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ORIGINAL ARTICLE

Global and regional cardiac function in lifelong endurance athletes with and without myocardial fibrosis

THIJS M. H. EIJSVOGELS[1,2], DAVID L. OXBOROUGH[1], RORY O'HANLON[3], SANJAY SHARMA[4], SANJAY PRASAD[5], GREG WHYTE[1], KEITH P. GEORGE[1], & MATHEW G. WILSON[6]

[1]*Research Institute for Sports and Exercise Sciences, Liverpool John Moores University, Liverpool, UK;* [2]*Department of Physiology, Radboud University Medical Center, Nijmegen, Netherlands;* [3]*St. Vincent's University Hospital and The Blackrock Clinic, Dublin, Ireland;* [4]*Department of Heart Muscle Disorders and Sports Cardiology, St. Georges Hospital, London, UK;* [5]*Department of Cardiac Magnetic Resonance Imaging, Royal Brompton and Harefield National Health Service Trust, London, UK &* [6]*ASPETAR, Qatar Orthopaedic and Sports Medicine Hospital, Doha, Qatar*

Abstract
The aim of the present study was to compare cardiac structure as well as global and regional cardiac function in athletes with and without myocardial fibrosis (MF). Cardiac magnetic resonance imaging with late gadolinium enhancement was used to detect MF and global cardiac structure in nine lifelong veteran endurance athletes (58 ± 5 years, 43 ± 5 years of training). Transthoracic echocardiography using tissue-Doppler and myocardial strain imaging assessed global and regional (18 segments) longitudinal left ventricular function. MF was present in four athletes (range 1–8 g) and not present in five athletes. MF was located near the insertion points of the right ventricular free wall on the left ventricle in three athletes and in the epicardial lateral wall in one athlete. Athletes with MF demonstrated a larger end diastolic volume (205 ± 24 vs 173 ± 18 ml) and posterior wall thickness (11 ± 1 vs 9 ± 1 mm) compared to those without MF. The presence of MF did not mediate global tissue velocities or global longitudinal strain and strain rate; however, regional analysis of longitudinal strain demonstrated reduced function in some fibrotic regions. Furthermore, base to apex gradient was affected in three out of four athletes with MF. Lifelong veteran endurance athletes with MF demonstrate larger cardiac dimensions and normal global cardiac function. Fibrotic areas may demonstrate some co-localised regional cardiac dysfunction, evidenced by an affected cardiac strain and base to apex gradient. These data emphasize the heterogeneous phenotype of MF in athletes.

Keywords: *Exercise, cardiac remodelling, echocardiography, late gadolinium enhancement*

Abbreviations

A	late flow velocity
A′	late diastolic myocardial velocities
BMI	body mass index
CMR	cardiac magnetic resonance imaging
ε	myocardial strain
E	early flow velocity
E′	early diastolic myocardial velocity
LGE	late gadolinium enhancement
LV	left ventricular
MF	myocardial fibrosis
RV	right ventricular
S′	systolic myocardial velocity
SRA	late diastolic strain rate
SRE	early diastolic strain rate
SRS	systolic strain rate

Introduction

Habitual physical activity is known to improve cardiovascular health and reduces the risk for cardiovascular morbidity and mortality in a dose-dependent fashion (Eijsvogels & Thompson, 2015). High volumes of exercise training typically lead to cardiac remodelling which is characterized by biventricular

Correspondence: Thijs M. H. Eijsvogels, Research Institute for Sports and Exercise Sciences, Liverpool John Moores University, Byrom Street, Tom Reilly Building, L3 3AF Liverpool, UK. E-mail: t.m.eijsvogels@ljmu.ac.uk

enlargement, increased left ventricular (LV) wall thickness and left atrial enlargement (Utomi et al., 2013). These exercise-induced adaptations are generally considered benign, but emerging evidence suggests that cardiac mal-adaptations may occur in a minority of endurance athletes after chronic exercise training (Eijsvogels, Fernandez, & Thompson, 2016).

Myocardial fibrosis (MF), or scarring of the heart tissue, is commonly found after myocardial ischemia, inflammation or hypertensive overload as part of pathophysiological cardiac remodelling processes (Hill & Olson, 2008) and is a strong predictor for major adverse cardiac events (Kwong et al., 2008). MF has been reported in 7.9–19.8% of the general population using cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) (Barbier, Bjerner, Johansson, Lind, & Ahlstrom, 2006; Schelbert et al., 2012; Turkbey et al., 2015). Somewhat counterintuitively, a high prevalence of MF has also been observed in veteran endurance athletes, with evidence of LGE in 12–50% of some athletic populations (Breuckmann et al., 2009; La Gerche et al., 2012; Wilson et al., 2011). A recent study confirmed the higher prevalence of MF in male veteran athletes compared to age-matched controls (Merghani et al., 2017). The occurrence and magnitude of MF have been positively related to the volume of the lifelong exercise training (Breuckmann et al., 2009; La Gerche et al., 2012; van de Schoor et al., 2016; Wilson et al., 2011). In cardiac patients, MF is associated with an increased risk of arrhythmias (Kramer et al., 2014), an increase in myocardial stiffness and a reduction of cardiac function (Sugihara et al., 1988). The impact of MF in athletes upon global and co-localised regional cardiac function remains to be fully examined.

The aim of this study was to compare cardiac structure as well as global and regional cardiac function in athletes with and without MF. For this purpose, we performed CMR imaging and transthoracic echocardiography imaging utilising global and regional assessment of myocardial strain (ε) in a small cohort of lifelong veteran endurance athletes (Wilson et al., 2011). We hypothesize that athletes with MF will present with similar cardiac structure and global cardiac function as athletes without MF. We speculate that regional dysfunction may be co-localised with MF in some athletes.

Methods

Data from the present study represent a sub-analyses of previous work from our group (Wilson et al., 2011). Cardiac structure and function measurements were performed in a subsample ($n = 9$ out of $n = 12$) of veteran athletes (6 runners, 2 rowers and 1 triathlete) that performed lifelong exercise training on a high intensity/frequency. One participant was a former elite athlete, all other athletes were highly trained amateurs. As previously described (Wilson et al., 2011), participants were recruited via an advertisement placed in the United Kingdom's 100 Marathon running club newsletter and the British Olympic Association's "Olympian" magazine. Given the inclusion criteria, we anticipated on a small sample size in this case series manuscript. Athletes were 58 ± 5 years old, had a BMI of 24.1 ± 2.5 kg/m^2, reported 43 ± 5 years of continuous exercise training and were free from (known) cardiovascular diseases and diabetes upon inclusion. Participants were asked to limit their volume of exercise training (i.e., <20 miles/week or an equivalent exercise load) in the week prior to study participation, with no training in the 48 hours prior to any scheduled measurements. The study received ethical approval from the Royal Brompton Hospital and the National Heart and Lung Institute research ethics committee. All participants provided written informed consent and the study was performed in line with the Declaration of Helsinki.

A standard cardiac volume, wall dimension, function and LGE sequence was performed on a dedicated scanner (Siemens Avanto 1.5-T, Erlangen, Germany), with full myocardial coverage. Left and right ventricular volumes, mass and function were quantified using customized analysis software (CMRtools, Cardiovascular Imaging Solutions, London, UK) by a blinded, single experienced investigator. Papillary muscles were included in the mass and excluded from the volume.

Identification of MF was performed as previously described (Wilson et al., 2011). In brief, imaging for LGE was performed 5–10 min after gadolinium contrast injection in identical short-axis planes to cine images using a breath-hold inversion-recovery (fast low-angle shot) gradient echo sequence. Inversion times were optimized to null normal myocardium. In all participants, LGE imaging was repeated for each short-axis image in two separate phase-encoding directions to exclude artefact. LGE images were analyzed quantitatively by two independent readers using customized software (MRI-MASS, Medis, Leiden, the Netherlands).

All echocardiographic images were acquired using a commercially available ultrasound system (Vivid Q, GE Medical, Horten, Norway) with a 1.5–4 MHz phased array transducer. Images were obtained by an experienced sonographer with the participant in the left lateral decubitus position. Images were recorded to DVD in raw DICOM format and data

were analysed offline by a single experienced researcher using commercially available software (EchoPac version 7, GE Medical, Horten, Norway).

Standard pulsed wave Doppler of transmitral flow was used to obtain early (E) and late (A) flow velocities and their ratio was calculated (E/A). In addition, a 4 mm pulsed wave tissue-Doppler sample was applied to the septal and lateral annuli in order to provide systolic (S'), early diastolic (E') and late diastolic myocardial velocities (A'). An average of the two sites was calculated and E/E' was derived as a marker of LV filling pressure.

For the assessment of longitudinal LV strain (ε), 2D speckle tracking images of the left ventricle were acquired from apical four, two and three chamber orientations and were optimised in order to maximise the signal to noise ratio and endocardial delineation. Frame rates were ≥40 fps whilst a single focal zone was positioned at mid-chamber to reduce the impact of beam divergence (Oxborough, George, & Birch, 2012). Offline analysis involved a region of interest being placed transmurally in all three apical orientations. This provided ε from 18 myocardial segments including basal, mid and apical inferoseptum, lateral wall, inferior wall, anterior wall, posterior wall and antero-septum. Regional peak longitudinal ε and systolic, early diastolic and late diastolic strain rates were obtained for each segment and an overall (global) ε value was calculated as an average of all 18 segments.

To assess the impact of MF on regional ε data, we combined CMR imaging and echocardiography data. The location of MF from CMR images was matched to ε data from 18 myocardial segments on an individual basis. The ε data in the athletes with MF were compared with non-fibrotic segments within the athlete and with the average ε data in the same segments in all athletes without MF. The difference in ε ($\Delta\varepsilon$) between athletes without and with MF was calculated. Base to apex gradient (%) was calculated in the MF-affected cardiac wall using the four chamber view. Time to peak stain (milliseconds) was calculated similarly to local ε data.

Data are reported as mean ± standard deviation or percentage unless specified otherwise. We did not perform statistical analyses due to the low sample size of our study population. Alternatively, descriptive statistics were provided to compare cardiac structure and function between veteran athletes with and without MF.

Results

There was no evidence of MF in five athletes. LGE, and thus MF, was present in four athletes, representing 1–8 gram (g) of the myocardium. The LGE pattern was non-specific in three athletes, with MF located near the insertion points of the right ventricular free wall on the left ventricle. One athlete demonstrated MF in the epicardial lateral wall, consistent with a previous episode of myocarditis. Age, anthropometric characteristics, blood pressure, heart rate and training history did not differ between athletes with MF ($n = 4$) and without MF ($n = 5$) (Table I).

Table I. Subject characteristics of the veteran athletes with and without myocardial fibrosis.

	Without fibrosis ($N = 5$)	With fibrosis ($N = 4$)
Age (yrs)	59 ± 2	57 ± 8
Height (cm)	180 ± 7	179 ± 6
Weight (kg)	80 ± 14	75 ± 7
BMI (kg/m^2)	24.6 ± 3.1	23.5 ± 1.7
BSA (m^2)	2.0 ± 0.2	1.9 ± 0.1
SBP (mmHg)	123 ± 4	120 ± 9
DBP (mmHg)	78 ± 9	75 ± 6
HR (bpm)	58 ± 8	50 ± 6
Exercise training (yrs)	44 ± 2	42 ± 8
Type of athlete		
Runner (n)	4	2
Rower (n)	1	1
Triathlete (n)	0	1

Notes: BMI: body mass index; BSA: body surface area; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.

Athletes with MF demonstrated a larger left ventricle end diastolic volume (205 ± 24 vs 173 ± 18 ml) compared to athletes without MF. LV end systolic volume was comparable between both groups (Table II). Right ventricular end-diastolic and end systolic volumes were comparable between athletes with and without MF. Posterior wall thickness was significantly larger in MF athletes (11 ± 1 mm) compared to peers without MF (9 ± 1 mm).

Global peak diastolic Doppler flow and regional tissue-Doppler velocities are summarized in Table II. E, A, E/A ratio as well as E' and A' myocardial velocities and the E/E' ratio were comparable between groups. Also, average S' did not differ between athletes with and without MF (9 ± 2 vs 9 ± 2 cm/s). Global LV longitudinal ε and strain rate data are presented in Table II and did not differ between athletes with and without MF.

Segmental analyses of longitudinal ε, base to apex gradient and time to peak strain in fibrotic *versus* non-fibrotic regions were summarized in Table III. Case #1 had improved ε values compared to his own non-fibrotic segments (21.5% ± 4.9%) but also compared to athletes without MF across all three segments ($\Delta\varepsilon$ range: 4.7–7.5%). In contrast, Case #2

Table II. Cardiac indices, diastolic function, LV global strain and strain rate characteristics of athletes with and without myocardial fibrosis.

	Without fibrosis ($N = 5$)	With fibrosis ($N = 4$)
Cardiac indices (MRI)		
LVEDV (ml)	173 ± 18	205 ± 24
LVESV (ml)	61 ± 17	74 ± 13
LVSV (ml)	112 ± 6	131 ± 22
LVEF (%)	65 ± 6	64 ± 4
LV length (mm)	86 ± 6	91 ± 7
LV mass (g)	140 ± 16	154 ± 14
RVEDV (ml)	177 ± 16	198 ± 32
RVESV (ml)	64 ± 14	69 ± 20
RVSV (ml)	114 ± 7	129 ± 18
RVEF (%)	64 ± 5	66 ± 6
IVSd (mm)	10 ± 1	12 ± 2
PWd (mm)	9 ± 1	11 ± 1
Diastolic function (Echo)		
E (cm/s)	65 ± 6	62 ± 10
A (cm/s)	60 ± 11	58 ± 5
E/*A* ratio	1.1 ± 0.3	1.1 ± 0.2
Septal *E* (cm/s)	10 ± 2	10 ± 2
A (cm/s)	11 ± 2	11 ± 1
Lateral *E* (cm/s)	11 ± 1	14 ± 3
A (cm/s)	11 ± 2	11 ± 1
Average *E* (cm/s)	11 ± 1	12 ± 2
A (cm/s)	11 ± 2	11 ± 1
E/*E*	6 ± 1	5 ± 2
Longitudinal strain (Echo)		
2CH (%)	−22.7 ± 1.9	−21.9 ± 4.4
4CH (%)	−21.7 ± 2.9	−22.6 ± 3.5
APLAX (%)	−20.7 ± 4.5	−21.3 ± 5.2
Overall (%)	−21.7 ± 1.8	−22.0 ± 4.3
Longitudinal strain rate (Echo)		
2CH *S* (l/s)	−1.06 ± 0.16	−0.95 ± 0.21
E (l/s)	0.85 ± 0.11	0.93 ± 0.16
A (l/s)	0.75 ± 0.15	0.56 ± 0.13
4CH *S* (l/s)	−1.05 ± 0.18	−1.03 ± 0.20
E (l/s)	0.96 ± 0.22	1.02 ± 0.30
A (l/s)	0.66 ± 0.25	0.60 ± 0.21
APLAX *S* (l/s)	−0.95 ± 0.16	−0.94 ± 0.19
E (l/s)	0.88 ± 0.28	0.91 ± 0.22
A (l/s)	0.57 ± 0.20	0.67 ± 0.16
Overall *S* (l/s)	−1.02 ± 0.11	−0.97 ± 0.19
E (l/s)	0.90 ± 0.15	0.95 ± 0.20
A (l/s)	0.66 ± 0.17	0.61 ± 0.16

Notes: LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVSV: left ventricular stroke volume; LVEF: left ventricular ejection fraction; LV: left ventricle; RVEDV: right ventricular end diastolic volume; RVESV: right ventricular end systolic volume; RVSV: right ventricular stroke volume; RVEF: right ventricular ejection fraction; IVSd: intraventricular septum thickness; PWd: Posterior wall thickness; 2CH: apical two chamber view; 4CH: apical four chamber view; APLAX: apical parasternal long axis view; *E*: early diastolic filling (E-wave); *A*: late diastolic filling (A-wave); *E* (cm/s): early diastolic velocity of mitral annulus; *A* (cm/s): late diastolic velocity of mitral annulus; *S* (l/s): systolic strain rate; *E* (l/s): early diastolic strain rate; *A* (l/s): late diastolic strain rate.

demonstrated similar ε in fibrotic compared to non-fibrotic segments, whereas local ε was comparable in the mid septum segment ($\Delta\varepsilon$: 0.9%) but reduced in the apical septum segment ($\Delta\varepsilon$: −7.7%) compared to athletes without MF. Case #3 demonstrated lower ε in fibrotic versus non-fibrotic segments, whereas local ε in MF segments was improved ($\Delta\varepsilon_{\text{mid anterior septum}}$: 2.2%) similar ($\Delta\varepsilon_{\text{mid septum}}$: −0.9%) and lower ($\Delta\varepsilon_{\text{basal septum}}$: −2.0%, $\Delta\varepsilon_{\text{basal anterior septum}}$: −3.4%) compared to athletes without MF. Case #4 demonstrated comparable (mid septum) and increased (apical septum) ε in fibrotic *versus* non-fibrotic segments, whereas local ε was lower ($\Delta\varepsilon_{\text{mid septum}}$: −4.2% and $\Delta\varepsilon_{\text{apical septum}}$: −7.0%) compared to values in athletes without MF (Table III). Base to apex gradient was similar for case #1, lower for case #2 and #4 and higher for case #3. No differences in time to peak strain were observed due to large variability across segments.

Discussion

This case series is the first to describe the cardiac structure as well as LV global and regional function in athletes with and without MF. We found that lifelong veteran athletes with MF had a larger LV dimension than peers without MF. The presence of MF, however, did not impact upon global systolic or diastolic function, including global longitudinal ε and strain rate. Co-localisation of MF and regional ε data revealed that some, but not all, athletes with MF-demonstrated attenuated regional cardiac function. Furthermore, base to apex gradient was affected in three out of four athletes with MF. Findings from this case series indicate that the impact of an MF phenotype on cardiac structure and function is highly variable across athletes and may result in co-localized cardiac dysfunction.

CMR imaging revealed that athletes with MF demonstrated larger cardiac dimensions (LV end diastolic volume and posterior wall thickness) compared to athletes without MF. These findings suggest that the hearts of athletes with MF are bigger than athletes without MF. Exercise training is a known stimulus for cardiac remodelling, and higher volumes of exercise result in greater remodelling.(Pluim, Zwinderman, van der Laarse, & van der Wall, 2000; Utomi et al., 2013) The training history of the veteran athletes with and without MF was comparable (42 ± 8 vs 44 ± 2 yrs) and is, therefore, unlikely to explain this finding. Alternatively, athletes with MF may be more prone to cardiac remodelling. Several cross sectional (George et al., 2011; Pelliccia, Maron, Spataro, Proschan, & Spirito, 1991) and longitudinal studies (Arbab-Zadeh et al., 2014;

Table III. A comparison of regional data between fibrotic and non-fibrotic segments within MF athletes and also in comparison with the same wall segment in athletes without MF.

	Athlete with MF			Athletes without MF (n = 5)		
	Longitudinal strain (%)	Base to apex gradient (%)	Time to peak strain (ms)	Longitudinal strain (%)	Base to apex gradient (%)	Time to peak strain (ms)
Case #1: *MF at epicardial lateral wall (8 g)*		−0.1			−1.1 ± 6.3	
4CH – Apical lateral	−26.5		405	−21.8 ± 2.4		376 ± 23
4CH – Mid lateral	−24.2		405	−16.7 ± 6.1		405 ± 80
4CH – Basal lateral	−26.4		473	−19.5 ± 4.9		403 ± 67
4CH – Non-fibrotic segments	−21.5 ± 4.9		427 ± 70	−22.8 ± 5.2		383 ± 46
Case #2: *MF at inferior insertion point mid and apical (3 g)*		−3.8			−10.4 ± 5.9	
4CH – Mid septum	−22.5		351	−21.6 ± 1.7		377 ± 44
4CH – Apical septum	−20.9		351	−28.6 ± 3.7		405 ± 51
4CH – Non-fibrotic segments	−20.8 ± 5.5		428 ± 98	−19.1 ± 4.4		388 ± 56
Case #3: *MF at basal and mid insertion point (3 g)*		−14.4			−10.4 ± 5.9	
4CH – Basal septum	−16.2		358	−18.2 ± 2.8		369 ± 43
4CH – Mid septum	−20.7		358	−21.6 ± 1.7		377 ± 44
4CH – Non-fibrotic segments	−29.1 ± 3.5		387 ± 19.5	−21.7 ± 6.1		397 ± 56
APLAX – Mid anterior septum	−26.5		426	−24.3 ± 3.9		430 ± 35
APLAX – Basal anterior septum	−18.5		497	−21.9 ± 6.7		419 ± 51
APLAX – Non-fibrotic segments	−28.2 ± 4.0		382 ± 34	−19.2 ± 6.0		376 ± 51
Case #4: *MF at insertion point inferior mid/apical (1 g)*		−5.4			−10.4 ± 5.9	
4CH – Mid septum	−17.4		326	−21.6 ± 1.7		377 ± 44
4CH – Apical septum	−21.6		407	−28.6 ± 3.7		405 ± 51
4CH – Non-fibrotic segments	−18.4 ± 1.7		326 ± 57	−19.1 ± 4.4		388 ± 56

Notes: MF: myocardial fibrosis; 4CH: apical four chamber view; APLAX: apical parasternal long axis view.

Weiner et al., 2015) demonstrated that the magnitude of exercise-induced cardiac remodelling differs substantially across athletes. Genetic, epigenetic and environmental factors may contribute to the inter-individual differences of remodelling (Eijsvogels & Thompson, 2017). Hence, athletes with MF may be predisposed to greater levels of cardiac adaptation, potentially leading to a shift of the physiological to pathological remodelling continuum and subsequently to the development of MF.

No differences in global diastolic function and indices of global longitudinal ε and strain rate were found between athletes with and without MF. These observations contradict findings in cardiovascular patients with MF. For example, patients with congenital aortic stenosis (Dusenbery et al., 2015), Fabry disease (Kramer et al., 2013) and hypertrophic cardiomyopathy (Saito et al., 2012) that had LGE demonstrated significant reductions in cardiac function compared to patients without LGE and healthy controls. Furthermore, ε patterns were related to the magnitude of MF (Kramer et al., 2013; Saito et al., 2012), indicating that higher volumes of MF are associated with further attenuation of global longitudinal ε. The low volumes of LGE in our cases may contribute to the lack of impact of MF on global indices of cardiac function in veteran athletes with MF. Alternatively, the physically active lifestyle of our study population may ameliorate the detrimental effects of MF on strain and strain rate.

Data from regional/segmental analyses (Table III) revealed a more variable and complex outcome compared to global measures of cardiac function. An attenuated LV longitudinal ε in fibrotic *versus* non-fibrotic segments was observed within an MF athlete (n = 1) and also compared to the control group (n = 3). Furthermore, a reduced base to apex gradient was observed in athletes with MF in the apical segment (case #2 and #4), whereas a larger gradient was found in an athlete with MF in the basal segment (case #3). These observations suggest that presence of subtle MF near the insertion point may impact cardiac function at a regional or local level. Interestingly, the case (#1) with the largest volume of MF (8 g) actually demonstrated a superior ε compared to the reference group of five athletes without MF. A different aetiology for the development of MF in case #1 *versus* cases #2, #3 and #4 may explain this observation. Case 1 presents an MF pattern which is consistent with a previous

episode of myocarditis whereas the other cases had a non-specific LGE pattern. Myocarditis is known to induce MF, but these pathological remodelling processes are mainly restricted to the epicardial wall (Pressler et al., 2011). Hence, the non-transmural nature of MF in case #1 may have been insufficient to impact regional ε patterns.

Findings from the present study may have clinical implications. Firstly, the observation that athletes with MF have bigger hearts than their non-fibrotic peers is of interest but requires confirmation in a larger population of athletes with and without MF. Furthermore, CMR imaging could be a potential valuable additional technique for risk stratification in lifelong athletes with cardiac dimensions near the upper limit of physiological remodelling. Secondly, our data demonstrates that the functional impact of MF in athletes is heterogeneous, with some athletes demonstrating a reduction in local ε patterns and base to apex gradient, whereas others demonstrate preserved cardiac function. Whether the observed regional dysfunction may contribute to adverse cardiovascular outcomes is unknown. A previous study demonstrated that German marathoners with MF had a higher incidence of revascularisation therapy (25% versus 1%, $p < .001$) and MF was associated with higher coronary artery calcification scores (192 *versus* 26, $p < .005$) compared to marathoners without MF (Breuckmann et al., 2009; Mohlenkamp et al., 2008). Therefore, future large sample-sized studies that explore the link between MF-induced regional dysfunction and long-term major adverse cardiovascular events are warranted.

An important limitation of this study is the limited number of athletes that were measured. Nevertheless, the prevalence of MF in athletes is low, and only 30 cases were identified worldwide (van de Schoor et al., 2016). This means that it is extremely hard to recruit a larger sample size. Further work utilising T1 mapping sequences to image interstitial fibrosis may prove promising in athletic heart assessment (Gormeli et al., 2016).

Conclusions

In conclusion, findings from the present case series suggest that the presence of MF may be associated with larger cardiac dimensions and regional cardiac dysfunction in lifelong veteran endurance athletes. It is important to emphasize that these characteristics are presented by some, but not all, athletes with MF. Findings from the present study should, therefore, be considered as hypothesis generating and should lead to novel studies in this field of exercise physiology and sports cardiology.

Disclosure statement

No potential conflict of interest was reported by the authors.

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