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Research article

# Cardiovascular magnetic resonance with parametric mapping in long-term ultra-marathon runners

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ABSTRACT

*Purpose:* There is a direct reverse dose-effect relationship between the amount of physical activity and cardiovascular risk. It is unknown whether this is true for extreme, persistent endurance training. The aim of the study was to assess structural changes of the heart in long-time ultra-marathon runners with special focus on myocardial fibrosis using parametric mapping.

*Method:* We studied a group of 30 healthy, male ultra-marathon runners (mean age 40.9 ± 6.6 yrs, median 9 yrs of running with frequent competitions) and 10 matched controls not engaged in any regular activities. All of them underwent cardiovascular magnetic resonance (CMR) with 3 T scanner including T1-mapping, late gadolinium enhancement (LGE) and extracellular volume (ECV) quantification.

*Results:* Athletes demonstrated significantly larger heart chambers and left ventricular (LV) mass. LV systolic function was unchanged. 73.3% of athletes fulfilled volumetric criteria for dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy. Non-ischemic, small volume LGE was found in 8 athletes and in 1 control (27% vs. 10%, $p = 0.40$). It was localised at insertion points (5 athletes, 1 control) or in the septum or infero-lateral wall (3 athletes). Athletes with insertion point LGE had higher right ventricular end-diastolic volume index in comparison to athletes without LGE ($p = 0.04$), which suggests its relation to volume overload. There were no differences between athletes and non-athletes in terms of ECV values (26.1% vs. 25%, $p = 0.29$).

*Conclusions:* Ultra-marathon runner's hearts demonstrate a high degree of structural remodelling, but there is no significant increase in focal or diffuse myocardial fibrosis.

## 1. Introduction

Regular physical activity has numerous positive health effects in humans, including decreased cardiovascular risk factors and diseases, which contribute towards greater life expectancy [1]. There is a direct cause-effect relationship between the amount of physical training and positive changes observed in the body [2]. However, it has also been postulated that this relationship may have a U-shape pattern, meaning that subjects who regularly participate in extremely long and/or intense methods of training may see the benefits offset by negative cardiovascular changes [3]. Marathon and ultra-marathon running are examples of extreme forms of training. Participation in these endurance competitions may lead to transient increases of serum troponin concentration (a biomarker of cardiac injury) and to reduced cardiac systolic function [4,5]. Although these changes have been shown to be only temporary and did not cause irreversible myocardial injury [6], it has been demonstrated that veteran athletes are more prone to atrial fibrillation, sinus node disease or even ventricular arrhythmias [3]. They were also shown to have more atherosclerotic plaques in the coronary bed, although these were more calcified and stable in comparison to controls [7]. Arrhythmias and conduction system disorders may be a consequence of increased myocardial fibrosis and higher atherosclerotic plaque burden may cause silent myocardial infarctions in this group of athletes [3].

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Myocardial fibrosis has traditionally been assessed in-vivo by cardiovascular magnetic resonance (CMR) with gadolinium contrast administration. The contrast remains for a prolonged time in areas of unperfused myocardium (scars) and changes the T1-relaxation time of the myocardium, which is visible as areas of late gadolinium enhancement (LGE). Most published CMR studies in athletes use this technique to assess fibrosis [8]. However, it only permits visualisation of large areas of necrotic tissue and does not allow analysis of diffuse rather than focal fibrosis. Novel parametric mapping techniques such as T1-mapping, T2-mapping and extracellular volume (ECV) quantification can detect subtle myocardial injury early in the disease process, but have only recently been applied in athletes [9,10].

Secondly, most of the studies on structural changes in endurance athletes were based on more accessible echocardiographic studies [11–13]. As CMR is becoming more frequently used in clinical practice it seems warranted presenting features of an ultra-endurance athlete's heart with this method.

Therefore, the aim of this study was to assess structural changes of the heart in long-time ultra-marathon runners using CMR, with particular focus on myocardial fibrosis using parametric mapping techniques.

## 2. Methods

### 2.1. Study group

40 participants volunteered to participate in the study. The study group consisted of 30 healthy, male, mainly high-level, long-term ultra-marathon runners compared with 10 age- and sex-matched healthy controls not engaged in any regular sport activities. Ultra-marathon runners were approached through running societies, while controls consisted mainly of physicians, technicians and colleagues approached through personal contacts. To ascertain the amount of physical training needed to meet the aim of the study, we recruited runners with several years of documented continuous training at high level (running at least 70 km/week) with frequent competitive starts in ultra-marathons (preferably longer than 100 km in distance). We confirmed the participation in competitions through enduhub.com webpage listing all races taking part in Poland or through race pages of international competitions. All of the volunteers underwent initial screening to exclude underlying medical conditions including a detailed medical history, height and weight assessment, baseline ECG, blood pressure measurement at rest, and whole blood count and creatinine concentration measurement on the day, but before cardiovascular magnetic resonance imaging. Subsequently all patients underwent CMR with parametric imaging (with pre-contrast T1- and T2-mapping) and gadolinium contrast administration followed by LGE and post-contrast T1-mapping. A cardiopulmonary exercise test (CPET) was performed within 4 weeks of the CMR.

### 2.2. Cardiovascular magnetic resonance (CMR)

CMR imaging was performed with a Siemens Magnetom Skyra 3 T scanner (Siemens, Erlangen, Germany). The protocol included initial scout images, followed by cine steady-state free precession (SSFP) breath-hold sequences in 2-, 3-, and 4-chamber views. Short axis was identified using the 2- and 4-chamber images and included the ventricles from the mitral and tricuspid valvular plane to the apex.

Pre-contrast T1-mapping and T2-mapping were performed right after acquisition of SSFP cine images using MyoMaps software (Siemens, Erlangen, Germany). For that purpose 3 short axis slices (one basal, one mid-ventricular and one apical) were obtained.

This was followed by the administration of 0.1 mmol/kg of a gadolinium contrast agent (gadobutrol – Gadovist ®, Bayer Pharma AG, Berlin, Germany) flushed with 30 ml of isotonic saline. This was immediately followed by post-contrast vibe sequence acquisition in the axial plane. LGE images in 3 long axis and a stack of short axis imaging planes were obtained with a breath-hold segmented inversion recovery sequence performed 10 min after the contrast injection. The inversion time was adjusted to completely null normal myocardium (typically between 250 and 350 ms). This was followed by post-contrast T1-mapping acquisition 15 min after the contrast injection in the same 3 short axis slices as the pre-contrast T1-mapping.

Images were analyzed with the use of dedicated scanner vendor software. Initially, short axis SSFP cine images were previewed from the base to the apex in a cinematic mode, then endocardial and epicardial contours for end-diastole and end-systole were manually traced. Delineated contours were used for the quantification of end-diastolic and end-systolic volumes, stroke volumes, ejection fraction, and biventricular masses, indexed to body surface area (BSA) where necessary. Three-chamber SSFP cine images were used to measure baseline linear dimensions of the left ventricle, left atrium and aorta. Four-chamber cine images were used to obtain the right ventricular diameter in end-diastole and biatrial areas in end-systole. The main pulmonary artery and left/right pulmonary artery diameters were measured on post-contrast vibe images.

All of the maps were of good quality. Pre-contrast T1 and T2 relaxation times and post-contrast T1 relaxation time were calculated from a 1.5 $cm^2$ region of interest (ROI) placed at the mid-ventricular short-axis slice in the mid-section of the interventricular septum. Caution was taken not to include LGE areas in the measurements and not to include blood pool in the ROI. For blood pool pre- and post-contrast T1 time a ROI of the same size was placed at the same level in the ventricular cavity, but separate from the papillary muscles or trabeculations. Extracellular volume (ECV) was calculated using the previously validated equation: ECV = (1-hematocrit)*[(1/T1myopost-1/T1myopre)/(1/T1bloodpost-1/T1bloodpre)] [14]. The presence and location of LGE was assessed visually by an experienced Level 3 CMR reader with 10-years of expertise in the field (L.A.M). We did not use any medication to control heart rate in ultra-marathon runners. Their heart rate was already low, which is a part of a physiological adaptation to exercise.

### 2.3. Cardiopulmonary exercise testing (CPET)

All subjects were submitted to a maximal exercise test on a treadmill (Saturn, h/p/cosmos, Nussdorf – Traunstein, Germany). Initially all participants performed a 10-minute warm-up on a treadmill consisting of jogging or slow running at their own pace. Ventilation and gas calibration of the system was performed before the test. Participants were then given a facial mask and baseline respiratory parameters were recorded. The subjects were breathing through a mask mounted with a head harness and connected to the ergospirometer. Starting treadmill velocity was set at 10 km/h and was increased by 1 km/h every 2 min. The treadmill elevation was maintained at baseline until the velocity of 13 km/h was reached. The gradient was then increased by 1% with each subsequent stage of the test. The test was terminated when the subject became sufficiently fatigued that they asked for it to end (cardio-respiratory exhaustion). The test was performed with continuous measurement of cardiopulmonary indices. Breath-by-breath data were averaged over 15 s. Using the portable metabolic system (Metamax 3B, Cortex Biophysik GmbH, Leipzig, Germany) minute ventilation (VE), maximal oxygen uptake ($VO_2$ max) and respiratory exchange ratio (RER) were measured.

### 2.4. Statistical methods

All results for categorical variables were presented as a number and a percentage. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normality of distribution assessed with the use of the chi-square test. Either the chi-square test or the Fisher exact test were

used for the comparison of categorical variables, when appropriate. The Student *t*-test or the Mann-Whitney test for unpaired samples were applied to compare cases and controls depending on the normality of the distribution. In order to assess the correlation between continuous variables, the r-Pearson or Spearman test were applied. All tests were two-sided with the significance level of $p < 0.05$. Statistical analyses were performed with MedCalc statistical software 10.0.2.0 (MedCalc, Mariakerke, Belgium).

### 2.5. Ethical considerations

The study had an approval of the Ethics Committee of the Regional Medical Chamber in Warsaw (no 52/17), with written informed consent obtained from all participants.

## 3. Results

### 3.1. Characteristics of the studied and control groups

The study group of athletes consisted of actively training individuals with long-term running history including a median of 6 years of ultra-marathon running (Table 1). Most participants started regular training around thirty years of age, and began ultra-marathon races at a median age of 34 years. The median total, life-time covered running distance by athletes was 25,000 km, with a median weekly running distance of 80 km. Participants regularly engaged in competitions including a median of 15 ultra races completed (a median of 3.5 races above 100 km long and a median of 5.5 starts in the last 2 years). Many participants placed highly in those competitions.

There were no significant differences in the baseline characteristics regarding age, anthropometric measures and blood pressure between the studied and control group (Table 2). As expected ultra-marathon runners demonstrated significantly better physical performance and lower resting heart rate comparing to the control group.

### 3.2. Size, function and mass of both ventricles

Ultra-marathon runners demonstrated significant symmetrical enlargement of both ventricles in comparison to controls: a 41% increase for left ventricular end-diastolic volume indexed to BSA – LVEDVI and a 42% increase for right ventricular end-diastolic volume indexed to BSA - RVEDVI. Both atria were also enlarged, but there was a disproportionate increase between the left and right atrial areas (LAA and RAA, respectively) in relation to controls (38% increase for RAA and 17% for LAA).

There was no difference between studied groups in terms of left and right ventricular ejection fraction (LVEF and RVEF) and regional wall motion, which remained normal. The ventricular mass index was increased in the left ventricle (LVMI), but not the right ventricle (RVMI), among athletes.

Differences in linear dimensions were observed for the left ventricular end-diastolic and end-systolic diameters (EDD and ESD), as well as the right ventricular diameter (RVD). Increased left ventricular mass was caused mainly by left ventricular enlargement and not by increased muscle thickness, as the interventricular septal diameter (IVSD) and the

**Table 1**
Baseline running characteristic of the study group of ultra-marathon runners.

| Parameter | Ultra-marathon runners n = 30, median (IQR) |
|---|---|
| Years of running | 9 (7-15) |
| Age at start of running | 29.5 (26-35) |
| Years of ultra running | 6 (5-8) |
| Age at start of ultra running | 34 (29-39) |
| Total covered distance (km) | 25 000 (20 000-40 000) |
| Weekly running distance (km) | 80 (70-90) |
| Number of ultra races completed | 15 (10-27.5) |
| Number of ultra races in the last 2 years | 5.5 (4-9) |
| Most frequent ultra race distance (km) | 100 (70-100) |
| Number of completed ultra races > 100 km | 3.5 (2-7) |
| Longest ultra race (km) | 150 (106-246) |
| Best place achieved in an ultra race | 5 (1-13) |

**Table 2**
Baseline, physical performance and CMR characteristics of the studied and control group.

| Parameter | Ultra-marathon runners n = 30 | Controls n = 10 | P |
|---|---|---|---|
| Age (yrs) | 40.9 ± 6.6 | 40.0 ± 8.2 | 0.76 |
| BSA | 1.89 ± 0.07 | 2.00 ± 0.11 | 0.11 |
| Height (cm) | 178 ± 5 | 179 ± 4 | 0.51 |
| Weight (kg) | 71.9 ± 4.7 | 83.0 ± 6.1 | 0.12 |
| BMI | 22.7 ± 1.5 | 26.1 ± 1.5 | 0.13 |
| Systolic BP (mmHg) | 128 ± 6 | 126 ± 7 | 0.78 |
| Diastolic BP (mmHg) | 78 ± 6 | 80 ± 5 | 0.35 |
| Hct (%/100) | 0.43 ± 0.03 | 0.45 ± 0.02 | 0.01 |
| Resting HR (bpm) | 54.9 ± 9.2 | 69.6 ± 11.0 | 0.005 |
| V02 max (L/min) | 4.43 ± 0.44 | 3.63 ± 0.63 | 0.005 |
| V02 max (ml/min/kg) | 61.0 ± 4.9 | 40.2 ± 4.6 | < 0.001 |
| VE max (L) | 150.4 ± 16.9 | 127.9 ± 25.3 | 0.03 |
| RER max | 1.08 ± 0.05 | 1.10 ± 0.04 | 0.17 |
| LVEDVI (ml/m2) | 110 ± 15 | 78 ± 10 | < 0.0001 |
| LVESVI (ml/m2) | 39 ± 9 | 27 ± 4 | < 0.0001 |
| LVSVI (ml/m2) | 71 ± 9 | 51 ± 9 | < 0.0001 |
| LVEF (%) | 65 ± 5 | 66 ± 5 | 0.59 |
| LVMI (g/m2) | 83 ± 11 | 66 ± 11 | 0.001 |
| RVEDVI (ml/m2) | 125 ± 20 | 88 ± 12 | < 0.0001 |
| RVESVI (ml/m2) | 52 ± 11 | 37 ± 6 | < 0.0001 |
| RVSVI (ml/m2) | 73 ± 11 | 51 ± 9 | < 0.0001 |
| RVEF (%) | 59 ± 4 | 58 ± 5 | 0.61 |
| RVMI (g/m2) | 24 ± 3.5 | 22 ± 5 | 0.24 |
| EDD (mm) | 54 ± 5 | 47 ± 4 | 0.0001 |
| ESD (mm) | 35 ± 5 | 30 ± 4 | 0.01 |
| IVSD (mm) | 11.5 ± 2 | 10.5 ± 1 | 0.32 |
| PWD (mm) | 10 ± 1 | 9 ± 1 | 0.17 |
| LA (mm) | 36 ± 3 | 34 ± 3 | 0.41 |
| RVD (mm) | 49 ± 4 | 46 ± 2 | 0.002 |
| RWT | 0.34 ± 0.1 | 0.40 ± 0.1 | 0.02 |
| LA area (cm2) | 27 ± 3 | 23 ± 2.5 | 0.001 |
| RA area (cm2) | 29 ± 4 | 21 ± 3 | < 0.0001 |
| Ao (mm) | 35.5 ± 3.5 | 35 ± 3.5 | 0.73 |
| Aa (mm) | 33 ± 3 | 31 ± 3 | 0.16 |
| MPA (mm) | 27 ± 2 | 25.5 ± 3 | 0.27 |
| RPA (mm) | 19 ± 1.5 | 19.5 ± 2 | 0.92 |
| LPA (mm) | 19.5 ± 1.5 | 19.5 ± 1.5 | 0.96 |
| LGE (n,%) | 8 (27) | 1 (10) | 0.40 |
| LGE type insertion point (n, %) midwall/subepicardial (n.%) subendocardial (n. %) | 5 (62.5) 3 (37.5) 0 | 1 (100) 0 0 | 0.22 |
| T1 pre (ms) | 1200 ± 59 | 1214 ± 32 | 0.33 |
| T1 post (ms) | 675 ± 46 | 663 ± 33 | 0.38 |
| T2 (ms) | 44 ± 5 | 41 ± 2 | 0.02 |
| ECV (%) | 26.1 ± 2.9 | 25.0 ± 2.5 | 0.29 |

Aa – ascending aorta, Ao – aortic bulb, BMI – body mass index, BP – blood pressure, BSA – body surface area, ECV – extracellular volume, EDD - left ventricular end-diastolic dimeter, ESD - left ventricular end-systolic diameter, Hct – hematocrit, HR – heart rate, IVSD – interventricular septal diameter, LA – left atrial diameter, LGE – late gadolinium enhancement, LPA – left pulmonary artery, LVEDVI – left ventricular end-diastolic volume index, LVEF – left ventricular ejection fraction, LVESVI – left ventricular end-systolic volume index, LVMI - left ventricular mass index, LVSVI – left ventricular stroke volume index, MPA – main pulmonary artery, PWD – left-ventricular posterior wall diameter, RA- right atrium, RER – respiratory exchange ratio, RPA – right pulmonary artery, RWT – relative wall thickness, RVD – right ventricular diameter, RVEF – right ventricular ejection fraction, RVEDVI – right ventricular end-diastolic volume index, RVESVI – right ventricular end-systolic volume index, RVMI - right ventricular mass index, RVSVI – right ventricular stroke volume index, VE – minute ventilation, V02 max – maximal oxygen consumption.

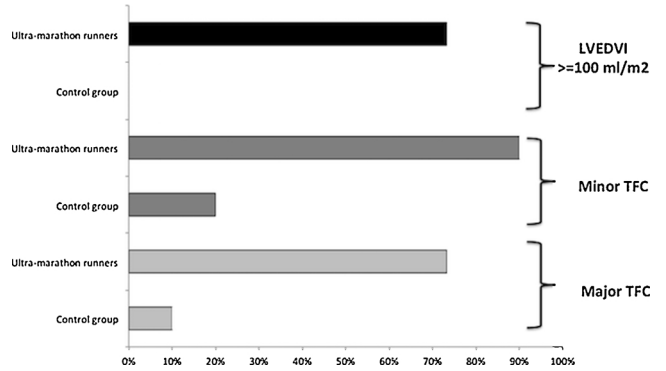


**Fig. 1.** Percentage of ultra-marathon runners and controls with left ventricular end-diastolic volume above reference values and right ventricular end-diastolic volume fulfilling volumetric Task Force Criteria for arrhythmogenic right ventricular cardiomyopathy.
LVEDVI – left ventricular end-diastolic volume index, minor TFC – minor Task Force Criterium for considering arrhythmogenic right ventricular cardiomyopathy in males (RVEDVI – right ventricular end-diastolic volume index > = 100 ml/m2), major TFC - major Task Force Criterium for considering arrhythmogenic right ventricular cardiomyopathy in males (RVEDVI – right ventricular end-diastolic volume index > = 110 ml/m2)

posterior wall diameter (PWD) in both groups were similar.

To analyse LV geometry we calculated relative wall thickness (RWT) as 2 *PWD/EDD [15]. Normal geometry is characterised by RWT ≤ 0.42 and normal LVMI, eccentric hypertrophy by RWT ≤ 0.42 and increased LVMI, concentric hypertrophy by RWT > 0.42 and increased LVMI and concentric remodelling by RWT > 0.42 and normal LVMI [15]. Athletes presented with eccentric hypertrophy (50%) or normal geometry (43%) with some cases of concentric remodelling (7%), while the control group had normal geometry (80%) or concentric remodelling (20%).

Given the significant structural changes amongst athletes, we analysed the percentage of ultra-marathon runners and controls in whom the left ventricular (LV) size, if examined in isolation, could lead to the suspicion of dilated cardiomyopathy (LVEDVI > = 100 ml/m2) or whose right ventricular (RV) dimension would meet the minor or major Task Force Criteria (TFC) for arrhythmogenic right ventricular cardiomyopathy (minor criterium -RVEDVI > = 100 ml/m2 and major criterium > = 110 ml/m2) [16,17]. The respective values would be as high as 73.3%, 90% and 73.3% in the study group and 0%, 20% and 10% in the control group (Fig. 1).

Finally, we did not find any significant valvular incompetence (only mild) in the studied group.

### 3.3. Late gadolinium enhancement

The presence of LGE did not differ significantly between both groups although it was numerically higher in athletes (Table 2). It was found in 8 ultra-marathon runners (27%) and in 1 control subject (10%). Patterns of LGE observed in the study group are presented in Fig. 1. The most frequent LGE pattern was a spotty-shaped, focal, mid-wall lower insertion point fibrosis (Fig. 2A). This was observed in 5 endurance athletes (62.5% of all cases with fibrosis in that group) and in 1 control subject. In 3 other athletes a mid-wall or sub-epicardial, linear, very limited LGE was observed in the infero-lateral LV segments (2 cases) or in the interventricular septum (1 case) (Fig. 2B). There were no cases of ischemic (sub-endocardial) LGE.

Subsequent analysis did not find differences in structural parameters (LVEDVI, RVEDVI, LVEF, RVEF) between ultra-marathon runners with LGE and without LGE, as well as for athletes with different patterns of fibrosis. The only significant difference found was higher RVEDVI in athletes with insertion point fibrosis than those without LGE (median 139.5 ml vs. 123 ml p = 0.04).

### 3.4. Parametric imaging

The application of parametric mapping demonstrated no difference between both studied groups in terms of pre- and post-contrast T1 relaxation times and ECV values. In all cases the respective values remained within the reference range [18,19]. Interestingly, athletes had higher T2 relaxation time in comparison to controls.

No difference was found in terms of T2 relaxation time and ECV values between athletes with and without LGE or with various patterns of LGE.

## 4. Discussion

### 4.1. Structural changes

We have demonstrated that the volume of ventricles in athletes is increased by over 40% in comparison to the control group. This is more than the 10–15% typically observed in endurance athletes [3,11–13]. An explanation for that could be the use of volumetric rather than linear measurements of ventricular size used in echocardiographic studies in athletes [3,11–13]. This is supported by the lack of such extreme adaptive changes in terms of linear dimensions measured in our group. In fact, a 3D echocardiographic study (volumetric analysis) in Olympic athletes found that LV end-diastolic volume was on average 50% higher than in untrained subjects [20]. Another reason may be the choice of a studied group consisting of ultra-marathon runners where adaptive changes can be increased to the extreme by presumptive long periods of volumetric overload related to long training hours and the frequent participation in long-distance competitions. Mean biventricular size found in our study group was similar to the recently published normal CMR reference values in male athlete's heart, but with higher upper limits [21]. One could argue that our relatively small control group might have influenced these differences, but the reference values in our control group and published normal values of CMR were similar [22,23].

Structural remodelling of the ventricles is paralleled by atrial enlargement. We observed a lower relative increase of the left atrial size in comparison to ventricular size between athletes and controls, but a similar degree of increase of the right atrial area. The lower left atrial changes may be due to the fact that we used area instead of volume to assess atrial size, but it also suggests that the chamber most prone to adaptive enlargement is the right atrium, where area changes were similar to the volumetric changes observed in the ventricles. The reason for that remains unknown. Another adaptive change observed in athletes consisted of increased left ventricular (but not right ventricular) mass, which was mainly secondary to increased ventricular volume and not muscle hypertrophy.

The previously underestimated degree of adaptive volumetric structural changes of the heart in this group should raise caution when suspecting the presence of cardiomyopathy. Most of those athletes would fulfil the volumetric criteria for dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy. Therefore those criteria, at least to the degree studied, should not lead to suspicion of cardiomyopathy in the absence of other changes not observed in healthy athletes such as globally decreased left or right ventricular function or the presence of regional wall motion abnormalities and/or symptoms and changes observed in other tests, as elegantly depicted in summative papers [24,25].

### 4.2. Myocardial fibrosis

In our study there were no signs of significantly increased fibrosis in athletes in comparison to controls, neither in cases of focal areas of fibrosis analysed by LGE nor diffuse fibrosis assessed with pre-and post-contrast T1-mapping or ECV. Similar findings have been recently reported in another study of myocardial fibrosis using parametric imaging

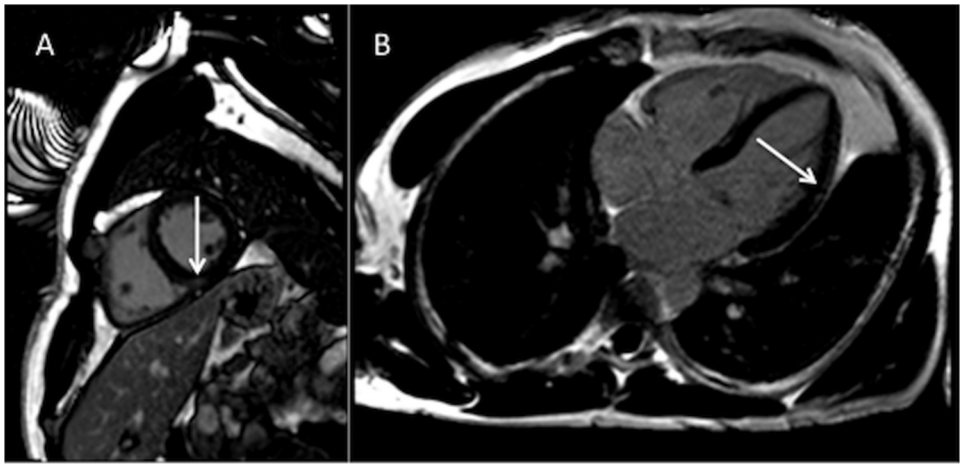


**Fig. 2.** Patterns of focal fibrosis observed in the study groups.
A. Short axis view of non-ischemic, mid-wall insertion point LGE (arrow) observed in athletes and in controls, B. 4-chamber view of non-ischemic sub-epicardial/mid-wall LGE (arrow) observed in athletes

on a group of triathletes, with only T1 relaxation time lower in athletes [10]. Mordi et al. demonstrated lack of significant changes in terms of fibrosis between athletes and controls [26]. In contrary, McDiarmid et al. found decreased ECV in endurance athletes [27], which was attributed to increased cardiomyocyte mass relative to extracellular volume as the main contributor to increased left ventricular mass in endurance athletes. The difference between McDiarmid's study and other reported studies on diffuse fibrosis was a significantly lower mean age of participants (over a decade in some cases), which may have influenced the results. It may be hypothesized that the difference in ECV between athletes and controls diminishes with age or with cumulative lifetime amount of training. However, to analyse that, other studies including athletes > 50 years of age would be necessary.

There were two non-ischemic patterns of LGE observed in the athletes we studied. Both types have been previously reported in athletes and the normal population [8]. Firstly, mid-wall fibrosis in the lower insertion point was also found in one patient from the control group. This type of fibrosis was reported not only in athletes and normal subjects, but also in patients with pulmonary arterial hypertension or hypertrophic cardiomyopathy with left ventricular outflow tract obstruction [28,29]. It is believed to be caused by volume or pressure overload, but does not seem to affect prognosis [28,29]. We have demonstrated for the first time in athletes that volume overload may indeed be the reason for such changes. In our group, athletes with this type of fibrosis had higher end-diastolic right ventricular volume in comparison to athletes without LGE. Secondly; sub-epicardial or mid-wall LGE in the infero-lateral segments or in the interventricular septum is most typical for previous, often subclinical, myocarditis [30]. High intensity training may compromise the immunological system and predispose these individuals to myocarditis in cases of seasonal viral respiratory tract infections [31,32]. However, small, silent, mid-wall areas of fibrosis have also been found in almost 4% of general population [33]. If these presumably post-myocarditis residual changes are limited in size, such as in our study, they do not seem to carry increased risk of arrhythmias. However, if they are large and form striae of fibrosis they may be responsible for ventricular arrhythmias as demonstrated in earlier studies [34,35]. We did not observe in our athletes a third pattern of fibrosis that has been observed in this population, which is ischemic, sub-endocardial fibrosis [8]. This may be due to the fact that we studied a relatively young cohort of athletes, while this type of focal fibrosis, typically secondary to silent myocardial infarction, is more commonly detected in veteran athletes over 50 year of age [8]. Also, contrary to other studies, we did not find increased ECV in the remote myocardium in athletes with LGE, which suggests that fibrosis is these cases is limited to observed areas of LGE [10].

Interestingly, we have for the first time demonstrated the use of T2-mapping in endurance athletes and found prolonged values in this group in comparison to controls. Increased values of T2 relaxation time were reported previously in patients with myocardial oedema such as in case of acute myocarditis [9]. However, these values were much higher than observed in our study. One of the explanations for our findings may be a previously described inverse relationship between heart rate and T2 relaxation time [36,37]. Similar inverse correlation was found in our group ($r = -0.40$, $p = 0.01$), which was however not the case for pre- or post-contrast T1 relaxation time. It may therefore be difficult to draw any conclusions from T2-mapping in athletes. One could expect that higher T2 relaxation times in athletes may also come from the fact that these individuals were during their peak training and racing season and thus might have signs of transient myocardial injury. This is unlikely, however, as prolongation of T2 relaxation times are usually paralleled by increase of T1 relaxation times and this was not the case in our study. We did not measure markers of cardiac necrosis, but all of the CMR studies were performed days apart from any ultra-marathon start.

### 4.3. Limitations

There are some limitations to our study. First of all, we were able to study only white, male subjects and it would be interesting to see how gender and race influence the observed changes. We focused on long-time athletes, but not veteran professionals or semi-professional athletes per se, as our participants started high-endurance training at 30 years of age and were examined over a decade later. This is a common group of athletes, but their baseline characteristics should be taken into consideration when comparing our results with other studies on athletes in terms of lifetime amount of training. Finally, we were unable to assess the relation between the presence of fibrosis and cardiac events or arrhythmias. However, none of the athletes demonstrated arrhythmias on ECG, presented any symptoms, or had any significant medical history.

## 5. Conclusions

Ultra-marathon runner's hearts demonstrate a high degree of structural remodelling in comparison to controls, including symmetric increases of left and right ventricular volume, higher bi-atrial size and left ventricular mass with unchanged systolic function of both ventricles. Myocardial wall thickness does not change significantly which

leads to preserved left ventricular geometry or eccentric remodelling. There is no significant increase in focal or diffuse myocardial fibrosis (as assessed by LGE and T1-mapping) in comparison to controls.

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## Declarations of interest

None.

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