Non-ischaemic fibrosis in male veteran endurance athletes: mechanisms and association with premature ventricular beats

Maryum Farooq  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Louise AE Brown  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Andrew Fitzpatrick  
Cardiac Investigations Unit, Leeds Teaching Hospitals NHS Trust

David A Broadbent  
Medical Physics and Engineering, Leeds Teaching Hospitals NHS Trust

Ali Wahab  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Joel Klassen  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Jonathan Farley  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Christopher ED Saunderson  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Arka Das  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Thomas Craven  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

Erica Dall’Armellina  
Biomedical Imaging Sciences Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds
Research Article

**Keywords:** Cardiovascular magnetic resonance, myocardial fibrosis, veteran athlete, ventricular arrhythmia

**Posted Date:** December 16th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-2378595/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.

Read Full License
Abstract

Purpose

Left ventricular fibrosis can be identified by late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) in some veteran athletes. We aimed to investigate prevalence of ventricular fibrosis in veteran athletes and its association with cardiac arrhythmia.

Methods

Fifty asymptomatic male endurance athletes (inclusion criteria: age ≥50, >10 hours/week training for >15 years) and 26 matched controls were recruited. They underwent CMR imaging including volumetric analysis, bright blood (BB) and dark blood (DB) LGE, motion corrected (MOCO) quantitative stress and rest perfusion and T1/T2/extracellular volume mapping. Athletes underwent 12-lead electrocardiogram (ECG) and 24-hour ECG.

Results

Myocardial fibrosis was identified in 24/50 (48%) athletes. All fibrosis was mid-myocardial in the basal-lateral wall of the left ventricle. Blood pressure was reduced in athletes without fibrosis compared to controls, a trend not seen in athletes with fibrosis. Fibrotic areas compared to healthy myocardium had longer T2 time (44±4 vs 40±2ms, p<0.0001), lower rest myocardial blood flow (MBF, 0.5±0.1 vs 0.6±0.1ml/g/min, p<0.0001) but no difference in stress MBF. On 24-hour ECG monitoring, athletes with fibrosis had a greater burden of premature ventricular beats (0.3±0.6 vs 0.05±0.2%, p=0.03), with higher prevalence of ventricular couplets and triplets (33 vs 8%, p=0.02).

Conclusion

In veteran endurance athletes, myocardial fibrosis is a common finding. Possible mechanisms for fibrosis include inflammation and blood pressure. Presence of myocardial fibrosis is associated with an increased burden of ventricular ectopy. Further studies are needed to establish whether fibrosis increases risk of malignant arrhythmic events.

Introduction

Sedentary lifestyle leads to shortened life expectancy and increased cardiovascular risk. Even moderate amounts of exercise can reduce cardiovascular risk via improvements in blood pressure, lipid profile and insulin resistance [1, 2]. Most developed countries recommend a minimum weekly amount of moderate intensity exercise. The British Association of Sports and Exercise Sciences recommends a minimum of 150 minutes moderate intensity or 75 minutes high intensity exercise per week [3].

Habitual moderate intensity exercise improves all cause and cardiovascular mortality, but it remains unclear if these benefits extend to those who participate in high intensity exercise into later life. Whilst
some studies have shown lower mortality in elite endurance athletes [4], others suggesting a loss of benefit have received significant attention from the popular media [5].

Several studies have reported myocardial fibrosis detected by late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) in veteran athletes although both pattern and prevalence (4-14%) have varied [6-8]. The presence of non-ischaemic fibrosis is associated with adverse outcomes including ventricular arrhythmia in a variety of conditions including dilated, hypertrophic and arrhythmogenic cardiomyopathies [9]. It is unknown whether non-ischaemic fibrosis is associated with adverse outcomes in healthy lifelong athletes.

The aim of this study was to evaluate the prevalence of myocardial fibrosis in male veteran athletes. We also aimed to evaluate associated clinical and sporting factors and if fibrosis was associated with abnormalities on the 12-lead electrocardiogram (ECG) and 24-hour cardiac monitor.

Materials And Methods

Participants

Athletes were recruited through advertisements at local cycling and triathlon clubs. Male athletes aged fifty and above who undertook >ten hours of training a week for >fifteen years and competed regularly were recruited. Age matched male sedentary control subjects who trained <3 hours per week were also recruited. Exclusion criteria for all participants included prior cardiovascular disease, use of cardiac medications, smoking and contraindication to CMR. The study was approved by the University of Leeds Research Ethics Committee and all participants gave written informed consent.

In a single visit, athletes underwent clinical assessment, contrast enhanced CMR, 12-lead and twenty-four hour ECG monitoring. Clinical assessment included body composition analysis (RD-545, Tanita, Tokyo, Japan). Both 12-lead ECG (MAC500, GE Medical Systems, Milwaukee, WI, USA) and 24-hour ECG monitoring (Lifecard CF holters, Spacelabs Healthcare, Washington, USA) analyses were blinded to clinical details [10]. Participants were also asked to report their lifetime competition history using a standardised questionnaire. For socioeconomic deprivation, publicly available data on English indices of multiple deprivation for 2019 was used [11], and deciles allocated based on participants postcodes.

Cardiovascular Magnetic Resonance Protocol

Participants underwent CMR on a 3.0 Tesla system (Prisma, Siemens Healthineers, Erlangen, Germany). All participants abstained from caffeine for twenty-four hours prior to the scan. A full blood count, for measurement of haematocrit, was taken at the time of intravenous cannulation prior to each CMR study.

Left ventricle function (cine) imaging was performed in standard long and short axis planes using a fast gradient echo sequence prior to contrast administration (10-12 slices, slice thickness 10mm with no gap, 25 cardiac phases).
Mapping and perfusion imaging were acquired in four short axis slices planned at end-systole (apex, mid, base and outflow levels). Imaging at the outflow level was included as this is a common site for fibrosis in athletes [12]. Native T1 mapping used a breath-held 5s(3s)3s Modified Look-Locker Inversion recovery (MOLLI) acquisition.

Hyperaemia was induced using an intravenous adenosine infusion at 140-210mcg/kg/min with dose increased if no symptomatic or haemodynamic response. Perfusion imaging was acquired using a previously validated automated method incorporating in-line motion correction and myocardial blood flow (MBF) quantification [13]. Data were acquired in four slices with the arterial input function measured from the basal slice to avoid outflow tract. Rest perfusion images were acquired once the effects of adenosine had subsided, at least fifteen minutes after the final stress perfusion sequence. Intravenous gadobutrol (Gadovist®, Bayer Pharma, Berlin, Germany) was administered at a dose of 0.05mmol/kg for each of stress, rest and top up.

Bright blood (BB) late gadolinium enhancement (LGE) was carried out six minutes after final contrast administration using a T1-weighted, segmented inversion-recovery sequence in multiple planes (free-breathing with MOCO). A further short axis stack of dark blood (DB) images with complete LV coverage were acquired [14].

Post contrast T1 mapping was carried out >15 minutes after final contrast injection using 4s(1s)3s(1s)2s MOLLI acquisition with positioning and planning as per the native T1 map.

**Cardiovascular Magnetic Resonance Analysis**

The CMR data was analysed using cvi42 software (Circle Cardiovascular Imaging Inc. Calgary, Canada). The protocol is summarised in Figure 1. Epicardial and endocardial borders were drawn on short axis cine stacks to calculate LV mass, LV and RV end-diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV) and ejection fraction (EF). Parameters were indexed to body surface area, calculated using the Mosteller equation.

The presence of fibrosis was assessed blinded to other results and was only included if it could be detected on at least two of BB LGE, DB LGE or ECV mapping. Myocardial fibrosis was quantified on short axis LGE images using the full width at half maximum (FWHM) technique.

Pre and post-contrast myocardial T1 values were measured from the basal and mid-ventricular short axis whole slices using 3-parameter exponential fit with Look-Locker correction. ECV was calculated using haematocrit, native and post-contrast T1 times for myocardium and blood pool as previously described [15]. Global T1, T2, ECV and MBF were measured from the basal and mid-ventricular short axis slices excluding areas of fibrosis. They were also measured in fibrotic and remote tissue by drawing regions of interest planned from LGE imaging.

For global measures apical and outflow tract slices were not included to avoid partial volume effects in thin myocardium. After exclusion of enhancing myocardium intracellular and extracellular compartment
volume was calculated using equations previously reported [15].

Coronary artery disease was excluded by visual assessment of regional ischaemia in a coronary distribution.

**Statistical Analysis**

Statistical analysis was performed using SPSS 23.0 (IBM SPSS, Armonk, NY, USA). The Shapiro-Wilk test was used to assess for normal distribution. Continuous variables are expressed as mean ± SD if normally distributed, or median and interquartile range if non-normally distributed. Categorical variables are expressed as N (%). Continuous data were compared using Student’s t test, and categorical using chi-squared test. P<0.05 was considered statistically significant.

**Results**

**Demographics and Exercise History**

Fifty male athletes were recruited between August and December 2018, with a median age of 56 (IQR: 53-64) years. Forty-one of the participants were cyclists (average 662 competitions spanning 26 years) and nine were triathletes (average 171 competitions spanning 25 years). There was no significant difference in socioeconomic deprivation, as assessed by the index of multiple deprivation, between athletes with and without fibrosis. Participant characteristics are shown in Table 1.

**Presence and Extent of Myocardial Fibrosis**

LGE was detected in 24/50 (48%) participants compared with only 4/26 (15%) matched sedentary controls (P=0.005). In all athletes, the fibrosis was non-ischaemic, located in the mid-myocardium of the basal lateral wall of the left ventricle. Mean fibrosis volume in athletes was 3 ± 4ml.

**Clinical and CMR differences between Athletes with and without fibrosis**

There was no significant difference in age between healthy controls, athletes with fibrosis (LGE+) and athletes without fibrosis (LGE-). The control group had a higher weight and body fat percentage compared to LGE+ and LGE- athletes. There were no differences in blood pressure between athletes with and without fibrosis, but LGE- athletes had significantly lower systolic and diastolic blood pressure than controls (113/70 vs 129/79mmHg). This pattern was not seen in LGE+ athletes. Participant characteristics according to presence of fibrosis are shown in Table 1.

The control group had lower left ventricular mass, left and right ventricular end-diastolic volumes, and higher left ventricular ejection fraction. LGE+ and LGE- athletes had comparable LV mass, left and right
ventricular end-diastolic volumes and ejection fractions. In addition, there was no difference in rest or stress myocardial blood flow between LGE+ and LGE- athletes. CMR characteristics according to presence of fibrosis are shown in Table 2.

In regards to competition history, there was no difference between LGE + and LGE – athletes in any of the parameters including number, distance or time spent in competitions. Cycling and triathlon competition history according to presence of fibrosis are presented in the supplementary material.

**ECG differences between Athletes with and without fibrosis**

There were no differences in any measured 12-lead ECG parameters between LGE+ and LGE- athletes. On 24-hour ECG monitoring, athletes with fibrosis had a greater burden of premature ventricular beats (PVBs) (0.3±0.6 vs 0.05±0.2%, p=0.03), with higher prevalence of ventricular couplets and triplets (33 vs 8%, p=0.02). ECG and 24-hour monitor findings according to presence of fibrosis are shown in Table 3.

**Myocardial Characteristics in Athletes with fibrosis**

Fibrotic areas compared to healthy myocardium had higher native T1 (1367±83 vs 1249±19ms, p<0.0001), ECV (32±7 vs 23±2%, p<0.0001) and T2 (44±4 vs 40±2ms, p<0.0001) (Figure 2 and Table 4). Rest myocardial blood flow was lower in fibrotic tissue (0.5±0.1 vs 0.6±0.1ml/g/min, p<0.0001) but there was no difference in stress myocardial blood flow.

**Discussion**

We have demonstrated a 48% prevalence of myocardial fibrosis in veteran endurance athletes (compared with 15% in matched sedentary controls). There were no differences in any measured 12-lead ECG or CMR parameters between athletes with and without fibrosis. Athletes without fibrosis had lower blood pressure than controls, possibly implicating subclinical hypertension in the aetiology of fibrosis. Fibrotic areas of myocardium also had higher T2 values, suggesting a possible inflammatory mechanism. Furthermore, athletes with fibrosis had a greater burden of PVBs, with higher rates of ventricular couplets and triplets (Figure 3).

**Prevalence of Fibrosis in Veteran Endurance Athletes**

We identified myocardial fibrosis in 48% of veteran athletes in this study. In previous studies, myocardial fibrosis was found in 4-14% of athletes with age >50 [6-8] and 9-17% in athletes age <50 years [12, 16]. Direct comparison with former studies is difficult due to different inclusion criteria and imaging techniques. There are several possible reasons why prevalence of fibrosis was increased in our study. Firstly, our inclusion criteria were relatively strict and we only included athletes with very high levels of competitive exercise. The stipulation of >15 years of training at this level meant that athletes had a very
high cumulative exposure of exercise. Secondly the average age of athletes in our study was older than any other contemporary study again increasing the lifetime exercise dose. Thirdly we have only studied male athletes, who are known to have a higher prevalence of fibrosis than females [7, 12]. Finally, we have used novel imaging techniques such as MOCO, DB LGE and ECV mapping that allowed us to identify relatively small areas of fibrosis with high diagnostic certainty.

The fibrosis identified in our study was exclusively mid-myocardial in the basal inferolateral segment. This pattern of fibrosis is the most commonly reported in other studies with similar inclusion criteria [6, 7, 12]. Tahir et al reported prevalence of fibrosis in 17% of male triathletes training >10 hours per week, with no fibrosis identified in female triathletes or controls [12]. Fibrosis was associated with exercise-induced hypertension and the cumulative distance raced. Other patterns of fibrosis including RV insertion point fibrosis in 38% [17] and ischaemic fibrosis in 5-7% have also been reported in athletes [6, 7].

**Possible Mechanisms for Fibrosis**

**Myocarditis/Inflammation**

All fibrosis detected in our study was mid-myocardial, in the basal lateral wall of the left ventricle. Similar patterns have been reported in patients with prior myocarditis. In the acute phase of myocarditis, subepicardial hyperenhancement in the basal lateral segment is the most common finding on LGE imaging [18]. However, in the chronic phase, after six months, the region of hyperenhancement shrinks and organises giving more varied patterns including mid-myocardial hyperenhancement similar to the pattern identified in our study [19].

Although no participant reported a history of clinically diagnosed myocarditis, subclinical myocarditis in participants cannot be excluded. Furthermore, it has been speculated that exercising during a viral illness can exacerbate myocarditis. Cabinian et al infected mice with coxsackievirus to induce myocarditis. Mice were assigned to groups for immunosuppressant therapy, exercise, both or none. After 21 days, mortality was greatest in the exercise group [20] suggesting exercise exacerbates myocardial damage.

In this present study, the T2 time was prolonged in regions of fibrosis, suggesting a possible inflammatory component. Initial screening studies of athletes affected by COVID-19 infection have suggested a variable prevalence of myocarditis [21][22]. Athletes in our study were scanned before the emergence of COVID-19 and future studies will be needed to establish if the pandemic leads to increased levels of long-term myocardial fibrosis in athletes.

**Subclinical Hypertension**

Athletes with myocardial fibrosis in our study had blood pressure which was similar to sedentary controls, whereas those without fibrosis had significantly lower blood pressure. Whilst the blood pressures recorded at rest in our study were well within the normal range it is well recognised that during sport there can be marked increases in blood pressure (particularly systolic). Tahir et al previously noted that young
athletes with non-ischaemic fibrosis had an increased incidence of hypertension during exercise [12]. The pattern of fibrosis seen in arterial hypertension is predominantly mid-myocardial and can affect any segment of the left ventricle although mid and basal inferior and inferolateral segments are the most commonly affected [23], and it is possible that exercise-induced hypertension may be a contributor to the findings of our study.

**Ischaemic Heart Disease**

Previous studies have identified ischaemic patterns of fibrosis in veteran athletes, although both studies predominantly examined runners [6, 7]. Merghani et al reported that male veteran athletes had a higher prevalence of coronary atherosclerotic plaques (44.3% versus 22.2%) compared with sedentary males with similar risk profile, however there was no association between the presence of atherosclerotic plaques and fibrosis. In our cohort of male athletes, there was no evidence of ischaemic subendocardial fibrosis or inducible ischaemia on stress perfusion imaging suggesting that asymptomatic coronary artery disease is unlikely to be the main mechanism for fibrosis.

**Chronic Volume Loading**

A similar pattern of basal lateral fibrosis has been reported in patients with chronic mitral regurgitation secondary to primary mitral valve disease. Long term participation in endurance sport may similarly lead to chronic volume loading of the left ventricle, with subsequent fibrosis from mechanical remodelling. In these patients with chronic mitral regurgitation basal lateral midwall fibrosis appears to be associated with ventricular arrhythmia [24, 25].

**Association between Fibrosis and Ventricular Arrhythmia**

This study has demonstrated a greater percentage of PVBs, including couplets and triplets, on 24-hour ECG monitoring of veteran endurance athletes with myocardial fibrosis compared to athletes without fibrosis. The presence of non-ischaemic fibrosis is associated with adverse outcomes including ventricular arrhythmia in a variety of conditions including dilated, hypertrophic and arrhythmogenic cardiomyopathies [9]. In non-athletic patients the presence and burden of ventricular ectopy are markers of incident heart failure and mortality [26]. The relationship between PVBs and outcomes is less clear in athletes. According to the 2015 recommendations of the American Heart Association and the American College of Cardiology, athletes with PVBs or couplets should be considered for imaging including CMR to identify cardiomyopathies, anomalous coronary artery origins, and subclinical myocarditis. In the absence of structural heart disease athletes should be considered eligible for all competitive sports but the recommended intensity of exercise is to remain under the threshold for the occurrence of arrhythmia-related symptoms such as presyncope, syncope or dyspnoea [27]. Prospective evidence that athletic myocardial fibrosis leads to ventricular arrhythmia is lacking. However, there are preclinical and retrospective data from symptomatic athletes that suggest myocardial fibrosis may be a substrate for ventricular arrhythmia. Rats forced to run an hour a day for up to 16 weeks develop physiological
myocardial hypertrophy and dilation [28]. Alongside the physiological remodelling they also developed fibrosis predominantly affecting the atria and right ventricles. Ventricular tachycardia could be induced in 5 of 12 exercise rats (42%) and only 1 of 16 sedentary rats (6%; \( P=0.05 \)). Interestingly there was reversal of fibrosis after 8 weeks of exercise cessation. Only rats that could maintain the very intense exercise regime were studied (selection bias) and it is not clear whether the mechanisms of fibrosis in rats undergoing short-term intense exercise is the same as in humans after a lifetime of endurance training.

In two publications of 27 and 37 athletes suffering ventricular arrhythmia, non-ischaemic fibrosis was found by LGE CMR in 22% [29, 30]. Zorzi et al reported the most common pattern of fibrosis was subepicardial/midmyocardial affecting the basal lateral wall in 77% of those with fibrosis [30]. Subjects for these studies were identified retrospectively after they presented with ventricular arrhythmia making findings vulnerable to selection bias. Furthermore, it is unclear as to what extent the fibrosis was caused by athletic training, co-existent cardiomyopathy or a combination of both.

Our data demonstrate that non-ischaemic fibrosis is common in high performance veteran athletes and is associated with ventricular ectopy. Further studies are needed to establish if non-ischaemic fibrosis is responsible for excess risk in veteran endurance athletes and the U-shaped association between exercise intensity.

**Limitations**

This small sample of veteran athletes underwent a limited duration of ECG monitoring, the duration of which was insufficient to capture malignant arrhythmias. Although we identified differences in PVBs rates, this may not necessarily reflect arrhythmic event rates in the future. Hence, long term studies reporting such events in such cohorts are required. As participants underwent 3-lead monitoring, precise localisation of the PVBs is not possible. Whilst there was no statistically significant different in blood pressure between groups, we cannot rule out variable exercise-induced blood pressure responses between groups.

Our findings in relation to competition history are based on self-reported data, which relies on the accuracy of recall of the athletes. The association with objective levels of fitness cannot be ruled out as participants did not undergo cardiopulmonary exercise tests. We also only recruited cyclists and triathletes; hence these findings may not be representative of other sports.

**Conclusions**

In veteran endurance athletes, myocardial fibrosis is a common finding. Screening by 12-lead ECG is insufficient to detect fibrosis. Possible mechanisms for fibrosis include inflammation and elevated arterial blood pressure. Presence of myocardial fibrosis is associated with an increased burden of ventricular ectopy. Further studies are needed to establish whether fibrosis increases risk of malignant arrhythmic events.
Abbreviations

BB LGE  Bright blood late gadolinium enhancement
CMR    Cardiovascular magnetic resonance
DB LGE  Dark blood late gadolinium enhancement
ECV    Extracellular volume fraction
LGE    Late gadolinium enhancement
MBF    Myocardial blood flow
MOCO   Motion corrected
MOLLI  Modified Look Locker inversion recovery

Declarations

Funding: This work was supported by the National Institute for Health Research, Leeds Clinical Research Facility and British Heart Foundation grants (CH/16/2/32089 and PG/21/10322).

Competing interests: The authors declare that they have no competing interests.

Authors’ contributions: MF- acquisition, analysis and interpretation of data in addition to statistical analysis and manuscript preparation. LAEB, AF, DAB, AW and JRLK- data acquisition and analysis. JF, CEDS, AD, TC, ED, EL, HX, PK, JPG and SP- study design and critical evaluation. PPS- study design, data acquisition, analysis and interpretation in addition to statistical analysis and manuscript preparation. All authors read and approved the final manuscript.

Ethics approval: The study was approved by the University of Leeds Research Ethics Committee.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Acknowledgements: We thank for their assistance David Shelley, Gavin Bainbridge and Margaret Saysell (CMR radiographers), and Petra Bijsterveld (CMR clinical research nurse).

References

1. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and


27. Zipes DP, Link MS, Ackerman MJ, Kovacs RJ, Myerburg RJ, Estes NAM, 3rd. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities:


Tables

Table 1: Clinical characteristics of control group and athletes according to the presence of fibrosis.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Control</th>
<th>Athlete LGE-</th>
<th>Athlete LGE+</th>
<th>P value Control vs LGE- athlete</th>
<th>P value Control vs LGE+ athlete</th>
<th>P value LGE- vs LGE+ athlete</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>26</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61.6 ± 7.6</td>
<td>56.8 ± 6.4</td>
<td>61.4 ± 8.0</td>
<td>0.067</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.6 ± 9.9</td>
<td>73.7 ± 6.9</td>
<td>72.9 ± 8.6</td>
<td><strong>0.001</strong></td>
<td><strong>&lt;0.001</strong></td>
<td>1.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.8 ± 6.9</td>
<td>175.3 ± 4.2</td>
<td>172.3 ± 6.1</td>
<td>1.0</td>
<td>0.42</td>
<td>0.23</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>24.9 ± 6.2</td>
<td>16.8 ± 4.3</td>
<td>17.8 ± 3.8</td>
<td><strong>&lt;0.001</strong></td>
<td><strong>&lt;0.001</strong></td>
<td>1.0</td>
</tr>
<tr>
<td>Lean muscle mass (kg)</td>
<td>59.5 ± 5.2</td>
<td>57.8 ± 4.1</td>
<td>56.6 ± 6.3</td>
<td>0.98</td>
<td>0.32</td>
<td>1.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.4 ± 17.8</td>
<td>113.4 ± 22.9</td>
<td>123.2 ± 13.4</td>
<td><strong>0.008</strong></td>
<td>0.72</td>
<td>0.20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.5 ± 7.1</td>
<td>70.2 ± 7.5</td>
<td>75.1 ± 8.0</td>
<td><strong>&lt;0.001</strong></td>
<td>0.35</td>
<td>0.07</td>
</tr>
<tr>
<td>Heart rate</td>
<td>64.0 ± 11.3</td>
<td>54.5 ± 9.8</td>
<td>53.1 ± 7.1</td>
<td><strong>0.002</strong></td>
<td><strong>&lt;0.001</strong></td>
<td>1.0</td>
</tr>
<tr>
<td>Index of Multiple Deprivation (Decile)</td>
<td>-</td>
<td>7.27 ± 2.31</td>
<td>7.04 ± 2.82</td>
<td>-</td>
<td>-</td>
<td>0.76</td>
</tr>
<tr>
<td>Training volume (hours per week)</td>
<td>-</td>
<td>11.4 ± 1.8</td>
<td>11.4 ± 2.0</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>Cumulative training (years)</td>
<td>-</td>
<td>24.7 ± 10.8</td>
<td>27.7 ± 14.1</td>
<td>-</td>
<td>-</td>
<td>0.40</td>
</tr>
<tr>
<td>Discipline:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycling</td>
<td>-</td>
<td>20</td>
<td>21</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Triathlon</td>
<td>-</td>
<td>6</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.

LGE- = Fibrosis absent; LGE+ = Fibrosis present.

Table 2: CMR characteristics of control group and athletes according to presence of fibrosis.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Control</th>
<th>Athlete LGE-</th>
<th>Athlete LGE+</th>
<th>P value Control vs LGE- athlete</th>
<th>P value Control vs LGE+ athlete</th>
<th>P value LGE- vs LGE+ athlete</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV indexed to BSA (ml/m²)</td>
<td>82.9 ± 16.5</td>
<td>104.7 ± 15.1</td>
<td>108.0 ± 16.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>63.6 ± 4.3</td>
<td>58.2 ± 6.2</td>
<td>58.2 ± 5.0</td>
<td>0.001</td>
<td>0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>LV mass indexed to BSA (g/m²)</td>
<td>57.9 ± 8.7</td>
<td>75.7 ± 7.7</td>
<td>80.1 ± 11.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>RVEDV indexed to BSA (ml/m²)</td>
<td>90.3 ± 15.7</td>
<td>106.8 ± 17.2</td>
<td>109.7 ± 19.2</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>57.5 ± 7.0</td>
<td>56.8 ± 8.8</td>
<td>54.7 ± 7.9</td>
<td>1.0</td>
<td>0.64</td>
<td>1.0</td>
</tr>
<tr>
<td>Fibrosis on LGE (%)</td>
<td>4 (15)</td>
<td>0 (0)</td>
<td>24 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ischaemic fibrosis</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-ischaemic fibrosis</td>
<td>3 (12)</td>
<td>0 (0)</td>
<td>24 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Global native T1 (ms)</td>
<td>1268.6 ± 39.6</td>
<td>1250.6 ± 19.4</td>
<td>1248.0 ± 19.0</td>
<td>0.07</td>
<td>0.03</td>
<td>1.0</td>
</tr>
<tr>
<td>Extracellular volume fraction (%)</td>
<td>23.7 ± 1.6</td>
<td>23.1 ± 1.6</td>
<td>22.6 ± 1.9</td>
<td>0.58</td>
<td>0.07</td>
<td>0.95</td>
</tr>
<tr>
<td>Global T2 (ms)</td>
<td>41.7 ± 2.7</td>
<td>40.5 ± 1.7</td>
<td>40.1 ± 1.7</td>
<td>0.16</td>
<td>0.04</td>
<td>1.0</td>
</tr>
<tr>
<td>Stress Myocardial Blood Flow (ml/g/min)</td>
<td>1.9 ± 0.5</td>
<td>2.3 ± 0.7</td>
<td>2.2 ± 0.6</td>
<td>0.13</td>
<td>0.49</td>
<td>1.0</td>
</tr>
<tr>
<td>Rest Myocardial Blood Flow (ml/g/min)</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.30</td>
<td>0.84</td>
<td>1.0</td>
</tr>
<tr>
<td>Myocardial Perfusion Reserve</td>
<td>3.1 ± 0.9</td>
<td>4.1 ± 1.2</td>
<td>3.9 ± 1.3</td>
<td>0.015</td>
<td>0.11</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Athlete LGE-</td>
<td>Athlete LGE+</td>
<td>P value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR interval (ms)</strong></td>
<td>181.0 ± 33.5</td>
<td>180.4 ± 46.2</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QRS duration (ms)</strong></td>
<td>97.6 ± 7.9</td>
<td>97.0 ± 7.9</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QTc (ms)</strong></td>
<td>402.6 ± 84.0</td>
<td>419.3 ± 29.7</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early repolarisation (n, %)</strong></td>
<td>9 (34.6)</td>
<td>12 (50.0)</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T wave inversion (n, %)</strong></td>
<td>0 (0)</td>
<td>2 (8.3)</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sokolow-Lyon criteria for LVH (n, %)</strong></td>
<td>16 (61.5)</td>
<td>11 (45.8)</td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Minimum heart rate</strong></td>
<td>45.1 ± 6.1</td>
<td>43.9 ± 5.4</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum heart rate</strong></td>
<td>119.3 ± 26.9</td>
<td>120.3 ± 30.4</td>
<td>0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proportion of time bradycardic (%)</strong></td>
<td>6.5 ± 13.0</td>
<td>6.3 ± 11.2</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of pauses</strong></td>
<td>490.9 ± 1663.8</td>
<td>201.2 ± 513.2</td>
<td>0.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Longest pause (s)</strong></td>
<td>1.2 ± 1.1</td>
<td>1.1 ± 1.1</td>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of PVBs</strong></td>
<td>31.1 ± 96.1</td>
<td>201.5 ± 449.9</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percentage PVBs (%)</strong></td>
<td>0.05 ± 0.2</td>
<td>0.3 ± 0.6</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients with couplets/triplets (n, %)</strong></td>
<td>2 (7.7)</td>
<td>8 (33.3)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, median (interquartile range) or n (%).

LGE- = Fibrosis absent; LGE+ = Fibrosis present; PVB = Premature ventricular beats.
Table 4: Characteristics of fibrotic myocardium and remote regions from LGE+ athletes.

<table>
<thead>
<tr>
<th></th>
<th>Fibrotic region</th>
<th>Remote region</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native T1 (ms)</td>
<td>1366.9 ± 82.8</td>
<td>1249.4 ± 19.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extracellular volume fraction (%)</td>
<td>32.2 ± 6.6</td>
<td>22.9 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T2 time (ms)</td>
<td>44.3 ± 4.2</td>
<td>40.3 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stress Myocardial Blood Flow (ml/g/min)</td>
<td>2.4 ± 1.0</td>
<td>2.2 ± 0.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Rest Myocardial Blood Flow (ml/g/min)</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial Perfusion Reserve</td>
<td>5.1 ± 1.8</td>
<td>4.0 ± 1.2</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.

Figures
Participants underwent CMR on a 3.0 Tesla Siemens Prisma system. The protocol consisted of cine, T1/T2 mapping, stress imaging using intravenous adenosine infusion, bright and dark blood imaging. LV = Left ventricle. LGE = Late gadolinium enhancement.
**Figure 2**

**Fibrotic myocardial tissues characterisation.** Multiparametric tissue characterisation of a single veteran athlete showing basal lateral mid wall fibrosis on bright blood LGE (upper left), dark blood LGE (upper right), native T1 mapping (lower left) and ECV mapping (lower right).
Figure 3

**Non-Ischaemic Fibrosis in Veteran Endurance Athletes – Mechanisms and Association with Ventricular Ectopy.** 50 veteran endurance athletes underwent cardiac MRI, 12-lead and 24-hour ECG monitoring. Fibrosis was a common finding, identified in the basal lateral left ventricular wall in 48% of participants. Potential risk factors for myocardial fibrosis include inflammation and hypertension. The presence of fibrosis was associated with a greater burden of ventricular ectopics, including couplets and triplets. LGE = Late gadolinium enhancement. ECV = Extra-cellular volume.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.docx](#)