuous outcomes were analyzed using the t-test or the Mann-Whitney test, depending on normality or non-normality of distribution. Odds ratios for estimating the probability of abnormal ECG findings were calculated by univariate logistic regression analyses. A p value of <0.05 was considered to be statistically significant.

Results

Baseline data of study participants and feasibility of ECG recording

Overall, 109 (99.1%) of 110 study participants took part, and 108 (98.2%) participants finished the 38th BMW BERLIN MARATHON 2011 in an average running time of 249±43 min. September 25, 2011, was a sunny day in Berlin and temperatures reached a maximum of 22 degrees Celsius. Data quality of long-term Holter-ECG was sufficient to ensure assessment of arrhythmias and ST-segment deviations in 107 (98.2%) athletes. In one athlete, a technical error occurred. Consistently wearing the ECG recorder on the upper arm using a carrier bag, the other athletes reported no problems in this regard. Baseline characteristics of those 107 participants are depicted in **Table 1**. The median age of these 107 participants was 48 years; 23.9% were female. The cardiovascular risk profile was low. The participants had attended a median of 5 marathon races within the last 5 years and a median of 8 marathon races in total. Their average weekly running distance prior to the race was 40 km (IQR 30-50 km). In addition, athletes regularly went cycling (44.9%; n=48); or swimming (18.7%; n=20), respectively.

Cardiac arrhythmias or ST-segment deviation during the marathon

During the race, mean heart rate was in 156.7±9.4 beats per minute. Minimum and maximum median heart rate were 133 (IQR 120-142) and 172 (IQR 166-177) beats per minute, respectively. We observed nsVT in 10 (9.4%) athletes (**Figure 1**), 2 (20%) of those athletes were female. We did not observe an AV block or a SVT. Atrial fibrillation was found in one male patient (0.9%). Filtering of the monitors allowed interpretation of ST-T wave changes in fashion similar to a standard ECG. Exercise-induced ST-segment deviations occurred in eight (7.5%) study participants during the marathon race (**Figure 2**), 2 (25%) of those athletes were female. One of those eight athletes also had nsVT. While four (3.7%) athletes reported palpitations during the marathon race, one of them had AF. No athlete reported cardiac pain or dyspnea.

An abnormal ECG according to pre-defined criteria was found in 16.8% (n=18) of all participants (**Table 2**). In univariate analysis, advanced age (OR 1.15 per year [95%CI 1.05-1.27]; p=0.004) and a longer marathon finishing time (OR 1.70 per 30 minutes [95%CI 1.18-2.43]; p=0.009) were associated with abnormal ECG findings, while sex, cardiovascular risk profile, hematocrit post-race and the number of previous marathons were not. In addition, athletes with an abnormal ECG had a higher frequency of PVCs (median 3.0 (IQR 1.0-12.3) versus 23.5 (IQR 10.0-44.0), p<0.001) during the marathon race.

Cardiac biomarkers and ECG changes during the marathon

At baseline, hsTNT was normal in all marathon runners (<0.050 µg/l). Within minutes after the race had finished, hsTNT was elevated above 0.050 µg/l) in 18 (16.8%) of participants and median hsTNT was 0.03 µg/l (IQR 0.02-0.04; range 0.01-0.22). CK and CK-MB were 130 U/l (IQR 103–176) and 20 U/l (IQR 17–24) pre-marathon, respectively. Post-marathon CK was 336 (IQR 252-417) U/l and CK-MB was 35 (IQR 29-41).

Comparing athletes with an elevated hsTNT post–marathon to those without, we found no difference in age, sex, cardiovascular risk factors, training level or post-marathon CK-MB values (**Table 3**). In runners with elevated hsTNT, we found more frequent ST-segment deviations (OR 11.0 [95%CI 2.35-51.7]; p<0.0001) but no association with cardiac arrhythmias. In addition, elevated hsTNT was found in individuals with a longer marathon finishing time (OR 1.5 per 30 minutes [95%CI 1.03-2.07]; p=0.040]. Within 48 hours post-marathon, hsTNT was within normal range in 106 (99.1%) athletes; one athlete with no substantial ECG alterations during the marathon showed a persisting hsTNT elevation but normal 12-lead ECG post-marathon.

Cardiac MRI in athletes with ST-segment deviation or elevated hsTNT

Cardiac MRI was offered to all study participants with ST-segment deviation or hsTNT elevation. Five out of eight athletes with ST-segment deviation as well as in five out of 18 athletes with hsTnT elevation underwent MRI within 10-42 days after the marathon race. Age, gender and cardiovascular risk factors did not differ in those 10 athletes undergoing cardiac MRI and those 14 athletes how did not undergo cardiac MRI. Cardiac MRI revealed no pathological findings for cardiac function and there was no late gadolinium enhancement, indicating myocardial fibrosis. Additional cardiac work-up was strongly recommended in all patients with pathological ECG-findings.

Discussion

This is the so far largest study demonstrating feasibility of ECG recording during a marathon race, which may help counseling a subset of endurance athletes regarding exercise-associated complications. One main finding of the “Berlin Beat of Running” study is the unexpectedly

high rate of abnormal ECG findings in 17% of leisure endurance athletes. Moreover, this is the first study reporting an association of transient ST-segment abnormalities during a marathon with elevated hsTNT levels after finishing the race.

So far, there is limited data on ECG abnormalities during vigorous exercise [30]. Franco et al. reported "no arrhythmias" in 19 male athletes during a marathon [12], while Aagaard et al. found "no ventricular arrhythmias" but atrial fibrillation in two (4%) of 49 male endurance runners during a 30 km race [1]. Luurila et al. reported the presence of ventricular premature complexes in 33 (89%) of 37 recreational athletes during a ski marathon as well as ST-segment deviations in 3 (8%) of these middle-aged men [23]. Most recently, Grabs et al. used a 1-lead wireless ECG and reported premature atrial contractions but no arrhythmias in 20 male runners during a marathon race [15]. In our prospective study, 10 (9.4%) out of 107 leisure endurance athletes had a non-sustained ventricular arrhythmia during the marathon and one (0.9%) athlete had AF. In addition, ST-segment deviations (**Figure 2**) were detected in 8 (7.5%) athletes. Advanced age or longer marathon finishing time was associated with abnormal ECG findings (**Table 2**). According to the hematocrit, the hydration status – potentially impacting on cardiac preload – was not linked to these findings.

Despite the fact that increased levels of physical activity were associated with a lower relative risk of myocardial infarction, 4% of patients with myocardial infarction report having performed strenuous exercise within hours before the cardiovascular event [25]. By using different cut-offs, transient elevations in the level of troponin T or troponin I has previously been reported in 18-69% of marathon runners [9,11,14,24]. In the "Berlin Beat of Running" cohort, hsTNT was elevated in 18 (17%) out of 107 athletes but normalized within 48 hours in 17 (94%) of those. Interestingly, elevation of hsTNT was not related to age, sex, training status, the cardiovascular risk profile or the presence of cardiac arrhythmias during the race,

but was related to exercise-induced ST-segment deviation ($p<0.0001$) and longer marathon finishing time ($p=0.040$).

Cardiac magnetic resonance imaging (MRI) is now the gold standard for detecting myocardial damage [31] and myocardial edema as well as decreased ventricular function after a marathon race [13,20]. We were not able to demonstrate late gadolinium enhancement as an indicator of permanent myocardial fibrosis in ten experienced but leisure athletes with ST-segment deviation or detected cardiac arrhythmia. This is in line with a previous study reporting no late gadolinium enhancement in 20 leisure athletes within 48 hours after a marathon race [13]. Interestingly, a transient cardiac edema was reported in 17 (85%) out of 20 marathon runners [13], but no correlation was reported between biomarkers and cardiac edema. As cardiac MRI was performed at later time points after the race in our study, we are unable to confirm a transient cardiac edema in marathon runners.

Taken together, vigorous exercise can go along with transient troponin elevation, ST-segment alterations or nsVT. However, these findings are likely to be benign in the absence of structural heart disease or obstructive coronary artery disease, which should be excluded in these athletes. Whether borderline cardiac damage by repetitive strenuous exercise could lead to permanent (potentially arrhythmogenic) cardiac remodeling is under debate [22,32].

Major limitations of the observational "Berlin Beat of Running" study, as it focused primary on the feasibility of portable ECG monitoring and detection of ECG changes during the race, are the missing echocardiography or cardiac stress MRI, limiting the clinical significance of the observed ST-segment changes and elevated hsTNT levels. Since only 25% of all athletes were female, the generalizability of our results is limited. Moreover, a valid multivariate analysis was not possible due to the limited number of participants, which was due to the complex nature of the study. In addition, there is a subsequent selection bias. Finally, exercise capacity testing would have allowed more accurate evaluation of training status.

Conclusion

ECG recording during a marathon race is feasible, which may be helpful in the diagnostic work-up of selected athletes. Cardiac arrhythmias or exercise-induced ST-segment deviations appear in a relevant subset of experienced leisure athletes during a marathon race, predominantly in older and athletes who are less fit. Marathon-induced ST-segment deviations were associated with elevated hsTnT values immediately after the race. Cardiac MRI detected no myocardial fibrosis by late gadolinium enhancement in a subset of these athletes.

List of abbreviations

atrial fibrillation, AF; AV, atrio-ventricular; CK, creatine kinase; CK-MB, myocardium- and brain-specific CK; electrocardiogram, ECG; hsTnT, high-sensitive troponin T; magnetic resonance imaging, MRI; SVT, supraventricular tachycardia; Tesla, T; non-sustainable ventricular tachycardia, nsVT.

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Competing interests

JH reports no conflict of interest. AT reports lecture fees from the Circle Institute. MK received consulting, lecture and advisory board fees from ALK, Berlin Chemie, Novartis, Mundipharma and Teva. LB reports research support from German Ministry of Research and Education. JBF reports the following board memberships, consultancies and/or payments for lectures including service on speaker's bureaus: Boehringer-Ingelheim, Lundbeck, BioClinica and Parexel. PUH reports research grants from the German Ministry of Research and Education, EU, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, Charité–Universitätsmedizin Berlin (within MonDAFIS; MonDAFIS is supported by an unrestricted research grant to the Charité from Bayer Healthcare), University Göttingen (within FIND-AF$_{randomized}$; FIND-AF$_{randomized}$ is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), and University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer Healthcare, BMS, Boehringer-Ingelheim), outside submitted work. GJJ has received funding from the German Ministry for Education and Research. He has served on the Critical Event committees of the SourceXT registry and the ProTAVI-C-study (Edwards Lifesciences, USA). He serves as a consultant for Cipio Partners (Munich, Germany and Elron, Tel Aviv, Israel). He has received speakers honoraria from Genzyme and Pfizer (2010-2013). ME and KGH report lecture fees and study grants from Sanofi-Aventis and Bayer Healthcare.

Author's contribution

JH has made substantial contributions to acquisition, analysis and interpretation of data and drafted the manuscript. AT and AW have made substantial contributions to data analysis and

interpretation of data. CK has made substantial contributions to design and acquisition of data. MK, LB, JL, JBF, WH and ME revised the manuscript critically for important intellectual content. PUH has made substantial contributions to analysis and interpretation of data and revised the manuscript critically for important intellectual content. GJJ has made substantial contributions to conception and design and revised the manuscript critically for important intellectual content. KGH has made substantial contributions to conception and design, analysis and interpretation of data and drafted the manuscript.

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Table 1: Baseline characteristics of the 107 participants of the "Berlin Beat of Running" study who finished the marathon and who had evaluable ECG data.

Age; mean; years; median [IQR]	48 [45-53]
Female gender; % (n)	24.3 (26)
Body mass index; kg/m^2; median [IQR]	23.4 [21.6-24.7]
Hypertension; % (n)	8.4 (9)
Diabetes mellitus; % (n)	0 (0)
Heart failure; % (n)	0 (0)
Coronary artery disease; % (n)	0 (0)
Hyperlipidemia; % (n)	2.8 (3)
Current smoking; % (n)	6.5 (7)

Table 2: Cardiovascular risk profile and training status in leisure athletes with or without abnormal ECG findings, respectively. ST segment deviation, atrio- or ventricular arrhythmias (atrio-ventricular block grade IIb or III, triplets, non-sustained ventricular tachycardia, supraventricular tachycardia) or atrial fibrillation were regarded as abnormal findings.

	Normal ECG n=89	**Abnormal ECG** n=18	**p-value ***
Age; years; median [IQR]	48 [44-50]	54 [48-59]	0.004
Female gender, % (n)	24.7 (22)	22.2 (4)	0.822
Physical activity			
Marathon runs ≤ 5 years; median [IQR]	5 [4 -10]	6 [4-7]	0.923
Marathon runs total; n; median [IQR]	9 [5-18]	7 [6-14]	0.573
Current running; km/week; median [IQR]	65 [50-80]	58 [50-70]	0.151
Regular running; km/ week; median [IQR]	40 [30-50]	40 [30-50]	0.409
Present marathon time; min; median [IQR]	238 [215-268]	275 [229-326]	0.009
Hematocrit post-race; %; median [IQR]	0.44 [0.41-0.45]	0.43 [0.41-0.45]	0.711
Body Mass Index; kg/m^2; mean ± SD	23.2±2.2	23.6±1.9	0.449
Comorbidities			
Hypertension; % (n)	6.7 (6)	16.7 (3)	0.166
Hyperlipidaemia; % (n)	2.2 (2)	2.8 (3)	0.438
Current smoking; % (n)	5.6 (5)	11.1 (2)	0.390

*Values are expressed in % (n), mean ± SD or median [IQR] as appropriate; * p-value calculated by chi^2-test or Mann-Whitney U test, as appropriate*

Table 3: Troponin elevation post-marathon in the 107 athletes who finished the marathon race and who had evaluable ECG data.

	Troponin < 0.050 µg/l n=89	**Troponin ≥ 0.050 µg/l** n=18	**p-value ***
Age; years; median [IQR]	48 [45-52]	49 [45-53]	0.605
Female gender; % (n)	21.3 (19)	38.9 (7)	0.114
Body mass index; kg/m^2; mean ± SD	23 [22-25]	23 [22-25]	0.723
Present marathon time; min; median [IQR]	236 [217-269]	268 [237-309]	0.040
Marathon runs ≤ 5 y; n; median [IQR]	6 [4-10]	5 [3-8]	0.327
Marathon runs total; n; median [IQR]	9 [6-18]	7 [5-12]	0.147
Regular weekly running; km; median [IQR]	40 [30-50]	40 [30-50]	0.791
Coexisting hypertension; % (n)	9.0 (8)	5.6 (1)	0.632
Hyperlipideamia; % (n)	3.4 (3)	0 (0)	0.429
ST segment deviation; % (n)	3.4 (3)	27.8 (5)	<0.0001
Arrhythmias; % (n)	11.2 (10)	5.6 (1)	0.469
Troponin pre-race; µg/l; median [IQR]	0.012 [0.012-0.012]	0.012 [0.012-0.012]	0.131
Creatinine pre-race; mg/dl; median [IQR]	0.86 [0.81-0.96]	0.85 [0.77-0.97]	0.761
Creatinine post-race; mg/dl; median [IQR]	1.27 [1.11-1.46]	1.34 [1.17-1.48]	0.424
CK post-race; U/l; median [IQR]	333 [250-412]	350 [291-611]	0.263
CK-MB post-race; U/l; median [IQR]	35 [28-41]	33 [29-52]	0.609

*Values are expressed in % (n), mean ± SD or median [IQR] as appropriate; * p-value calculated by chi^2 – test or Mann-Whitney U test, as appropriate*

Figure 1: Non-sustained ventricular tachycardia in a well-trained 48-year old male endurance runner without other cardiovascular risk factors than current smoking.

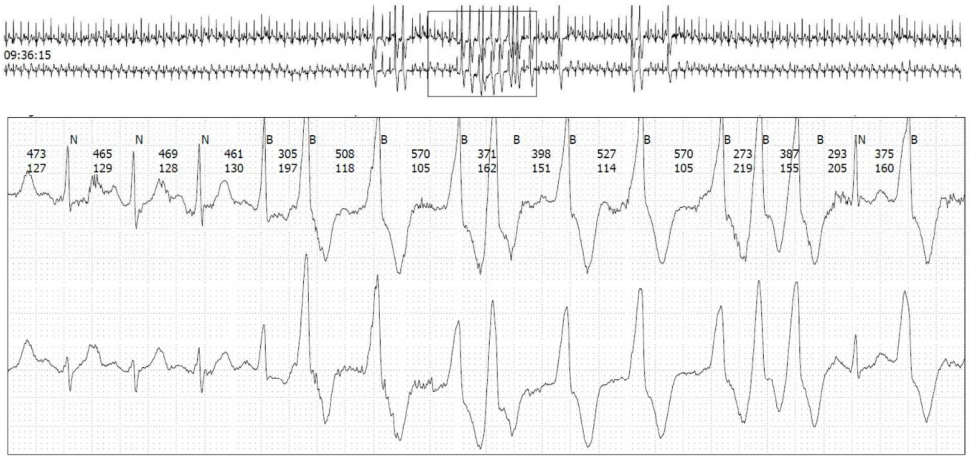

Figure 1

1260x770mm (72 x 72 DPI)

Figure 2: ECG at rest (A) and exercise-induced ST segment deviations (B) in a 60-year old male endurance runner without cardiovascular risk.

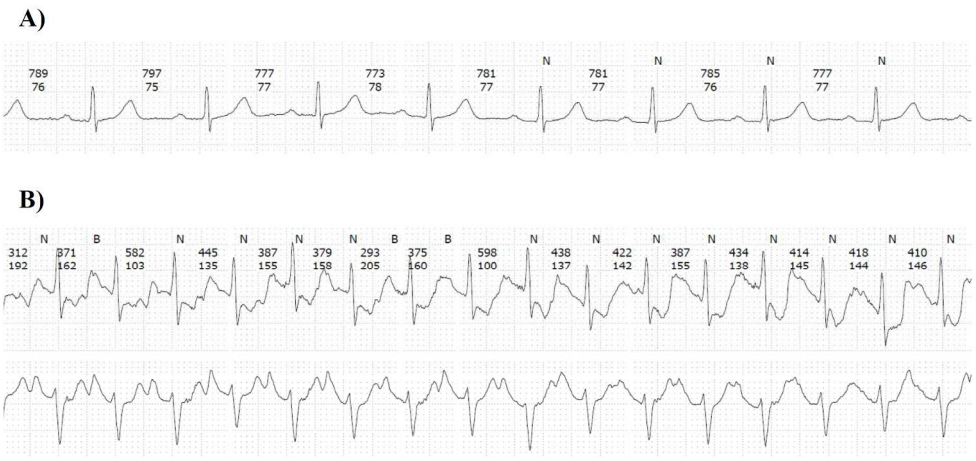

Figure 2

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Exercise-induced ST-segment deviations and cardiac arrhythmias in leisure endurance athletes during a marathon race: Results of the Berlin Beat of Running study

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Exercise-induced ST-segment deviations and cardiac arrhythmias in leisure endurance athletes during a marathon race: Results of the Berlin Beat of Running study

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Short title: ECG changes during a marathon race

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Abstract

Introduction The "Berlin Beat of Running" study focused on ECG-monitoring during strenuous exercise. *Methods and Results* Experienced marathon runners wore a portable electrocardiogram (ECG) recorder during a marathon race, and underwent blood tests 2-3 days prior, directly after and 1-2 days afterwards. Overall, 108 athletes (median 48 years (IQR 45-53), 24% female) completed the marathon in 249±43 min. Blinded ECG-analysis revealed abnormal findings during the marathon in 18 (16.8%) athletes. Ten (9.3%) athletes had at least one episode of non-sustained ventricular tachycardia, one of whom had atrial fibrillation; eight (7.5%) individuals showed transient ST-segment deviations. Abnormal ECG-findings were associated with advanced age (OR 1.11 per year [95%CI 1.01-1.23]); sex and cardiovascular risk profile had no impact. Directly after the race, high-sensitive troponin T was elevated in 18 (16.7%) athletes and associated with ST-segment deviation (OR 9.9 [95%CI 1.9-51.5], while age, sex and cardiovascular risk profile had no impact.

Conclusion ECG-monitoring during a marathon is feasible. Abnormal ECG-findings were present in every sixth athlete. Exercise-induced transient ST-segment deviations were associated with elevated hsTnT values.

Trial registration: clinicaltrials.gov NCT01428778.

Keywords: Marathon – ECG – magnetic resonance imaging – arrhythmia – troponin

Strengths and limitations

- This is the so far largest study demonstrating feasibility of non-invasive ECG recording during a marathon race.

- More than one hundred experienced marathon runners underwent blood sampling within 2-3 days prior, directly after and 1-2 days after the race.
- Cardiac MRI was performed in a subset of athletes with abnormal ECG findings and/or elevated troponin T values.
- Serial echocardiography and a standardized exercise capacity testing would have allowed for a more encompassing interpretation of the results.

Introduction

Regular physical exercise has many health benefits: Improving blood pressure control, insulin sensitivity and lipid profiles, it reduces overall mortality and disability [1] and the number of cardiovascular events [2,3]. Moreover, regular physical exercise also reduces the risk of certain cancers [4] and the number of mood disorders [5]. However, highly strenuous physical exercise may have a negative impact on cardiovascular health [6]. While marathon running has become a popular sport, cardiac arrest is rare but occurs in about 1:100,000 marathon runners, most commonly in those with hypertrophic cardiomyopathy or atherosclerotic coronary disease [7]. Available data on incidence of myocardial infarction after running a marathon is limited to case reports [8] and the prospective *RACE* Paris Registry [9], but elevated levels of troponin – a sensitive biomarker of cardiac injury – were reported in a relevant subset of asymptomatic marathon runners [10–12]. Other potentially harmful effects of strenuous exercise, like right ventricular dysplasia and ventricular arrhythmia, have also been reported for triathletes and other ultra-endurance athletes [13–15]. Moreover, a meta-analysis of mostly retrospective and small case-control series as well as a recent cohort study

indicated that intense endurance sport increases the long-term risk of atrial fibrillation [16,17]. The EHRA consortium has recently updated its recommendations regarding abnormal ventricular arrhythmias in endurance athletes and stated that a non-sustained ventricular tachycardia (nsVT) requires diagnostic evaluation for latent hypertrophic cardiomyopathy or ischemic heart disease, especially if these occur under physical exercise [18]. However, there are very few publications regarding cardiac arrhythmias occurring during endurance sport so far [19–22].

Herewith, we report the results of the "Berlin Beat of Running" study [23], demonstrating feasibility of continuous ECG-monitoring in 108 leisure endurance athletes during a marathon race. We focus on the frequency of cardiac arrhythmias and ST-segment deviations.

Methods

Study design

The "Berlin Beat of Running" study is a prospective, observational, investigator-initiated study. The study design has been published in detail [23]. In short, all pre-registered participants were informed by the organizers of the marathon about the study, and they contacted the study personnel if they were interested. Participants aged 35-60 years with at least 2 marathon runs within the last 5 years and an average training of 40 km running per week were enrolled after giving written informed consent. Exclusion criteria included known cardiac disease or arrhythmia, prior stroke, tumor or infectious disease, severe liver or kidney disease, hyperthyroidism, pregnancy or lactation. Continuous ECG recording (using the CardioMem® CM 4000 provided by GETEMED AG, Teltow, Germany) was started in 109

study patients at up to 74 hours before the 38th BMW BERLIN MARATHON and continued throughout the entire race and for up to 58 hours afterwards. Laboratory assessment including hsTnT measurement with chemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany; cut-off 12 µg/L) was performed at up to 74 hours before, within 30 minutes post-race, and for up to 58 hours after the race. The study protocol is in accordance with the Helsinki declaration and was approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin (EA4/042/11). The primary hypothesis was: Cardiac arrhythmias and especially AF is frequently found in experienced marathon runners. Therefore, the primary outcome is the number of marathon runners with newly diagnosed cardiac arrhythmias. The main secondary hypotheses were: (1) There are predictable risk factors associated with cardiac arrhythmias in marathon runners; (2) Pathological laboratory findings are (in part) associated with cardiac arrhythmias; (3) Marathon runners with elevated troponin levels do not have MRI-detected myocardial scars suggestive for myocardial infarction. Follow-up information on past medical history was assessed one year after the marathon.

MRI analysis

A cardiac MRI after the race was offered to all study participants with either ST-segment deviation or hsTnT elevation. 3T MRI (Magnetom Tim Trio; Siemens AG, Erlangen, Germany) was performed using a phased array receiver coil during breath-holds gated to the electrocardiogram (Body Matrix-coil #TATS; Siemens AG). Cine images of 3 long-axis and 14-18 short-axis views (slices of 4 mm) were created using a steady state free precision technique [24]. Eight minutes after i.v. administration of 10-12 ml Gadovist® (Bayer Schering

Pharma AG, Berlin, Germany) at a concentration of 1 mmol/ml, these views were repeated using a short inversion recovery sequence and continuously adjusting the inversion time [25].

ECG analysis

ECG monitoring was performed using the two-channel portable ECG recorder (CardioMem® CM 4000; GETEMED AG, Teltow, Germany). The cardiologists (AT, AW, WH), who analyzed the ECG data, were blinded for demographic, clinical or laboratory data. The five recorded leads were placed as follows in order to obtain two independent bipolar channels: left (1) and right (2) on the first intercostal space, right on the sixth intercostal space parasternal (3) and mid-clavicular line (4), left ninth intercostal space mid-clavicular line (5). As there are no published recommendations on interpretation of a Holter-ECG in athletes, we took into consideration recommendations available for interpreting a 12-lead ECG in athletes [26] as well as recent EHRA guidelines on ventricular arrhythmias [18]. In line with this, we defined an abnormal ECG as presence of ST-segment deviation under physical exercise or arrhythmias. Low-pass-filtering was set at 0.05 Hz in order to detect changes in the ST-T-segment. The ST-segment was considered abnormal in the virtually artifact free 2-lead ECG if horizontal or down-sloping ≥ 1 mm occurred over the 60 ms after the J-junction (80 ms if the heart rate was <120 beats/min) [27]. ST-segments were analyzed in relation to the TP segment. Segments were analyzed after recording of stable isoelectric TP segments in three consecutive beats. If single QRS complexes showed notching, slurring or fragmentation, QRS and ST intervals were excluded from further analysis. Episodes lasting more than 30 seconds preceded and followed by regular ECG recording were also considered abnormal. Drezner et

al. defined atrial arrhythmias as atrio-ventricular (AV) block grade IIb or III, atrial fibrillation or supraventricular tachycardia (SVT) [26]. Ventricular arrhythmias were defined as nsVT of at least three premature ventricular complexes (PVC) and a heart rate of ≥100 beats per minute [18,26].

Statistical analysis

In accordance with the sample size calculation, we planned to include 110 participants into the study [23]. For categorical data, absolute and relative frequencies were calculated using SPSS statistics 22. In the case of continuous variables with nearly normal distribution, we used the arithmetic mean, standard deviation, minimal and maximal values, otherwise median, quartiles, minimal and maximal values. The *Chi* quadrat test was used to compare proportions for dichotomous outcomes between independent groups or to test independency of two dichotomous variables within a population. Outcomes in an ordinal scale or continuous outcomes were analyzed using the t-test or the Mann-Whitney test, depending on normality or non-normality of distribution. A p value of <0.05 was considered to be statistically significant. In multivariate analysis, potential impact factors identified on a $p<0.05$ level in univariate analysis were entered in a binary logistic regression model using backwards selection.

Results

Baseline data of study participants and feasibility of ECG recording

Overall, 109 (99.1%) of 110 study participants took part, and 108 (98.2%) participants finished the 38th BMW BERLIN MARATHON 2011 in an average running time of 249±43 min. September 25, 2011, was a sunny day in Berlin and temperatures reached a maximum of 22 degrees Celsius. Data quality of long-term Holter-ECG was sufficient to ensure assessment of arrhythmias and ST-segment deviations in 107 (98.2%) athletes, although motion and perspiration artifacts were present in the majority of athletes. In one athlete, a technical error occurred. Consistently wearing the ECG recorder on the upper arm using a carrier bag, no athlete reported problems in this regard. No athlete stopped wearing the ECG device prematurely. Baseline characteristics of those 107 participants are depicted in **Table 1**. The median age of these 107 participants was 48 years; 23.9% were female. The cardiovascular risk profile was low. The participants had attended a median of 5 marathon races within the last 5 years and a median of 8 marathon races in total. Their average weekly running distance prior to the race was 40 km (IQR 30-50 km). In addition, athletes regularly went cycling (44.9%; n=48); or swimming (18.7%; n=20), respectively.

Cardiac arrhythmias or ST-segment deviation during the marathon

During the race, mean heart rate was in 156.7±9.4 beats per minute. Minimum and maximum median heart rate were 133 (IQR 120-142) and 172 (IQR 166-177) beats per minute, respectively. We observed nsVT in 10 (9.4%) athletes (**Figure 1**), 2 (20%) of those athletes

were female. In athletes with nsVTs the median number of beats was 3 (IQR 3-5; range 3-9), median rate was 166 beats per minute (IQR 149-188; range 133-224) and median duration of the recorded nsVT was 1121 ms (IQR 919-1841; range 901-4400). We did not observe an AV block or a SVT. Persistent atrial fibrillation was found in one male patient (0.9%). Filtering of the monitors allowed interpretation of ST-T wave changes in fashion similar to a standard ECG. Exercise-induced ST-segment deviations occurred in eight (7.5%) study participants during the marathon race (**Figure 2**), 2 (25%) of those athletes were female. Characteristics of all athletes with ST-segment deviation are displayed in the *online supplement*. Intensity of ST-segment deviation in terms of ST-level was -0.7mV (IQR -0.8 to -0.3; range -0.9 to -0.16). ECG monitoring was prolonged for up to 54 hours (median 28 hours) after the marathon race. ST-segment deviations were not found in any athlete with ST-segment deviation during the marathon. One of those eight athletes also had nsVT. While four (3.7%) athletes reported palpitations during the marathon race, one of them had AF, one had a single nsVT (lasting nine beats) and another athlete had multiple supraventricular premature beats (62/hour). No athlete reported cardiac pain or dyspnea. An abnormal ECG according to pre-defined criteria was found in 16.8% (n=18) of all participants. In univariate analysis, advanced age (p=0.004) and a longer marathon finishing time (p=0.009) were associated with abnormal ECG findings, while sex, cardiovascular risk profile, hematocrit post-race and the number of previous marathons were not. In multivariate analysis, advanced age remained significant (OR 1.11 per year [95%CI 1.01-1.23]) (**Table 2**). In addition, athletes with an abnormal ECG had a higher frequency of PVCs (median 3.0 (IQR 1.0-12.3) versus 23.5 (IQR 10.0-44.0), p<0.001) during the marathon race.

Cardiac biomarkers and ECG changes during the marathon

At baseline, hsTnT was normal in all marathon runners (<50 ng/L). Within minutes after the race had finished, hsTnT was elevated above 50 ng/L) in 18 (16.8%) of participants and median hsTnT was 3 ng/L (IQR 2-4; range 1-22). Median hsTnT values in 18 athletes with elevated hsTnT was 68.5 ng/L (IQR 62.8-85.5, range 50-216). Characteristics of all athletes with elevated hsTnT are displayed in the *online supplement*. In all athletes, median creatinine kinase (CK) and CK-MB were 130 U/l (IQR 103–176) and 20 U/l (IQR 17–24) pre-marathon, respectively. Post-marathon CK was 336 (IQR 252-417) U/l and CK-MB was 35 (IQR 29-41) U/l.

Comparing athletes with an elevated hsTnT post–marathon to those without, we found no difference in age, sex, cardiovascular risk factors, training level or post-marathon CK-MB values (**Table 3**). In runners with elevated hsTnT, we found more frequent ST-segment deviations (p<0.0001) but no association with cardiac arrhythmias. In addition, elevated hsTnT was found in individuals with a longer marathon finishing time (p=0.040). Athletes with elevated hsTnT had a lower hematocrit compared to athletes without hsTnT elevation (p=0.003). In multivariate analysis, ST-segment deviation (OR 9.9 [95%CI 1.9-51.5]]) as well as hematocrit (OR 0.76 per percent [95%CI 0.62-0.92]) remained statistically significant. Within 48 hours post-marathon, hsTnT was within normal range in 106 (99.1%) athletes; one athlete with no substantial ECG alterations during the marathon showed a persisting hsTnT elevation but normal 12-lead ECG post-marathon. Follow-up information was available in all

eight athletes with ST-segment deviation and in eight out of ten patients with nsVT during the race. None of the athletes reported a cardiovascular event within one year after the race.

Cardiac MRI in athletes with ST-segment deviation or elevated hsTnT

Cardiac MRI was offered to all study participants with ST-segment deviation or hsTnT elevation. Five out of eight athletes with ST-segment deviation and hsTnT elevation as well as in five out of 18 athletes with hsTnT elevation but without ST-segment deviation underwent MRI within 10-42 days after the marathon race. Age, gender and cardiovascular risk factors did not differ in those 10 athletes undergoing cardiac MRI and those 14 athletes how did not undergo cardiac MRI. Cardiac MRI revealed no pathological findings for cardiac function and there was no late gadolinium enhancement, indicating myocardial fibrosis. Additional cardiac work-up was strongly recommended in all patients with pathological ECG-findings.

Discussion

This is the so far largest study demonstrating feasibility of ECG recording during a marathon race, which may help counseling a subset of endurance athletes regarding exercise-associated complications. One main finding of the “Berlin Beat of Running” study is the unexpectedly high rate of abnormal ECG findings in 17% of leisure endurance athletes. Moreover, this is the first study reporting an association of transient ST-segment abnormalities during a

marathon with elevated hsTnT levels after finishing the race. However, we cannot be sure that the observed ST-segment deviations are definitively based on silent ischemia.

So far, there is limited data on ECG abnormalities during vigorous exercise [28]. Franco et al. reported "no arrhythmias" in 19 male athletes during a marathon [21], while Aagaard et al. found "no ventricular arrhythmias" but atrial fibrillation in two (4%) of 49 male endurance runners during a 30 km race [22]. Luurila et al. reported the presence of ventricular premature complexes in 33 (89%) of 37 recreational athletes during a ski marathon as well as ST-segment deviations in 3 (8%) of these middle-aged men [20]. Most recently, Grabs et al. used a 1-lead wireless ECG and reported premature atrial contractions but no arrhythmias in 20 male runners during a marathon race [19]. In our prospective study, 10 (9.4%) out of 107 leisure endurance athletes had a non-sustained ventricular arrhythmia during the marathon and one (0.9%) athlete had AF. In addition, ST-segment deviations (**Figure 2**) were detected in 8 (7.5%) athletes. Advanced age was associated with abnormal ECG findings (**Table 2**). According to the hematocrit, low hydration– potentially impacting on cardiac preload – was not linked to abnormal ECG findings.

Despite the fact that increased levels of physical activity were associated with a lower relative risk of myocardial infarction, 4% of patients with myocardial infarction report having performed strenuous exercise within hours before the cardiovascular event [3]. By using different cut-offs, transient elevations in the level of troponin T or troponin I has previously been reported in 18-69% of marathon runners [10–12,29]. In the "Berlin Beat of Running" cohort, hsTnT was elevated in 18 (17%) out of 107 athletes but normalized within 48 hours in 17 (94%) of those. Interestingly, elevation of hsTnT was not related to age, sex, training

status, the cardiovascular risk profile or the presence of cardiac arrhythmias during the race, but was related to exercise-induced ST-segment deviation ($p<0.0001$) and inversely correlated with the hematocrit (measured immediately after the race).

Cardiac magnetic resonance imaging (MRI) is now the gold standard for detecting myocardial damage [30] and myocardial edema as well as decreased ventricular function after a marathon race [31,32]. We were not able to demonstrate late gadolinium enhancement as an indicator of permanent myocardial fibrosis in ten experienced but leisure athletes with ST-segment deviation or detected cardiac arrhythmia. This is in line with a previous study reporting no late gadolinium enhancement in 20 leisure athletes within 48 hours after a marathon race [31]. Interestingly, a transient cardiac edema was reported in 17 (85%) out of 20 marathon runners [31], but no correlation was reported between biomarkers and cardiac edema. We, however, are unable to exclude a transient cardiac edema in marathon runners, because cardiac MRI was performed within 10-42 days after the marathon race.

Taken together, vigorous exercise can go along with transient troponin elevation, ST-segment alterations or nsVT in a fit and active population. However, athletes with ST-segment deviation or nsVT during the race did not report a cardiovascular event within one year afterwards. Thus, these findings are likely to be benign, but structural heart disease or obstructive coronary artery disease was recommended to be ruled out in these athletes. Our results strengthen the assumption that hsTnT elevation originates from the heart and not primarily from non-cardiac sources [8]. However, we are unable to draw final conclusions. Whether borderline cardiac damage by repetitive strenuous exercise could lead to permanent (potentially arrhythmogenic) cardiac remodeling is under debate [6,33].

Major limitations of the observational "Berlin Beat of Running" study, as it focused primary on the feasibility of portable ECG monitoring and detection of ECG changes during the race, are the missing (serial) echocardiography or cardiac stress MRI, limiting the clinical significance of the observed ST-segment changes and elevated hsTnT levels. Furthermore, a normal cardiac MRI within days after the race does not completely rule out (transient) exercise-induced cardiac damage [34]. Since only one fourth of all athletes were and because of a potential selection bias during enrolment, the generalizability of our results is limited. Moreover, due to the limited number of endpoints observed, we believe that the results of the multivariate analysis should be interpreted with caution. Combining nsVT and ST-segment deviations for statistical analysis may have introduced an information bias. Finally, exercise capacity testing would have allowed more accurate evaluation of training status.

Conclusion

ECG recording during a marathon race is feasible, which may be helpful in the diagnostic work-up of selected athletes. Cardiac arrhythmias or exercise-induced ST-segment deviations appear in a relevant subset of experienced leisure athletes during a marathon race and predominantly in older athletes. Marathon-induced ST-segment deviations were associated with elevated hsTnT values immediately after the race. Cardiac MRI detected no myocardial fibrosis by late gadolinium enhancement in a subset of these athletes.

List of abbreviations

atrial fibrillation, AF; AV, atrio-ventricular; CK, creatine kinase; CK-MB, myocardium- and brain-specific CK; electrocardiogram, ECG; hsTnT, high-sensitive troponin T; magnetic resonance imaging, MRI; SVT, supraventricular tachycardia; Tesla, T; non-sustainable ventricular tachycardia, nsVT.

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Competing interests

JH reports no conflict of interest. AT reports lecture fees from the Circle Institute. MK received consulting, lecture and advisory board fees from ALK, Berlin Chemie, Novartis, Mundipharma and Teva. LB reports research support from German Ministry of Research and Education. JBF reports the following board memberships, consultancies and/or payments for lectures including service on speaker's bureaus: Boehringer-Ingelheim, Lundbeck, BioClinica and Parexel. PUH reports research grants from the German Ministry of Research and Education, EU, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, Charité–Universitätsmedizin Berlin (within MonDAFIS; MonDAFIS is supported by an unrestricted research grant to the Charité from Bayer Healthcare), University Göttingen (within FIND-AF$_{randomized}$; FIND-AF$_{randomized}$ is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), and University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer Healthcare, BMS, Boehringer-Ingelheim), outside submitted work. GJJ has received funding from the German Ministry for Education and Research. He has served on the Critical Event committees of the SourceXT registry and the ProTAVI-C-study (Edwards Lifesciences, USA). He serves as a consultant for Cipio Partners (Munich, Germany and Elron, Tel Aviv, Israel). He has received speakers honoraria from Genzyme and Pfizer (2010-

2013). ME and KGH report lecture fees and study grants from Sanofi-Aventis and Bayer Healthcare.

Contributorship statement

JH has made substantial contributions to acquisition, analysis and interpretation of data and drafted the manuscript. AT and AW have made substantial contributions to data analysis and interpretation of data. CK has made substantial contributions to design and acquisition of data. MK, LB, JL, JBF, WH and ME revised the manuscript critically for important intellectual content. PUH has made substantial contributions to analysis and interpretation of data and revised the manuscript critically for important intellectual content. GJJ has made substantial contributions to conception and design and revised the manuscript critically for important intellectual content. KGH has made substantial contributions to conception and design, analysis and interpretation of data and drafted the manuscript.

Data Sharing Statement

There are no additional data available for this study.

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Table 1: Baseline characteristics of the 107 participants of the "Berlin Beat of Running" study who finished the marathon and who had evaluable ECG data.

Age; mean; years; median [IQR]	48 [45-53]
Female gender; % (n)	24.3 (26)
Body mass index; kg/m^2; median [IQR]	23.4 [21.6-24.7]
Hypertension; % (n)	8.4 (9)
Diabetes mellitus; % (n)	0 (0)
Heart failure; % (n)	0 (0)
Coronary artery disease; % (n)	0 (0)
Hyperlipidemia; % (n)	2.8 (3)
Current smoking; % (n)	6.5 (7)
Medication at enrolment	
Antiplatelet; % (n)	0.9 (1)
Oral anticoagulant; % (n)	0
Beta-blocker; % (n)	1.9 (2)
Statin; % (n)	1.9 (2)
Antihypertensive; % (n)	6.5 (7)

Table 2: Cardiovascular risk profile and training status in leisure athletes with or without abnormal ECG findings, respectively. ST segment deviation, atrio- or ventricular arrhythmias (atrio-ventricular block grade IIb or III, triplets, non-sustained ventricular tachycardia, supraventricular tachycardia) or atrial fibrillation were regarded as abnormal findings.

	Normal ECG n=89	**Abnormal ECG** n=18	**Univariate Analysis p-value ***	**Multivariate Analysis OR (95%CI)**
Age; years; median [IQR]	48 [44-50]	54 [48-59]	0.004	1.11 (1.01-1.23)
Female gender, % (n)	24.7 (22)	22.2 (4)	0.822	
Physical activity				
Marathon runs ≤ 5 years; median [IQR]	5 [4 -10]	6 [4-7]	0.923	
Marathon runs total; n; median [IQR]	9 [5-18]	7 [6-14]	0.573	
Current running; km/week; median [IQR]	65 [50-80]	58 [50-70]	0.151	
Regular running; km/ week; median [IQR]	40 [30-50]	40 [30-50]	0.409	
Present marathon time; min; median [IQR]	238 [215-268]	275 [229-326]	0.009	1.44 (0.98-2.12)
Hematocrit post-race; %; median [IQR]	0.44 [0.41-0.45]	0.43 [0.41-0.45]	0.711	
Body Mass Index; kg/m^2; mean ± SD	23.2±2.2	23.6±1.9	0.449	
Comorbidities				
Hypertension; % (n)	6.7 (6)	16.7 (3)	0.166	
Hyperlipidaemia; % (n)	2.2 (2)	2.8 (3)	0.438	

Current smoking; % (n)	5.6 (5)	11.1 (2)	0.390

*Values are expressed in % (n), mean ± SD or median [IQR] as appropriate; * p-value calculated by chi^2-test or Mann-Whitney U test, as appropriate. Multivariate analysis was calculated in a binary logistic regression model using backwards selection.*

Table 3: Troponin T elevation post-marathon in the 107 athletes who finished the marathon race and who had evaluable ECG data.

	Troponin T < 50 ng/L n=89	**Troponin T ≥ 50 ng/L** n=18	**Univariate Analysis p-value ***	**Multivariate Analysis OR (95%CI)**
Age; years; median [IQR]	48 [45-52]	49 [45-53]	0.605	
Female gender; % (n)	21.3 (19)	38.9 (7)	0.114	
Body mass index; kg/m^2; mean ± SD	23 [22-25]	23 [22-25]	0.723	
Present marathon time; min; median [IQR]	236 [217-269]	268 [237-309]	0.040	1.25 (0.83 – 1.87)
Marathon runs ≤ 5 y; n; median [IQR]	6 [4-10]	5 [3-8]	0.327	
Marathon runs total; n; median [IQR]	9 [6-18]	7 [5-12]	0.147	
Regular weekly running; km; median [IQR]	40 [30-50]	40 [30-50]	0.791	
Coexisting hypertension; % (n)	9.0 (8)	5.6 (1)	0.632	
Hyperlipideamia; % (n)	3.4 (3)	0 (0)	0.429	
ST-segment deviation; % (n)	3.4 (3)	27.8 (5)	<0.0001	9.9 (1.90 – 51.5)
Arrhythmias; % (n)	11.2 (10)	5.6 (1)	0.469	
Troponin pre-race; µg/L; median [IQR]	0.012 [0.012-0.012]	0.012 [0.012-0.012]	0.131	
Creatinine pre-race; mg/dL; median [IQR]	0.86 [0.81-0.96]	0.85 [0.77-0.97]	0.761	
Creatinine post-race; mg/dL; median [IQR]	1.27 [1.11-1.46]	1.34 [1.17-1.48]	0.424	
CK post-race; U/L; median [IQR]	333 [250-412]	350 [291-611]	0.263	

CK-MB post-race; U/L; median [IQR]	35 [28-41]	33 [29-52]	0.609	
Hematocrit post-race; %; median [IQR]	44 [42-46]	41 [39-44])	0.003	0.76 (0.62 – 0.92)

*Values are expressed in % (n), mean ± SD or median [IQR] as appropriate; * p-value calculated by chi^2 – test or Mann-Whitney U test, as appropriate. Multivariate analysis was calculated in a binary logistic regression model using backwards selection.*

Figure 1: Non-sustained ventricular tachycardia in a well-trained 48-year old male endurance runner without cardiovascular risk factors despite smoking.

Figure 2: ECG at rest (A) and exercise-induced ST segment deviations (B) in a 60-year old male endurance runner without cardiovascular risk.

ONLINE SUPPLEMENT High-sensitive troponin T (hsTnT) values returned to normal within up to 58 hours after the marathon race in almost all athletes (95%). Creatine kinase (CK) remains elevated in all 21 athletes (with ST-segment deviation and/or hsTnT elevation).

Table ONLINE SUPPLEMENT: Characteristics of 21 athletes with either ST-segment deviation (>1 mm) and hsTnT elevation (≥50 ng/L) (n=5), ST-segment deviation (n=3) or hsTnT elevation (n=13). Pathological findings are labeled in bold.

Age	Sex	Medication	Cardiovascular risk factors	NSVT[§]	ST-segment deviation	hsTnT[$] ng/L[*]	hsTnT ng/L[**]	CK-MB mg/dL[*]	CK-MB mg/dL[**]	CK mg/dL[*]	CK mg/dL[**]	Cardiac MRI
45	Female	None	No	No	**Yes**	**91**	19	21	32	877	1194	Yes
45	Female	L-Thyroxin	No	No	**Yes**	**71**	12	18	16	243	235	Yes
53	Male	None	No	No	**Yes**	**63**	14	14	35	893	2121	Yes
59	Male	None	No	No	**Yes**	**66**	12	19	54	406	2236	Yes
60	Male	None	Smoker	**Yes**	**Yes**	**70**	12	27	72	2867	3625	Yes
48	Male	None	No	No	**Yes**	32	16	18	44	381	1719	No
55	Male	None	No	No	**Yes**	21	12	21	35	201	489	No
60	Male	Antihypertensive	Hypertension	No	**Yes**	27	13	28	44	767	1979	No
44	Female	None	Smoker	No	No	**78**	12	26	20	306	192	Yes
48	Male	None	No	No	No	**138**	20	59	67	325	2186	Yes
49	Female	None	No	No	No	**63**	12	22	41	205	1357	Yes
50	Male	None	No	No	No	**87**	29	30	73	360	3462	Yes
60	Female	None	No	No	No	**216**	64	33	14	455	169	Yes
39	Male	None	No	No	No	**59**	23	47	87	583	2756	No
40	Female	None	No	No	No	**85**	12	42	33	696	914	No
45	Male	None	No	No	No	**83**	29	175	157	195	605	No
47	Male	None	No	No	No	**52**	12	37	42	309	1983	No
48	Male	None	No	No	No	**64**	12	52	101	405	4604	No
50	Female	Antihypertensive	Hypertension	No	No	**50**	12	29	28	315	485	No
53	Female	None	No	No	No	**62**	12	30	24	339	448	No
54	Male	None	No	No	No	**67**	15	33	23	234	409	No

[§] non-sustained ventricular tachycardia; [$] high-sensitive Troponin T; [*] within 30 minutes post-race; [**] up to 58 hours after the race

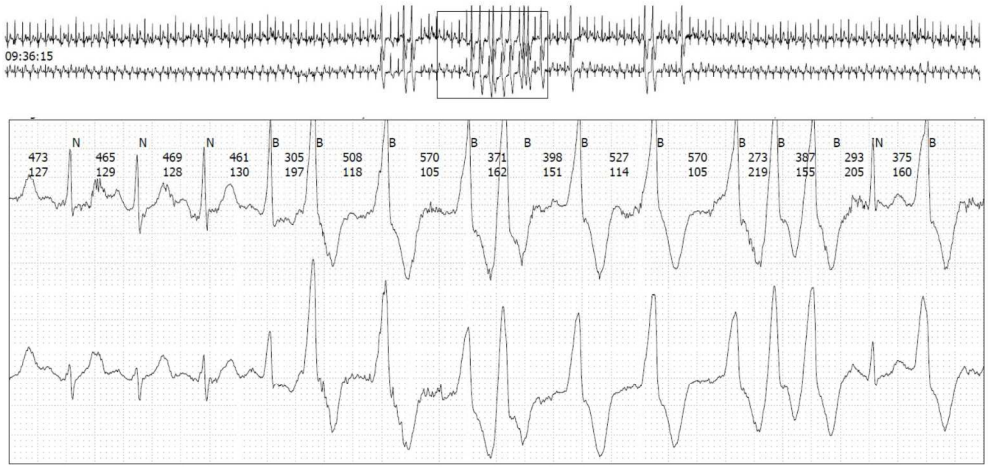

Figure 1: Non-sustained ventricular tachycardia in a well-trained 48-year old male endurance runner without cardiovascular risk factors despite smoking.

297x151mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	page	Recommendation
Title and abstract	1	2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
			Introduction
Background/rationale	2	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	4	State specific objectives, including any prespecified hypotheses
			Methods
Study design	4	4	Present key elements of study design early in the paper
Setting	5	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	4	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	5-6	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	13	Describe any efforts to address potential sources of bias
Study size	10	4 (Ref. to design paper)	Explain how the study size was arrived at
Quantitative variables	11	7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	7	(*a*) Describe all statistical methods, including those used to control for confounding
		7	(*b*) Describe any methods used to examine subgroups and interactions
		n.a.	(*c*) Explain how missing data were addressed
		n.a.	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
	n.a.	(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-10
		(*b*) Report category boundaries when continuous variables were categorized	7-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Frequency of exercise-induced ST-segment deviations and cardiac arrhythmias in recreational endurance athletes during a marathon race: results of the prospective observational Berlin Beat of Running study

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Frequency of exercise-induced ST-segment deviations and cardiac arrhythmias in recreational endurance athletes during a marathon race: results of the prospective observational Berlin Beat of Running study

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Short title: ECG changes during a marathon race

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Abstract

Objectives: While regular physical exercise has many health benefits, strenuous physical exercise may have a negative impact on cardiac function. The "Berlin Beat of Running" study focused on feasibility and diagnostic value of continuous ECG-monitoring in recreational endurance athletes during a marathon race. We hypothesized that cardiac arrhythmias and especially atrial fibrillation are frequently found in a cohort of recreational endurance athletes. The main secondary hypothesis was that pathological laboratory findings in these athletes are (in part) associated with cardiac arrhythmias.

Design: Prospective observational cohort study including healthy volunteers.

Setting & Participants: One hundred and nine experienced marathon runners wore a portable electrocardiogram (ECG) recorder during a marathon race in Berlin, Germany. Athletes underwent blood tests 2-3 days prior, directly after and 1-2 days after the race.

Results: Overall, 108 athletes (median 48 years (IQR 45-53), 24% female) completed the marathon in 249±43 min. Blinded ECG-analysis revealed abnormal findings during the marathon in 18 (16.8%) athletes. Ten (9.3%) athletes had at least one episode of non-sustained ventricular tachycardia, one of whom had atrial fibrillation; eight (7.5%) individuals showed transient ST-segment deviations. Abnormal ECG-findings were associated with advanced age (OR 1.11 per year [95%CI 1.01-1.23]); while sex and cardiovascular risk profile had no impact. Directly after the race, high-sensitive troponin T was elevated in 18

(16.7%) athletes and associated with ST-segment deviation (OR 9.9 [95%CI 1.9-51.5]), while age, sex and cardiovascular risk profile had no impact.

Conclusions: ECG-monitoring during a marathon is feasible. Abnormal ECG-findings were present in every sixth athlete. Exercise-induced transient ST-segment deviations were associated with elevated hsTnT values.

Trial registration: clinicaltrials.gov NCT01428778.

Keywords: Marathon – ECG – magnetic resonance imaging – arrhythmia – troponin

Strengths and limitations

- This is so far the largest study demonstrating feasibility of non-invasive ECG recording during a marathon race.
- More than one hundred experienced marathon runners underwent a unique serial blood sampling within 2-3 days before the marathon, directly after crossing the finish-line and 1-2 days after the marathon race.
- Cardiac MRI was performed in a subset of athletes with abnormal ECG findings and/or elevated troponin T values.
- Serial echocardiography and a standardized exercise capacity testing would have allowed for a more comprehensive interpretation of the results.

Introduction

Regular physical exercise has many health benefits: improving blood pressure control, insulin sensitivity and lipid profiles, it reduces overall mortality and disability [1] and the number of

cardiovascular events [2,3]. Moreover, regular physical exercise also reduces the risk of certain cancers [4] and the number of mood disorders [5]. However, highly strenuous physical exercise may have a negative impact on cardiovascular health [6]. While marathon running has become a popular sport, cardiac arrest is rare but occurs in about 1:100,000 marathon runners, most commonly in those with hypertrophic cardiomyopathy or atherosclerotic coronary disease [7]. Available data on incidence of myocardial infarction after running a marathon is limited to case reports [8] and the prospective *RACE* Paris Registry [9], but elevated levels of troponin – a sensitive biomarker of cardiac injury – were reported in a relevant subset of asymptomatic marathon runners [10–12]. Other potentially harmful effects of strenuous exercise, like right ventricular dysplasia and ventricular arrhythmia, have also been reported for triathletes and other ultra-endurance athletes [13–15]. Moreover, a meta-analysis of mostly retrospective and small case-control series as well as a recent cohort study indicated that intense endurance sport increases the long-term risk of atrial fibrillation [16,17]. The EHRA consortium has recently updated its recommendations regarding abnormal ventricular arrhythmias in endurance athletes and stated that a non-sustained ventricular tachycardia (nsVT) requires diagnostic evaluation for latent hypertrophic cardiomyopathy or ischemic heart disease, especially if these occur under physical exercise [18]. However, there are so far very few publications regarding cardiac arrhythmias occurring during endurance sport [19–22].

Herewith, we report the results of the prospective observational “Berlin Beat of Running” study [23], demonstrating feasibility of continuous ECG-monitoring in 108 recreational endurance athletes during a marathon race. The pre-defined primary aim of the study was to

analyze the frequency of cardiac arrhythmias and especially atrial fibrillation in a cohort of recreational endurance athletes. Pre-defined secondary aims were as follows: (1) to assess risk factors associated with cardiac arrhythmias in marathon runners; (2) to analyze the association between laboratory findings and the presence of cardiac arrhythmias during the race and (3) to investigate whether marathon runners with elevated troponin levels (after the race) have MRI-detected myocardial scars suggestive of previous myocardial infarction.

Methods

Study design

The "Berlin Beat of Running" study is a prospective, observational, investigator-initiated cohort study. The study design has been published in detail [23]. In short, all pre-registered participants were informed by the organizers of the marathon about the study, and they contacted the study personnel if they were interested. Participants aged 35-60 years with at least 2 marathon runs within the last 5 years and an average training of 40 km running per week were enrolled after giving written informed consent. Exclusion criteria included known cardiac disease or arrhythmia, prior stroke, tumor or infectious disease, severe liver or kidney disease, hyperthyroidism, pregnancy or lactation. Continuous ECG recording (using the CardioMem® CM 4000 provided by GETEMED AG, Teltow, Germany) was started in 109 study participants up to 74 hours before the 38th BMW BERLIN MARATHON and continued throughout the entire race and for up to 58 hours afterwards. Laboratory assessment including hsTnT measurement with chemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany; cut-off 12 µg/L) was performed up to 74 hours before, within 30 minutes post-race

and for up to 58 hours after the race. The study protocol is in accordance with the Helsinki declaration and was approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin (EA4/042/11). The primary hypothesis was: Cardiac arrhythmias and especially atrial fibrillation is frequently found in experienced marathon runners. Therefore, the primary outcome is the number of marathon runners with newly diagnosed cardiac arrhythmias. The main secondary hypotheses were: (1) There are predictable risk factors associated with cardiac arrhythmias in marathon runners; (2) Pathological laboratory findings are (in part) associated with cardiac arrhythmias; (3) Marathon runners with elevated troponin levels do not have MRI-detected myocardial scars suggestive of myocardial infarction. Follow-up information on past medical history was assessed one year after the marathon.

MRI analysis

A cardiac MRI after the race was offered to all study participants with either ST-segment deviation or hsTnT elevation. 3T MRI (Magnetom Tim Trio; Siemens AG, Erlangen, Germany) was performed using a phased array receiver coil during breath-holds gated to the electrocardiogram (Body Matrix-coil #TATS; Siemens AG). Cine images of 3 long-axis and 14-18 short-axis views (slices of 4 mm) were created using a steady state free precision technique [24]. Eight minutes after i.v. administration of 10-12 ml Gadovist® (Bayer Schering Pharma AG, Berlin, Germany) at a concentration of 1 mmol/ml, these views were repeated using a short inversion recovery sequence and continuously adjusting the inversion time [25].

ECG analysis

ECG monitoring was performed using a two-channel portable ECG recorder (CardioMem® CM 4000; GETEMED AG, Teltow, Germany). The cardiologists (AT, AW, WH) who analyzed the ECG data were blinded for demographic, clinical or laboratory data. The five recorded leads were placed as follows in order to obtain two independent bipolar channels: left (1) and right (2) on the first intercostal space, right on the sixth intercostal space parasternal (3) and mid-clavicular line (4), left ninth intercostal space mid-clavicular line (5). As there are no published recommendations on interpretation of a Holter-ECG in athletes, we followed recommendations available for interpreting a 12-lead ECG in athletes [26] as well as recent EHRA guidelines on ventricular arrhythmias [18]. In line with this, we defined an abnormal ECG as presence of ST-segment deviation under physical exercise or arrhythmias. Low-pass-filtering was set at 0.05 Hz in order to detect changes in the ST-T-segment. The ST-segment was considered abnormal in the virtually artifact free 2-lead ECG if horizontal or down-sloping ≥ 1 mm occurred over the 60 ms after the J-junction (80 ms if the heart rate was <120 beats/min) [27]. ST-segments were analyzed in relation to the TP segment. Segments were analyzed after recording of stable isoelectric TP segments in three consecutive beats. If single QRS complexes showed notching, slurring or fragmentation, QRS and ST intervals were excluded from further analysis. Episodes lasting more than 30 seconds preceded and followed by regular ECG recording were also considered abnormal. Drezner et al. defined atrial arrhythmias as atrio-ventricular (AV) block grade IIb or III, atrial fibrillation or supraventricular tachycardia (SVT) [26]. Ventricular arrhythmias were defined as nsVT of at least three premature ventricular complexes (PVC) and a heart rate of ≥100 beats per minute [18,26].

Statistical analysis

In accordance with the sample size calculation, we planned to include 110 participants into the study [23]. For categorical data, absolute and relative frequencies were calculated using SPSS statistics 22. In the case of continuous variables with nearly normal distribution, we used the arithmetic mean, standard deviation, minimal and maximal values, otherwise median, quartiles, minimal and maximal values. The *Chi* quadrat test was used to compare proportions for dichotomous outcomes between independent groups or to test independency of two dichotomous variables within a population. Outcomes in an ordinal scale or continuous outcomes were analyzed using the t-test or the Mann-Whitney test, depending on normality or non-normality of distribution. A p-value of <0.05 was considered to be statistically significant. In multivariate analysis, potential impact factors identified on a $p<0.05$ level in univariate analysis were entered in a binary logistic regression model using backwards selection.

Results

Baseline data of study participants and feasibility of ECG recording

Overall, 109 (99.1%) of 110 study participants took part, and 108 (98.2%) participants finished the 38th BMW BERLIN MARATHON 2011 in an average running time of 249±43 min. September 25, 2011, was a sunny day in Berlin and temperatures reached a maximum of 22 degrees Celsius. Data quality of long-term Holter-ECG was sufficient to ensure assessment of arrhythmias and ST-segment deviations in 107 (98.2%) athletes, although motion and

perspiration artifacts were present in the majority of athletes. In one athlete's device, a technical error occurred. Consistently wearing the ECG recorder on the upper arm using a carrier bag, no athlete reported problems in this regard. No athlete stopped wearing the ECG device prematurely. Baseline characteristics of these 107 participants are depicted in **Table 1**. The median age of these 107 participants was 48 years; 23.9% were female. The cardiovascular risk profile was low. The participants had run a median of 5 marathon races within the last 5 years and a median of 8 marathon races in total. Their average weekly running distance prior to the race was 40 km (IQR 30-50 km). In addition, athletes regularly went cycling (44.9%; n=48) or swimming (18.7%; n=20), respectively.

Cardiac arrhythmias or ST-segment deviation during the marathon

During the race, mean heart rate was 156.7±9.4 beats per minute. Minimum and maximum median heart rate were 133 (IQR 120-142) and 172 (IQR 166-177) beats per minute, respectively. We observed nsVT in 10 (9.4%) athletes (**Figure 1**), 2 (20%) of whom were female. In athletes with nsVTs, the median number of beats was 3 (IQR 3-5; range 3-9), median rate was 166 beats per minute (IQR 149-188; range 133-224) and median duration of the recorded nsVT was 1121 ms (IQR 919-1841; range 901-4400). We did not observe an AV block or a SVT. Persistent atrial fibrillation was found in one male patient (0.9%). Filtering of the monitors allowed interpretation of ST-T wave changes in fashion similar to a standard ECG. Exercise-induced ST-segment deviations occurred in eight (7.5%) study participants during the marathon race (**Figure 2**), 2 (25%) of whom were female. Characteristics of all athletes with ST-segment deviation are displayed in the *online supplement*. Intensity of ST-

segment deviation in terms of ST-level was -0.7 mV (IQR -0.8 to -0.3; range -0.9 to -0.16). ECG monitoring was prolonged for up to 54 hours (median 28 hours) after the marathon race. ST-segment deviations were not found in any athlete with ST-segment deviation during the marathon. One of these eight athletes also had nsVT. While four (3.7%) athletes reported palpitations during the marathon race, one had AF, one had a single nsVT (lasting nine beats) and another athlete had multiple supraventricular premature beats (62/hour). No athlete reported cardiac pain or dyspnea. An abnormal ECG according to pre-defined criteria was found in 16.8% (n=18) of all participants. In univariate analysis, advanced age (p=0.004) and a longer marathon finishing time (p=0.009) were associated with abnormal ECG findings, while sex, cardiovascular risk profile, hematocrit post-race and the number of previous marathons were not. In multivariate analysis, advanced age remained significant (OR 1.11 per year [95%CI 1.01-1.23]) (**Table 2**). In addition, athletes with an abnormal ECG had a higher frequency of PVCs (median 3.0 (IQR 1.0-12.3) versus 23.5 (IQR 10.0-44.0), p<0.001) during the marathon race.

Cardiac biomarkers and ECG changes during the marathon

At baseline, hsTnT was normal in all marathon runners (<50 ng/L). Within minutes after the race was finished, hsTnT was elevated above 50 ng/L) in 18 (16.8%) participants and median hsTnT was 3 ng/L (IQR 2-4; range 1-22). Median hsTnT values in 18 athletes with elevated hsTnT was 68.5 ng/L (IQR 62.8-85.5, range 50-216). Characteristics of all athletes with elevated hsTnT are displayed in the *online supplement*. In all athletes, median creatinine kinase (CK) and CK-MB were 130 U/l (IQR 103–176) and 20 U/l (IQR 17–24) pre-marathon,

respectively. Post-marathon CK was 336 (IQR 252-417) U/l and CK-MB was 35 (IQR 29-41) U/l.

Comparing athletes with an elevated hsTnT post–marathon to those without, we found no difference in age, sex, cardiovascular risk factors, training level or post-marathon CK-MB values (**Table 3**). In runners with elevated hsTnT, we found more frequent ST-segment deviations ($p<0.0001$) but no association with cardiac arrhythmias. In addition, elevated hsTnT was found in individuals with a longer marathon finishing time ($p=0.040$). Athletes with elevated hsTnT had a lower hematocrit compared to athletes without hsTnT elevation ($p=0.003$). In multivariate analysis, ST-segment deviation (OR 9.9 [95%CI 1.9-51.5]]) as well as hematocrit (OR 0.76 per percent [95%CI 0.62-0.92]) remained statistically significant. Within 48 hours post-marathon, hsTnT was within normal range in 106 (99.1%) athletes; one athlete with no substantial ECG alterations during the marathon showed a persisting hsTnT elevation but normal 12-lead ECG post-marathon. Follow-up information was available for all eight athletes with ST-segment deviation and for eight out of ten patients with nsVT during the race. None of the athletes reported a cardiovascular event within one year after the race.

Cardiac MRI in athletes with ST-segment deviation or elevated hsTnT

Cardiac MRI was offered to all study participants with ST-segment deviation or hsTnT elevation. Five out of eight athletes with ST-segment deviation and hsTnT elevation as well as in five out of 18 athletes with hsTnT elevation but without ST-segment deviation underwent MRI within 10-42 days after the marathon race. Age, sex and cardiovascular risk factors did not differ in the 10 athletes undergoing cardiac MRI and the 14 athletes who did

not undergo cardiac MRI. Cardiac MRI revealed no pathological findings for cardiac function and there was no late gadolinium enhancement indicating myocardial fibrosis. Additional cardiac work-up was strongly recommended in all patients with pathological ECG-findings.

Discussion

This is so far the largest study demonstrating feasibility of ECG recording during a marathon race, which may help counseling a subset of endurance athletes regarding exercise-associated complications. One main finding of the "Berlin Beat of Running" study is the unexpectedly high rate of abnormal ECG findings in 17% of recreational endurance athletes. Moreover, this is the first study reporting an association of transient ST-segment abnormalities during a marathon with elevated hsTnT levels after finishing the race. However, we cannot be sure that the observed ST-segment deviations are definitively based on silent ischemia.

So far, there is limited data on ECG abnormalities during vigorous exercise [28]. Franco et al. reported "no arrhythmias" in 19 male athletes during a marathon [21], while Aagaard et al. found "no ventricular arrhythmias" but atrial fibrillation in two (4%) of 49 male endurance runners during a 30 km race [22]. Luurila et al. reported the presence of ventricular premature complexes in 33 (89%) of 37 recreational athletes during a ski marathon as well as ST-segment deviations in 3 (8%) of these middle-aged men [20]. Most recently, Grabs et al. used a 1-lead wireless ECG and reported premature atrial contractions but no arrhythmias in 20 male runners during a marathon race [19]. In our prospective study, 10 (9.4%) out of 107 recreational endurance athletes had a non-sustained ventricular arrhythmia during the

marathon and one (0.9%) athlete had AF. In addition, ST-segment deviations (**Figure 2**) were detected in 8 (7.5%) athletes. Advanced age was associated with abnormal ECG findings (**Table 2**). According to the hematocrit, low hydration – potentially impacting on cardiac preload – was not linked to abnormal ECG findings. However, analyzing athletes with ST-segment deviations, atrial fibrillation or ventricular arrhythmias, the underlying mechanisms of these pathological conditions may differ and the results of the multivariate analysis do not apply to a single condition.

Despite the fact that increased levels of physical activity were associated with a lower relative risk of myocardial infarction, 4% of patients with myocardial infarction report having performed strenuous exercise within hours before the cardiovascular event [3]. By using different cut-offs, transient elevations in the level of troponin T or troponin I have previously been reported in 18-69% of marathon runners [10–12,29]. In the "Berlin Beat of Running" cohort, hsTnT was elevated in 18 (17%) out of 107 athletes but normalized within 48 hours in 17 (94%) athletes. Interestingly, elevation of hsTnT was not related to age, sex, training status, the cardiovascular risk profile or the presence of cardiac arrhythmias during the race, but was related to exercise-induced ST-segment deviation ($p<0.0001$) and inversely correlated with the hematocrit (measured immediately after the race).

Cardiac magnetic resonance imaging (MRI) is now the gold standard for detecting myocardial damage [30] and myocardial edema as well as decreased ventricular function after a marathon race [31,32]. We were not able to demonstrate late gadolinium enhancement as an indicator of permanent myocardial fibrosis in ten experienced recreational athletes with ST-segment deviation or detected cardiac arrhythmia. This is in line with a previous study reporting no

late gadolinium enhancement in 20 recreational athletes within 48 hours after a marathon race [31]. Interestingly, a transient cardiac edema was reported in 17 (85%) out of 20 marathon runners [31], but no correlation was reported between biomarkers and cardiac edema. We are, however, unable to exclude a transient cardiac edema in marathon runners because cardiac MRI was performed within 10-42 days after the marathon race.

Taken together, vigorous exercise can go along with transient troponin elevation, ST-segment alterations or nsVT in a fit and active population. However, athletes with ST-segment deviation or nsVT during the race did not report a cardiovascular event within one year afterwards. Thus, these findings are likely to be benign, but it was still recommended to rule out structural heart disease or obstructive coronary artery disease in these athletes. Our results strengthen the assumption that hsTnT elevation originates from the heart and not primarily from non-cardiac sources [8]. However, we are unable to draw final conclusions. Whether borderline cardiac damage by repetitive strenuous exercise could lead to permanent (potentially arrhythmogenic) cardiac remodeling is under debate [6,33].

Focusing primarily on the feasibility of portable ECG monitoring and detection of ECG changes during the race, major limitations of the observational "Berlin Beat of Running" study are the missing (serial) echocardiography or cardiac stress MRI, thus limiting the clinical significance of the observed ST-segment changes and elevated hsTnT levels. Furthermore, a normal cardiac MRI within days after the race does not completely rule out (transient) exercise-induced cardiac damage [34]. Since only one fourth of all athletes were female and because of a potential selection bias during enrolment, the generalizability of our results is limited. Moreover, due to the limited number of endpoints observed, we believe that

the results of the multivariate analysis should be interpreted with caution. Combining nsVT and ST-segment deviations for statistical analysis may have introduced an information bias. Unfortunately, it was impossible to assess the mean duration of ST-segment deviation in more detail, as ST-segment changes were present intermittently. Finally, exercise capacity testing would have allowed more accurate evaluation of training status.

Conclusion

ECG recording during a marathon race is feasible, which may be helpful in the diagnostic work-up of selected athletes. Cardiac arrhythmias or exercise-induced ST-segment deviations appear in a relevant subset of experienced recreational athletes during a marathon race and predominantly in older athletes. Marathon-induced ST-segment deviations were associated with elevated hsTnT values immediately after the race. Cardiac MRI detected no myocardial fibrosis by late gadolinium enhancement in a subset of these athletes.

List of abbreviations

atrial fibrillation, AF; AV, atrio-ventricular; CK, creatine kinase; CK-MB, myocardium- and brain-specific CK; electrocardiogram, ECG; hsTnT, high-sensitive troponin T; magnetic resonance imaging, MRI; SVT, supraventricular tachycardia; Tesla, T; non-sustainable ventricular tachycardia, nsVT.

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Competing interests

JH reports no conflict of interest. AT reports lecture fees from the Circle Institute. MK received consulting, lecture and advisory board fees from ALK, Berlin Chemie, Novartis, Mundipharma and Teva. LB reports research support from the German Ministry of Research and Education. JBF reports the following board memberships, consultancies and/or payments for lectures including service on speaker's bureaus: Boehringer-Ingelheim, Lundbeck, BioClinica and Parexel. PUH reports research grants from the German Ministry of Research and Education, EU, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, Charité–Universitätsmedizin Berlin (within MonDAFIS; MonDAFIS is supported by an unrestricted research grant to the Charité from Bayer Healthcare), University Göttingen (within FIND-AF$_{randomized}$; FIND-AF$_{randomized}$ is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), and University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer Healthcare, BMS, Boehringer-Ingelheim), outside submitted work. GJJ has received funding from the German Ministry for Education and Research. He has served on the Critical Event committees of the SourceXT registry and the ProTAVI-C-study (Edwards Lifesciences, USA). He serves as a consultant for Cipio Partners (Munich, Germany and Elron, Tel Aviv, Israel). He has received speakers' honoraria from Genzyme and Pfizer

(2010-2013). ME and KGH report lecture fees and study grants from Sanofi-Aventis and Bayer Healthcare.

Contributorship statement

JH has made substantial contributions to acquisition, analysis and interpretation of data and drafted the manuscript. AT and AW have made substantial contributions to data analysis and interpretation of data. CK has made substantial contributions to design and acquisition of data. MK, LB, JL, JBF, WH and ME revised the manuscript critically for important intellectual content. PUH has made substantial contributions to analysis and interpretation of data and revised the manuscript critically for important intellectual content. GJJ has made substantial contributions to conception and design and revised the manuscript critically for important intellectual content. KGH has made substantial contributions to conception and design, analysis and interpretation of data and drafted the manuscript.

Data Sharing Statement

There are no additional data available for this study.

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Table 1: Baseline characteristics of the 107 participants of the "Berlin Beat of Running" study who finished the marathon and who had evaluable ECG data.

Age; mean; years; median [IQR]	48 [45-53]
Female gender; % (n)	24.3 (26)
Body mass index; kg/m^2; median [IQR]	23.4 [21.6-24.7]
Hypertension; % (n)	8.4 (9)
Diabetes mellitus; % (n)	0 (0)
Heart failure; % (n)	0 (0)
Coronary artery disease; % (n)	0 (0)
Hyperlipidemia; % (n)	2.8 (3)
Current smoking; % (n)	6.5 (7)
Medication at enrolment	
Antiplatelet; % (n)	0.9 (1)
Oral anticoagulant; % (n)	0
Beta-blocker; % (n)	1.9 (2)
Statin; % (n)	1.9 (2)
Antihypertensive; % (n)	6.5 (7)

Table 2: Cardiovascular risk profile and training status of recreational athletes with or without abnormal ECG findings, respectively. ST segment deviation, atrio- or ventricular arrhythmias (atrio-ventricular block grade IIb or III, triplets, non-sustained ventricular tachycardia, supraventricular tachycardia) or atrial fibrillation were regarded as abnormal findings.

	Normal ECG n=89	**Abnormal ECG** n=18	**Univariate Analysis p-value ***	**Multivariate Analysis OR (95%CI)**
Age; years; median [IQR]	48 [44-50]	54 [48-59]	0.004	1.11 (1.01-1.23)
Female gender, % (n)	24.7 (22)	22.2 (4)	0.822	
Physical activity				
Marathon runs ≤ 5 years; median [IQR]	5 [4 -10]	6 [4-7]	0.923	
Marathon runs total; n; median [IQR]	9 [5-18]	7 [6-14]	0.573	
Current running; km/week; median [IQR]	65 [50-80]	58 [50-70]	0.151	
Regular running; km/ week; median [IQR]	40 [30-50]	40 [30-50]	0.409	
Present marathon time; min; median [IQR]	238 [215-268]	275 [229-326]	0.009	1.44 (0.98-2.12)
Hematocrit post-race; %; median [IQR]	0.44 [0.41-0.45]	0.43 [0.41-0.45]	0.711	
Body Mass Index; kg/m^2; mean ± SD	23.2±2.2	23.6±1.9	0.449	
Comorbidities				
Hypertension; % (n)	6.7 (6)	16.7 (3)	0.166	

Hyperlipidaemia; % (n)	2.2 (2)	2.8 (3)	0.438
Current smoking; % (n)	5.6 (5)	11.1 (2)	0.390

*Values are expressed in % (n), mean ± SD or median [IQR] as appropriate; * p-value calculated by chi^2-test or Mann-Whitney U test, as appropriate. Multivariate analysis was calculated in a binary logistic regression model using backwards selection.*

Table 3: Troponin T elevation post-marathon in the 107 athletes who finished the marathon race and who had evaluable ECG data.

	Troponin T < 50 ng/L n=89	**Troponin T ≥ 50 ng/L** n=18	**Univariate Analysis p-value ***	**Multivariate Analysis OR (95%CI)**
Age; years; median [IQR]	48 [45-52]	49 [45-53]	0.605	
Female gender; % (n)	21.3 (19)	38.9 (7)	0.114	
Body mass index; kg/m^2; mean ± SD	23 [22-25]	23 [22-25]	0.723	
Present marathon time; min; median [IQR]	236 [217-269]	268 [237-309]	0.040	1.25 (0.83 – 1.87)
Marathon runs ≤ 5 y; n; median [IQR]	6 [4-10]	5 [3-8]	0.327	
Marathon runs total; n; median [IQR]	9 [6-18]	7 [5-12]	0.147	
Regular weekly running; km; median [IQR]	40 [30-50]	40 [30-50]	0.791	
Coexisting hypertension; % (n)	9.0 (8)	5.6 (1)	0.632	
Hyperlipideamia; % (n)	3.4 (3)	0 (0)	0.429	
ST-segment deviation; % (n)	3.4 (3)	27.8 (5)	<0.0001	9.9 (1.90 – 51.5)
Arrhythmias; % (n)	11.2 (10)	5.6 (1)	0.469	
Troponin pre-race; µg/L; median [IQR]	0.012 [0.012-0.012]	0.012 [0.012-0.012]	0.131	
Creatinine pre-race; mg/dL; median [IQR]	0.86 [0.81-0.96]	0.85 [0.77-0.97]	0.761	
Creatinine post-race; mg/dL; median [IQR]	1.27 [1.11-1.46]	1.34 [1.17-1.48]	0.424	
CK post-race; U/L; median [IQR]	333 [250-412]	350 [291-611]	0.263	

CK-MB post-race; U/L; median [IQR]	35 [28-41]	33 [29-52]	0.609	
Hematocrit post-race; %; median [IQR]	44 [42-46]	41 [39-44])	0.003	0.76 (0.62 – 0.92)

*Values are expressed in % (n), mean ± SD or median [IQR] as appropriate; * p-value calculated by chi^2 – test or Mann-Whitney U test, as appropriate. Multivariate analysis was calculated in a binary logistic regression model using backwards selection.*

Figure 1: Non-sustained ventricular tachycardia in a well-trained 48-year old male endurance runner without cardiovascular risk factors despite smoking.

Figure 2: ECG at rest (A) and exercise-induced ST segment deviations (B) in a 60-year old male endurance runner without cardiovascular risk.

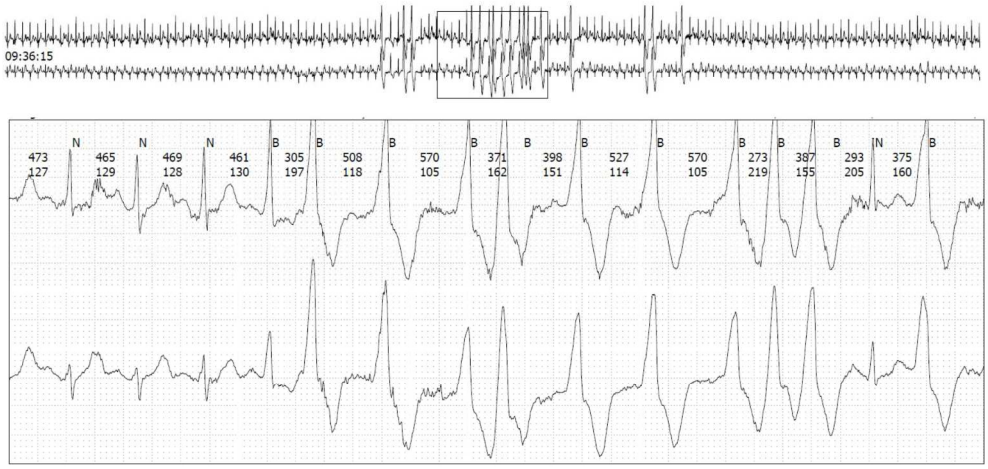

Figure 1: Non-sustained ventricular tachycardia in a well-trained 48-year old male endurance runner without cardiovascular risk factors despite smoking.

297x151mm (300 x 300 DPI)

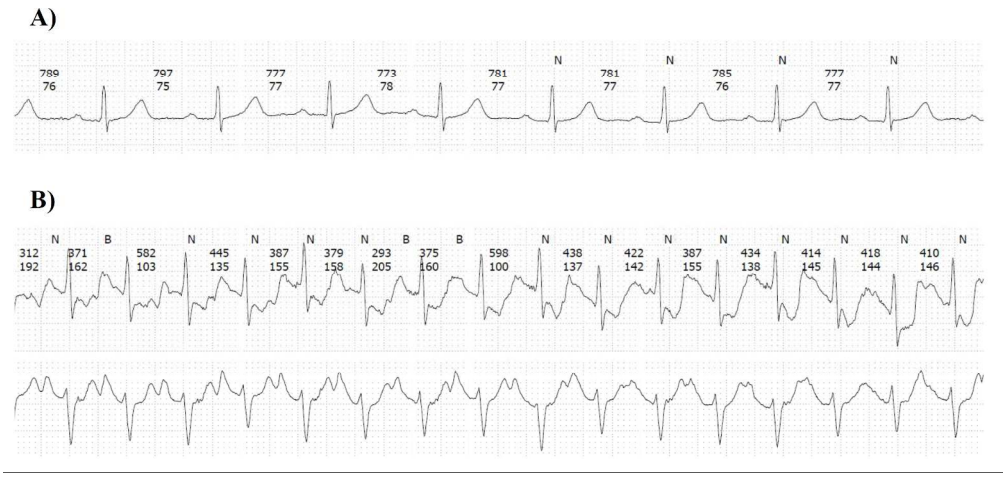

Figure 2: ECG at rest (A) and exercise-induced ST segment deviations (B) in a 60-year old male endurance runner without cardiovascular risk.

301x149mm (300 x 300 DPI)

ONLINE SUPPLEMENT High-sensitive troponin T (hsTnT) values returned to normal within up to 58 hours after the marathon race in almost all athletes (95%). Creatine kinase (CK) remains elevated in all 21 athletes (with ST-segment deviation and/or hsTnT elevation).

Table ONLINE SUPPLEMENT: Characteristics of 21 athletes with either ST-segment deviation (>1 mm) and hsTnT elevation (≥50 ng/L) (n=5), ST-segment deviation (n=3) or hsTnT elevation (n=13). Pathological findings are labeled in bold.

Age	Sex	Medication	Cardiovascular risk factors	NSVT[§]	ST-segment deviation	hsTnT[$] ng/L[*]	hsTnT ng/L[**]	CK-MB mg/dL[*]	CK-MB mg/dL[**]	CK mg/dL[*]	CK mg/dL[**]	Cardiac MRI
45	Female	None	No	No	**Yes**	**91**	19	21	32	877	1194	Yes
45	Female	L-Thyroxin	No	No	**Yes**	**71**	12	18	16	243	235	Yes
53	Male	None	No	No	**Yes**	**63**	14	14	35	893	2121	Yes
59	Male	None	No	No	**Yes**	**66**	12	19	54	406	2236	Yes
60	Male	None	Smoker	**Yes**	**Yes**	**70**	12	27	72	2867	3625	Yes
48	Male	None	No	No	**Yes**	32	16	18	44	381	1719	No
55	Male	None	No	No	**Yes**	21	12	21	35	201	489	No
60	Male	Antihypertensive	Hypertension	No	**Yes**	27	13	28	44	767	1979	No
44	Female	None	Smoker	No	No	**78**	12	26	20	306	192	Yes
48	Male	None	No	No	No	**138**	20	59	67	325	2186	Yes
49	Female	None	No	No	No	**63**	12	22	41	205	1357	Yes
50	Male	None	No	No	No	**87**	29	30	73	360	3462	Yes
60	Female	None	No	No	No	**216**	64	33	14	455	169	Yes
39	Male	None	No	No	No	**59**	23	47	87	583	2756	No
40	Female	None	No	No	No	**85**	12	42	33	696	914	No
45	Male	None	No	No	No	**83**	29	175	157	195	605	No
47	Male	None	No	No	No	**52**	12	37	42	309	1983	No
48	Male	None	No	No	No	**64**	12	52	101	405	4604	No
50	Female	Antihypertensive	Hypertension	No	No	**50**	12	29	28	315	485	No
53	Female	None	No	No	No	**62**	12	30	24	339	448	No
54	Male	None	No	No	No	**67**	15	33	23	234	409	No

[§] non-sustained ventricular tachycardia; [$] high-sensitive Troponin T; [*] within 30 minutes post-race; [**] up to 58 hours after the race

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	page	Recommendation
Title and abstract	1	2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
			Introduction
Background/rationale	2	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	4	State specific objectives, including any prespecified hypotheses
			Methods
Study design	4	4	Present key elements of study design early in the paper
Setting	5	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	4	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	5-6	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	13	Describe any efforts to address potential sources of bias
Study size	10	4 (Ref. to design paper)	Explain how the study size was arrived at
Quantitative variables	11	7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	7	(*a*) Describe all statistical methods, including those used to control for confounding
		7	(*b*) Describe any methods used to examine subgroups and interactions
		n.a.	(*c*) Explain how missing data were addressed
		n.a.	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
	n.a.	(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-10
		(*b*) Report category boundaries when continuous variables were categorized	7-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.