Myocardial Fibrosis in Athletes

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ABSTRACT

Myocardial fibrosis (MF) is a common phenomenon in late stages of diverse cardiac diseases and is a predictive factor for sudden cardiac death. MF detected by magnetic resonance imaging (MRI) has also been reported in athletes. Regular exercise improves cardiovascular health, but there may be a limit of benefit in the exercise dose-response relationship. Intense exercise training could induce pathologic cardiac remodeling ultimately leading to MF, but the clinical implications of MF in athletes are unknown. For this comprehensive review, we performed a systematic search using PubMed and MEDLINE databases up to June 2016. Key MeSH terms and keywords pertaining to *myocardial fibrosis* and *exercise (training)* were included. Articles were selected for inclusion if they represented primary data of MF in athletes. We identified a total of 65 athletes with MF from 19 case studies/series and 14 athletic population studies. MF in athletes was predominantly identified in the intraventricular septum and where the right ventricle joins the septum. Although the underlying mechanisms are unknown, we summarize the evidence for genetic predisposition, silent myocarditis, pulmonary artery pressure overload, and prolonged exercise-induced repetitive micro-injury as contributors to the development of MF in athletes. We also discuss the clinical implications and potential treatment strategies of MF in athletes.

Keywords: Athletes heart, cardiac remodeling, endurance exercise, running, marathon, triathlon.

ARTICLE HIGHLIGHTS

- Habitual physical activity is known to reduce the risk for future cardiovascular morbidity and mortality. Several studies explored the relationship between physical activity and cardiovascular health and reported a curvilinear association. However, emerging evidence suggest that cardiac maladaptations may occur in a minority of endurance athletes that perform exercise at the upper end of the physical activity continuum. Among other observations (i.e. enhanced coronary artery calcification / cardiac dysfunction / cardiac biomarker release / arrhythmias), evidence of myocardial fibrosis have been reported in case reports and athletic population studies.
- Myocardial fibrosis is typically observed in cardiac patients and is a predictive factor for adverse cardiac outcome, such as sudden cardiac death. Whether the development of myocardial fibrosis in athletes is related to their exercise training and competition regimes or secondary to (subclinical) cardiovascular disease is key, as this provides essential insight in the underlying mechanisms.
- Characterization of the phenotype of myocardial fibrosis is important to allow early identification of athletes at risk. Furthermore, the pattern, location and quantification of myocardial fibrosis may importantly drive the choice for specific treatment strategies and lifestyle advices.

Abbreviations

CMR	cardiac magnetic resonance imaging
LGE	late gadolinium enhancement
LV	left ventricle
MF	myocardial fibrosis
RV	right ventricle

INTRODUCTION

Cardiac remodeling is a common adaptation in trained athletes, which consists of increased left and right ventricular dimensions and atrial cavity size, associated with normal systolic and diastolic function [1, 2]. The increase in cardiac dimensions typical of an athlete's heart facilitates an increase in stroke volume and cardiac output during exercise [3].

It is generally accepted that exercise benefits cardiovascular health [4], but myocardial fibrosis (MF) has been detected in endurance athletes by cardiac magnetic resonance (CMR) imaging using late gadolinium enhancement (LGE) [5-11]. MF is defined by a significant increase in the collagen volume of myocardial tissue. It is a complex process that involves all components of the myocardial tissue and can be triggered by tissue injury from myocardial ischemia (hypoxia), inflammation, and hypertensive overload [12]. Fibrosis generally occurs with cardiac remodeling secondary to diseases such as heart failure, hypertension, and valvular dysfunction [13]. MF leads to increased myocardial stiffness [14], which increases left ventricular end-diastolic and left atrial pressures. MF in animal models and patients studies is also associated with reduced ventricular systolic function [15]. Patients with MF have a higher incidence of ventricular arrhythmias [16, 17], and more adverse cardiac outcomes [18].

Not all endurance athletes demonstrate MF [19-23] making the relationship between lifelong endurance exercise and the development of MF unclear. Furthermore, the clinical implications of MF in athletes are unknown. This systematic review summarizes the available data on the prevalence of MF in physically active individuals in order to identify predictors and the potential mechanism(s) for MF development and its clinical implications.

METHODS

MF assessment. MF can be determined by microscopic examination of tissues samples and/or by cardiac magnetic resonance (CMR) imaging. Myocardial tissue is obtained in vivo by transvenous endomyocardial biopsy of the right ventricle. Fibrillar collagen can then be quantified under polarized light after picrosirius red [24] or Masson's Trichrome staining [25]. CMR to assess late gadolinium enhancement (LGE), a sign of myocardial fibrosis, is the preferred method for assessment of focal MF because it is readily available, non-invasive and has the capacity to assess all the cardiac chambers. Alternatively, CMR based contrast enhanced T1 mapping can be used to assess diffuse MF [26, 27].

Search strategy. We performed a systematic search of peer-reviewed studies that examined MF in athletes using cardiac biopsies or CMR. The literature was searched using PubMed and MEDLINE databases up to June 2016. Key MeSH terms and keywords pertaining to myocardial fibrosis (delayed (gadolinium) enhancement, pathological late gadolinium enhancement, myocardial late gadolinium enhancement, abnormal late gadolinium enhancement, fibrosis, myocardium, myocardial fibrosis, papillary muscles/pathology, ventricular dysplasia, ventricular torsion) and exercise training (exercise, athletes, sports, sport, motor activity, marathon, triathlon, bicycling, swimming, physical endurance, marathon running, sports medicine, exercise-induced) were included.

Selection of studies. The selection process of reviewing titles, abstracts and full-texts was performed by two authors (F.R.S. and T.M.H.E.) who later met to reach mutual consensus. Inclusion criteria were 1. fibrosis established by validated techniques, and 2. the study population consisted of athletes, defined as "individuals who are proficient in sports, have

routinely performed exercise training for an extended period of time and participate in sporting events". The only exclusion criteria was 1. underlying (genetic) cardiovascular disease such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy.

RESULTS

Our systematic search yielded 33 studies: 19 case reports/series using biopsy (n=17) and CMR (n=2) to determine MF, and 14 studies in athletic populations using CMR to determine MF (Figure 1).

Table 1. Characteristics of case series and reports of myocardial fibrosis in athletes

Study	Type of athlete	Years of exercise/hours of sport per week/ number of marathons	Age (years)	Sex	Description of MF	Mode of diagnosis
Thiene 1983 [28]	Soccer player (n=1)	Not specified	24	Male	Patchy fibrosis, scattered myofibrillar degeneration with contraction bands and initial polymorphonuclear neutrophil infiltration.	Biopsy (post-mortem)
Bharati 1988 [29]	Runner (n=1)	Trained on regular bases	47	Male	Myocardial disarray, fibrosis, fatty infiltration, mono-nuclear cell infiltration of the left-sided bundle of His and fibrosis of the right bundle branch. Patchy fibrosis of the left side of the septum.	Biopsy (post-mortem)
Rowe 1991 [30]	Marathon runner (n=1)	Completed 524 marathons, most in less than 4 hours. Also cross country ski and canoe races, triathlons and ultramarathons.	62	Male	Focal fibrosis of the left ventricular papillary muscles consistent with remote ischemia.	Biopsy (post-mortem)
Zeppilli 1993 [31]	Basketball player (n=1) Soccer players (n=2) Volleyball (n=1) Waterskier (n=1)	Not specified	17-23	60% male	1. Fibrosis prevailing in the right ventricle with occasional focus of cellular necrosis (basketball). 2. Focal nonspecific fibrosis (soccer). 3. Diffuse, nonspecific fibrosis (soccer). 4. Myocarditis with fibrosis largely prevailing in the right ventricle (volleyball). 5. Mild focal increase of the interstitial fibrous tissue, suggesting active myocarditis (water-skier).	Biopsy (minor arrhythmias and/or echocardiographic abnormalities)
Kindermann 1998 [32]	Endurance athlete (n=1)	Weekly 10 hours of endurance training including	32	Male	Focal fibrosis.	Biopsy (drop of performance)

		50km running and 1-2 hours of mountain bike				
Larsson 1999 [33]	Orienteers (n=2)	One case was ranked within national elite class.	27, 28	100% male	Myocarditis-healed, fibrosis, hypertrophy. Hypertrophy, fibrosis.	Biopsy (post-mortem)
Lesauskaite 1998 [34]	Runner (n=1) Soccer player (n=1)	Rated officially as a first-class runner. Middle and long distances. Not specified	22 20	100% male	Scar tissue (foci of connective and granulation tissue) in (posterior wall) of LV and interventricular septum. Foci of connective tissue in the LV and interventricular septum.	Biopsy (post-mortem)
Heidbüchel 2003 [35]	Endurance athletes (n=3)	≥3 x 2h/week for ≥5 years	Not specified	Not specified	Fibrosis (with fat in one patient)	Biopsy (ventricular arrhythmias)
Murty 2008 [36]	Not specified (n=1)	Not specified	16	Male	There were wide swaths of myocardial fibrosis consistent with areas of old healed infarction, as well as areas of recent infarction. Other areas in the heart showed myocardial fatty infiltration, fibrosis and marked myofibrillary disarray.	Biopsy (post-mortem)
Ottaviani 2008 [37]	Soccer player (n=1)	Not specified	13	Male	The lateral wall of the left ventricle presented an area of myocardial fibrosis, characterized by replacement of the necrotic fibers by dense collagenous scarring.	Biopsy (post-mortem)
Lakhan 2008 [38]	Power lifter (n=1)	Participated regularly in aerobic activity and traveled frequently	73	Female	Wide spread interstitial myocardial fibrosis in right and left ventricles, mostly prevalent in the endomyocardium and affecting 25% of the myocardium.	Biopsy (post-mortem)
Whyte 2009 [39]	Marathon runner (n=1)	Running for 20 years, completed multiple marathons, personal best 2 hours and 30 minutes	57	Male	Fibrosis throughout both chambers, predominating in the LV. Widespread replacement fibrosis in the lateral and posterior ventricular walls, and interstitial fibrosis in the inner layer of the myocardium.	Biopsy (post-mortem)

Harper 2009 [40]	Triathlete (n=1)	Averaged 10-15 events per year Former world champion.	32	Female	Patchy interstitial fibrosis in RV.	Biopsy (exercise induced recurrent ventricular tachycardia)
La Gerche 2010 [41]	Endurance athletes (n=3)	≥3h/week of sport with a moderate to intense dynamic component, competitively or recreationally for ≥5 years.	Not specified	Not specified	Septal fibrosis	Biopsy (RV arrhythmias)
Bhella 2010 [42]	Runner (n=1)	After running 1460 km and ascending over 2600 m the run was ended. In support of the event, after a 3 day rest, the subject cycled an additional 1580 km in 9 days ascending another 1190 m	46	Male	At the inferior insertion of the RV and in the interventricular septum that may represent subtle inflammation secondary to a combined exercise and altitude effect.	CMR
Sivridis 2010 [43]	Competitive high-school athlete (n=1)	Not specified	14	Female	Extensive areas of interstitial fibrosis involving the posterior left ventricular wall, the interventricular septum and the papillary muscles.	Biopsy (post-mortem)
Pressler 2011 [44]	Soccer player (n=1)	Professional soccer player	18	Male	Epimyocardial LGE in the lateral and parts of the apical and posterior walls.	Biopsy (return-to-field examination after severe myocarditis)
Poussel 2012 [45]	Cyclist (n=1)	23000km per year for 14 years	30	Male	Focal fibrosis of the left ventricle and intracardiac dimensions consistent with physiologic remodeling.	Biopsy (palpitations)
Schnell 2015 [46]	Cyclists (n=5) Football player (n=1)	≥6h/week for ≥5 years	19-32	86% male	LGE predominantly in the lateral wall. Size of 20.3±7.7 grams. Subepicardial (cyclist, football player, basketball player). Transmural patches (cyclist).	CMR (pathological T-wave inversions on ECG

Basketball player (n=1)	Intramural patches (cyclists). Likely to reflect chronic scarring.	(n=4) or ventricular arrhythmias (n=3)

RV = Right ventricle. LV = Left ventricle. LGE = Late gadolinium enhancement. CMR = cardiac magnetic resonance imaging. ECG = electrocardiogram. N indicates the number of athletes.

MF reported in case studies/series

Case reports/series included 35 athletes (, Table 1), participating in a wide range of sports: orienteering [33], power lifting [38], basketball [46], volleyball [31], waterskiing [31], soccer [28, 31, 34, 37, 44], (marathon) running [29, 30, 34, 39, 42], cycling [45, 46], and triathlon [40]. To our knowledge, the first report of MF in athletes was published in 1983 and described MF in one soccer player [28]. Athletes ranged in age from 13 to 73 years at MF diagnosis, whereas 76% of the population was male. Although sex and age of n=6 cases was not reported,[35, 41] most athletes with MF were young (20 of 35, ≤ 30 years). In 12 athletes (34%) biopsies were taken post-mortem.

MF reported in athletic populations

The existence of MF was also assessed by CMR in athletic populations (Table 2). A total of 509 endurance exercise athletes were examined and seven studies confirmed the presence of MF in athletes, whereas 7 studies did not. Overall 89% of the population was male and MF was reported in 30 of the 509 athletes (5.9%). Interestingly, the lifetime exercise exposure (1 to 100 completed marathons) and age (26 to 72 years) varied substantially across participants, but most reports occurred in long-term endurance athletes.

Table 2. Prevalence and patterns of myocardial fibrosis in athletic populations using CMR

Study	Study population	Exercise exposure	Age (years)	Sex	Prevalence of MF	Pattern/location of MF
Wilson 2011 [5]	Lifelong veteran endurance athletes (n=12)	43±6 years of competitive exercise training	57±6	100% male	50%	1. Septal and lateral wall. 2. Epicardial lateral wall. 3. Basal and midinsertion point. 4. Inferior insertion point mid and apical. 5. Insertion point inferior mid/apical. 6. Inferior insertion point.
	Veteran sedentary controls (n=20)	No exercise training	60±5		0%	
	Young endurance athletes (n=17)	18±7 years of competitive exercise training	31±5		0%	
La Gerche 2012 [6]	Marathon runners (n=7)	>10h of intense training per week	37±8	90% male	12.8%	Interventricular septum, frequently in vicinity of the RV attachment.
	Endurance triathletes (n=11)	Finished within the first 25% of the field in a recent endurance event				
	Alpine cyclists (n=9)					
	Ultra-triathletes (n=13)					
Breuckmann 2009 [7]	Marathon runners (n=102)	≥5 marathons in ≤3 years	57±6	100% male	Athletes 12%	Athletes 1. 42% Involving the subendocardial layer and partial transmural spreading. 2. 58% Atypical patchy to streaky subepicardial to midmyocardial hyperenhancement which may
	Sedentary controls (n=102)	No exercise training			Controls 4%	

						represent interstitial fibrosis or myocardial fiber disarray for various potential reasons. Sedentary controls 1. 50% CAD pattern. 2. 50% non-CAD pattern.
Mordi 2015 [8]	Aerobic exercise (n=21), predominantly running	> 6h intensive aerobic exercise per week at amateur level	46±11	100% male	9,5%	Small amounts of LGE at RV insertion points
Karlstedt 2012 [9]	Marathon runners (n=25)	47±7 miles/week ≥3 marathons in the past 2 years	55±4	84% male	8%	Anterior wall of the LV myocardium in subendocardial distribution prior to running the marathon, with concomitant evidence of obstructive LAD artery disease.
Erz 2013 [10]	Runners (n=23) Triathletes (n=16) Cyclists (n=5) Speed skater (n=1)	7 hours/week, for ≥2 years	40±9	100% male	2.2%	Posterolateral wall of the LV, indicative of non-ischemic scarring; most likely due to former myocarditis.
Mangold 2013 [11]	Long-distance runners (n=39) Cyclists (n=8) Triathletes (n=34) Handball players (n=13) Speed skater (n=1)	13.1±4.2 hours/week, for ≥2 years	35±11	77% male	2,1% (2 cyclists)	1. Spot-shaped pattern consistent with a non-ischemic, post-inflammation. 2. Disseminated and intramural myocardial hyperenhancement.
Mousavi 2009 [19]	Moderately trained marathon runners (n=10) Highly trained marathon runners (n=4)	26±8 miles/week 53±12 miles/week	33±6	57% male	0%	Not applicable.
Hanssen 2011 [20]	Marathon runners (n=28)	Mean training mileage was 43±17km/week in	41±5	100% male	0%	Not applicable.

		the 10 weeks before the marathon. Median finish time was 245±55min.				
Trivax 2010 [21]	Marathon runners (n=25)	Previous 6 months: 30.2±11.4 miles/week Past 5 years: 17.0±11.8 miles/week	39±9	52% female	0%	Not applicable.
Gaudreault 2013 [22]	Marathon runners (n=20)	8.1±2.3 hours/week 9±8 marathons over 14±5 years	45±8	70% male	0%	Not applicable.
O'Hanlon 2010 [23]	Marathon runners (n=17)	7 hours/week	34±7	100% male	0%	Not applicable.
Heidbüchel 2003 [35]	Endurance athletes (n=28)	≥3 x 2h/week for ≥5 years	Not specified	Not specified	0%	Not applicable.
Scharhag 2006 [47]	Mountain bike marathon cyclists (n=15) Marathon runners (n=5)	Training history in endurance exercise of 7±3 years and trained 9±4 h per week	36±7	100% male	0%	Not applicable.

Studies are arranged from highest to lowest MF prevalence. LAD = left anterior descending. N indicates the number of athletes.

Patterns, location and quantification of MF

The pattern of MF in athletes determined by microscopic examination varies (Table 1) and this likely represents different causes. Fourteen of the 35 athletes with MF (40%) included in the case reports/series demonstrated a non-specific LGE pattern, while the remaining athletes demonstrated an ischemic (7/35, 20%), myocarditic (7/35, 20%), or hypertrophic (1/22, 3%) MF pattern (Figure 2).

Findings from the CMR studies confirm the variation in MF patterns (Table 2). The majority of athletes with MF (12/30, 40%) show a non-specific LGE pattern [5, 7, 11]. A subendocardial pattern, typically seen after ischemic myocardial injury because the subendocardium is the region most vulnerable to reduced coronary blood flow, was observed in 8 of 30 athletes with MF (27%) [5, 7, 9]. There are also several reports of probable scarring from myocarditis (3/30, 10%) and mechanical overload (7/28, 23%, Figure 2) [5, 8, 10, 11].

The location of MF determined by biopsy (case studies/series) and CMR-LGE (athletic population studies) varies substantially (Figure 3). La Gerche *et al.* reported that the MF was confined to the interventricular septum, frequently where the right ventricle attaches to the septum (the hinge points) [6]. Overall, a significant proportion of the MF in athletes is found in the septum (19/65, 29%) [5, 6, 34, 41-43] and right ventricle (RV) insertion points (12/65, 19%) [5, 6, 8, 42]. Some have speculated that the distention of the right ventricle during endurance exercise due to an acute increase in RV work with exercise may be responsible for this interventricular scar pattern [6].

The quantification of MF is poorly reported: only 3 case reports and 1 CMR study describe the extent of fibrosis. The volume of the scar in a biopsy taken from a runner confirmed that MF was present in 2.9% of the left ventricle and 3.5% of the interventricular septum [34]. In another case it was reported that approximately 25% of the myocardium was

involved in some kind of MF [38]. Breuckmann *et al.* reinforced the heterogeneity of the percentage of LGE-positive myocardium (range: 0.5%–17.8%) in German marathon runners [7]. Also, these authors demonstrated that the median percentage of MF was comparable between runners with a subendocardial LGE pattern (0.9%), runners with a non-specific pattern (1.2%) and physically inactive controls (2.2%). Lastly, the volume of the LGE region in the study of Schnell *et al.* was 20.3±7.7 grams, which was the equivalent of 12±4.8% of the LV mass. [46]

DISCUSSION

The present review reveals that the phenotype of MF in athletes demonstrates large variance in patterns, location and quantification among individuals. Nonetheless, a non-specific LGE pattern, located in the right ventricle or septum, and representing 1–3% of the myocardium, seems the most common description of MF typically found in athletes by MRI. The phenotype of MF in athletes differs from that in the general population, and this difference may provide insight into the underlying mechanisms and clinical prognosis of MF in assumingly healthy athletes.

MF in athletes *versus* controls

The prevalence of MF varied from 0% to 50% in often small scale athlete populations. Only 2 studies compared MF prevalence between athletes and age and sex matched physically inactive controls [5, 7]. Breuckmann *et al.* found that MF was more prevalent in athletes (n = 102) than controls (n = 102) (12% *versus* 4%, p = 0.077) [7]. Wilson *et al.* observed MF in 6 of 12 lifelong veteran endurance athletes, but not in any of 20 sedentary peers [5]. Although both studies reported a higher prevalence of MF in athletes *versus* physically inactive controls, the

presence of MF in these control groups was lower compared to recent observations in the general population. In a large American cohort study of non-athletes (68±9 yrs), MF was found in 146 of 1840 participants (7.9%) [48]. Population studies from Iceland (n=936) [49] and Sweden (n=248) [50] demonstrate even a higher prevalence of unknown MF (17.0% and 19.8%, respectively). These findings highlight the need for additional high quality studies comparing the prevalence and extent of MF in large populations of physically active and inactive individuals. Future studies should consider the amount and intensity of exercise training, as well as the lifelong exercise exposure, to test the hypothesis that MF prevalence differs between athletes and the general population.

Focal *versus* diffuse MF

CMR studies assessing MF in athletes included predominantly LGE measurements. Although CMR-LGE is a validated technique to assess quantification of focal MF, it does not provide information about the presence of diffuse MF. This may lead to underestimating the true prevalence of MF in athletes, and limit the generalizability of our findings. Nevertheless, two recent studies used T1 and T2 mapping to assess (diffuse) MF in athletes. [8, 51] In a Scottish study, no difference in native T1, T2 relaxation time and extracellular volume (ECV) was observed between athletes (n=21, ≥6 hrs/week of exercise training) and healthy controls (n=21).[8] In contrast, significantly higher native T1 values of the LV and interventricular septum were found in Turkish athletes (≥6 hrs/week intense exercise training) compared to age and sex matched controls (<3 hrs/week moderate exercise). Moreover, athletes reporting ≥5 years of exercise training demonstrated a higher T1 values indicating more diffuse fibrosis compared to athletes exercising < 5 years ($p<0.05$).[51] These findings suggest a higher prevalence of diffuse MF in Turkish athletes *versus* controls. Apart from the age

difference between Scottish (46±11 yrs) and Turkish athletes (25±3 yrs), there is no clear explanation for the conflicting outcomes. We therefore recommend that future studies include measurements of T1 relaxation times before and after contrast administration to determine the myocardial extracellular volume fraction and to quantify diffuse MF in addition to LGE based assessment of focal MF. Also, the use of free-breathing, motion-corrected, averaged late-gadolinium-enhancement (moco-LGE) CMR measurements, may improve image quality of the RV [52]. Use of these novel imaging techniques should further improve our understanding of the development, progression and clinical interpretation of MF in athletes.

Factors Associated with MF

Several studies identified factors that are associated with the presence of MF in athletes. La Gerche *et al.* reported that athletes with LGE had participated in endurance exercise longer (20 ± 16 years) than athletes without MF (8 ± 6 years, $p = 0.043$) [6]. Similarly, Wilson *et al.*, reported that LGE was related to the years of training ($p < 0.001$) and the number of completed competitive marathons ($p < 0.001$) or ultra-endurance marathons (>50 miles, $p = 0.007$) [5]. Möhlenkamp *et al.* reported an association ($p = 0.02$) between the number of completed marathons and LGE [53]. Evidence from case reports/series confirms that athletes diagnosed with MF demonstrate high doses of exercise for many years (Table 1). For example, one athlete trained 10 hours/week, including 50 km of running and 1-2 hours of mountain biking [32], while another athlete cycled an average of 23,000 km/year for 14 years [45]. These studies and case reports suggest a dose-response relationship between lifetime exercise exposure and MF development. Indeed, Wilson *et al.* demonstrated that the prevalence of MF was the highest (50%) in veteran endurance athletes (57 ± 6 years) who

had been involved in lifelong competitive training for an average of 43 ± 6 years [5]. Studies including predominately younger participants and/or less trained individuals generally fail to find MF [19-23].

Potential mechanisms for MF development

Evidence for MF in athletic populations is exclusively based on observational studies, which do not provide insight into potential underlying mechanisms. However, we summarize available evidence for four different pathways based on the subject characteristics, location and patterns of MF, and the identified predictors.

1) Genetic predisposition

10 case reports describe the presence of MF in 28 young athletes (≤ 30 years). Their young age raises the question whether genetic predisposition contributes to MF development. Hypertrophic cardiomyopathy is the most common genetic heart disease [54] and is associated with a high prevalence of MF [55]. LGE in hypertrophic cardiomyopathy varies from very limited to large, confluent, infarct-like patches occupying significant proportions of the LV [56] and localizes preferentially to the most hypertrophied regions of the ventricle [54]. Furthermore, hypertrophic cardiomyopathy is a frequent cause of sudden cardiac death in young competitive athletes [57]. Mutations in genes coding for sarcomere proteins, Z-disk or calcium-handling proteins are responsible for the phenotype of hypertrophic cardiomyopathy [58]. However, variability can be so striking among individuals with the same genetic defect that little if any relationship can be established between mutations, phenotype, clinical course and patient outcome. Similarly, genetic factors may contribute to the variability of MF presentations in athletes.

2) Silent myocarditis

Five biopsy studies and three CMR-LGE studies suggest that myocarditis is responsible for LGE and this is probably true in some (n = 10), but not all, athletes (n = 65). LGE has a high specificity for the detection of injury in myocarditis, but LGE has a variable sensitivity to detect active or chronic inflammation [59]. This might be due to limited areas of necrotic myocytes which cannot be visualized because of limited pixel size in CMR images compared to larger regions of scarring in ischemic necrosis. Myocarditis is defined as inflammatory cellular infiltrate, whereas associated myocyte necrosis may be present on stained heart-tissue sections.[60] Myocarditis usually results from infections with viruses, such as coxsackievirus B3, adenoviruses, parvovirus B19, but may also result from other pathogens such as the protozoan Trypanosoma cruzi (Chagas disease), toxic or hypersensitivity drug reactions (anticonvulsants, antibiotics and antipsychotics), giant-cell myocarditis, or sarcoidosis. [61] Interestingly, several animal studies demonstrated that exercise itself may cause myocarditis and lead to development of MF. [62-64]. MF disappeared in a rat model of exercise training, after cessation of the exercise. [62] We are unaware of evidence that exercise can produce myocarditis in humans.

Many patients with myocarditis have minimal or no symptoms [65]. Despite this, the infection may cause ventricular dilation or fibrosis [66]. A mouse model demonstrated that physical activity during a 'silent' myocarditis may exaggerate damage to the heart [67]. Mice were infected with coxsackie virus to induce myocarditis and divided into 4 groups: group I received immunosuppression with daily doses of cyclosporine and an antithymocyte monoclonal antibody, group II performed daily swimming exericise, group III received both interventions and group IV served as control. After 21 days, mortality rates were highest in

the exercise only group [67]. Hence, it is possible that continued exercise training accelerates myocardial damage and myocardial fibrosis during a silent myocarditis.

3) Pulmonary artery pressure overload

The volume of LGE is typically small and confined to the septum or RV insertion points in 48% of the athletes diagnosed with MF by MRI-LGE. This may result from local mechanical stress due to prolonged exercise. Interestingly, MF in this cardiac location is also observed in patients with pulmonary arterial hypertension [68, 69]. LGE was present at a similar anatomical location in adults whose RV was forced to produce systemic pressures after atrial redirection surgery for transposition of the great vessels [70]. Focal LGE has been reported at the superior and inferior insertion points of the right and left ventricles in 36% and 89% of these patients, respectively [70]. Exercise produces a greater relative increase in pulmonic than aortic systolic pressure, resulting in an increase in wall stress of 125% *versus* 4% for the right and left ventricles, respectively [71]. The thinner wall of the right ventricle may facilitate the progression from increased wall stress to cardiomyocyte damage, more than in the left ventricle. Although echocardiography studies show that acute exercise-induced changes in right ventricular structure and function fully recover within days [6], chronic structural changes from repetitive prolonged exercise are possible. MF in athletes may therefore result from chronic endurance exercise training and competition and the associated repetitive exercise-induced elevations in pulmonary artery pressures.

4) Repetitive micro-damage

Cardiac troponin I and T are the standard biomarkers used to serologically identify myocardial damage. Many studies have demonstrated increases in cardiac troponin levels

after prolonged exercise [72]. Elevated troponin levels were found in 100% of Boston Marathon participants [73] and are directly related to exercise intensity [74]. Exercise-induced troponin elevations are hypothesized to be benign and to represent reversible cardiomyocyte membrane damage [3], but they may represent micro-damage to cardiomyocytes. Accordingly, repetitive exposure to high-intensity endurance exercise-induced cardiac micro-damage, evidenced by minor troponin elevations, could lead to MF development following lifelong exercise training, as observed in veteran athletes [5].

Clinical implications of MF

The presence of MF is an important risk factor for adverse cardiac outcomes in clinical populations [18, 75-78]. However, the impact of MF on cardiovascular health has not been carefully studied in athletes. 25% of 12 German marathon runners with LGE required revascularization during 21 ± 3 months of follow-up compared to 1% of 90 runners without LGE ($p<0.001$) [7]. Half of the MF runners, however, had a LGE pattern suggestive of ischemic myocardial injury. The increased risk of MF on adverse outcomes persisted during 74 ± 12 months of follow-up [79]. Runners with coronary events had a higher prevalence of LGE (57%) compared to peers without coronary events (8%, $p = 0.003$), despite comparable 10-year Framingham Risk Scores (7.9 ± 2.3% *versus* 7.0 ± 3.7%) [79]. The presence of LGE in this cohort was also associated with higher coronary artery calcification scores (median Agatston coronary artery calcium scores: 192 *versus* 26, $p = 0.0046$) [53], demonstrating that the increased incidence of cardiovascular events in some runners with LGE is due to atherosclerosis and prior infarction. Other studies in other subjects do not support atherosclerosis and prior infarction as the cause of the LGE. Although the German findings suggest a worse prognosis in athletes with MF, it must be emphasized that these data are

derived from a single cohort. Nevertheless, athletes with LGE patterns consistent with coronary artery disease and prior infarction or those with evidence of active myocardial inflammation should be pharmacologically treated to reduce their risk for an acute cardiac event and to treat their myocarditis, respectively.

The prognostic significance of non-specific MF patterns seen in athletes is unknown. There is no evidence that athletes with this pattern should be restricted from exercise. Additional clinical testing should be recommended based on the individual's symptoms and clinical profile. MF detected by LGE in cardiac studies of asymptomatic athletes done for other nonclinical reasons should be treated as an incidental finding and not pursued.

The impact of lifelong exercise training on cardiovascular health is under debate [3, 80]. Although some studies report a U-shaped association between exercise volume and cardiovascular risk[81, 82], the majority of available evidence suggest a curvilinear relationship with greater health benefits at larger exercise doses [83-85]. Furthermore, there is substantial evidence that longevity benefits are most prominent in the most active individuals (i.e. elite athletes)[86]. Nevertheless, data from CMR athletic population studies suggest that some long-term endurance athletes develop MF.

CONCLUSION

Myocardial fibrosis has been reported in some lifelong endurance athletes. The pattern of LGE is heterogeneous, which may represent different causation and could contribute to the difference in MF locations between case studies/series and athletic population studies. In a few of these athletes, CMR detected LGE is consistent with coronary artery disease and prior infarction and appears to be associated with increased risk of cardiovascular events. Other middle-aged and older athletes demonstrate LGE largely confined to the interventricular

septum often near the hinge points between the right ventricle and the septum. This pattern appears more common in long-term endurance athletes and may represent the effect of repetitive myocardial micro trauma or repetitive dilatation of the right ventricle with exercise. Athletes with underlying cardiovascular disease should receive pharmacological treatment to reduce the risk for secondary events. The significance of non-specific MF is largely unknown and future studies investigating the functional and clinical consequences of myocardial fibrosis in athletes are warranted.

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REFERENCES

1. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation.* 2000;101:336-344.

2. Utomi V, Oxborough D, Whyte GP, et al. Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. *Heart.* 2013;99:1727-1733.

3. Eijsvogels TM, Fernandez AB, Thompson PD. Are There Deleterious Cardiac Effects of Acute and Chronic Endurance Exercise? *Physiol Rev.* 2016;96:99-125.

4. Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the Extremes: The Amount of Exercise to Reduce Cardiovascular Events. *J Am Coll Cardiol.* 2016;67:316-329.

5. Wilson M, O'Hanlon R, Prasad S, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol (1985).* 2011;110:1622-1626.

6. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J.* 2012;33:998-1006.

7. Breuckmann F, Mohlenkamp S, Nassenstein K, et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. *Radiology.* 2009;251:50-57.

8. Mordi I, Carrick D, Bezerra H, Tzemos N. T1 and T2 mapping for early diagnosis of dilated non-ischaemic cardiomyopathy in middle-aged patients and differentiation from normal physiological adaptation. *Eur Heart J Cardiovasc Imaging.* 2015.

9. Karlstedt E, Chelvanathan A, Da Silva M, et al. The impact of repeated marathon running on cardiovascular function in the aging population. *J Cardiovasc Magn Reson.* 2012;14:58.

10. Erz G, Mangold S, Franzen E, et al. Correlation between ECG abnormalities and cardiac parameters in highly trained asymptomatic male endurance athletes: evaluation using cardiac magnetic resonance imaging. *Int J Cardiovasc Imaging.* 2013;29:325-334.

11. Mangold S, Kramer U, Franzen E, et al. Detection of cardiovascular disease in elite athletes using cardiac magnetic resonance imaging. *Rofo.* 2013;185:1167-1174.

12. Zannad F, Radauceanu A. Effect of MR blockade on collagen formation and cardiovascular disease with a specific emphasis on heart failure. *Heart failure reviews.* 2005;10:71-78.

13. Hill JA, Olson EN. Cardiac plasticity. *N Engl J Med.* 2008;358:1370-1380.

14. Sugihara N, Genda A, Shimizu M, et al. [Diastolic dysfunction and its relation to myocardial fibrosis in essential hypertension]. *J Cardiol.* 1988;18:353-361.

15. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol.* 2008;52:1574-1580.

16. Diez J. Mechanisms of cardiac fibrosis in hypertension. *J Clin Hypertens (Greenwich).* 2007;9:546-550.

17. McLenachan JM, Dargie HJ. Ventricular arrhythmias in hypertensive left ventricular hypertrophy. Relationship to coronary artery disease, left ventricular dysfunction, and myocardial fibrosis. *Am J Hypertens.* 1990;3:735-740.

18. Kwong RY, Sattar H, Wu H, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation.* 2008;118:1011-1020.

19. Mousavi N, Czarnecki A, Kumar K, et al. Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. *Am J Cardiol.* 2009;103:1467-1472.

20. Hanssen H, Keithahn A, Hertel G, et al. Magnetic resonance imaging of myocardial injury and ventricular torsion after marathon running. *Clin Sci (Lond).* 2011;120:143-152.

21. Trivax JE, Franklin BA, Goldstein JA, et al. Acute cardiac effects of marathon running. *J Appl Physiol (1985).* 2010;108:1148-1153.

22. Gaudreault V, Tizon-Marcos H, Poirier P, et al. Transient myocardial tissue and function changes during a marathon in less fit marathon runners. *Can J Cardiol.* 2013;29:1269-1276.

23. O'Hanlon R, Wilson M, Wage R, et al. Troponin release following endurance exercise: is inflammation the cause? a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson.* 2010;12:38.

24. Lattouf R, Younes R, Lutomski D, et al. Picrosirius red staining: a useful tool to appraise collagen networks in normal and pathological tissues. *The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society.* 2014;62:751-758.

25. Roberts WC, Siegel RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol.* 1987;60:1340-1355.

26. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2011;57:891-903.

27. Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart.* 2013;99:932-937.

28. Thiene G, Pennelli N, Rossi L. Cardiac conduction system abnormalities as a possible cause of sudden death in young athletes. *Human pathology.* 1983;14:704-709.

29. Bharati S, Dreifus LS, Chopskie E, Lev M. Conduction system in a trained jogger with sudden death. *Chest.* 1988;93:348-351.

30. Rowe WJ. A world record marathon runner with silent ischemia without coronary atherosclerosis. *Chest.* 1991;99:1306-1308.

31. Zeppilli P, Santini C, Palmieri V, Vannicelli R, Giordano A, Frustaci A. Role of myocarditis in athletes with minor arrhythmias and/or echocardiographic abnormalities. *Chest.* 1994;106:373-380.

32. Kindermann W, Janzen I, Urhausen A, Schieffer HJ. [Heart enlargement in an athlete--a diagnostic challenge]. *Zeitschrift fur Kardiologie.* 1998;87:105-110.

33. Larsson E, Wesslen L, Lindquist O, et al. Sudden unexpected cardiac deaths among young Swedish orienteers--morphological changes in hearts and other organs. *APMIS.* 1999;107:325-336.

34. Lesauskaite V, Valanciute A. Causes of sudden cardiac death in young athletes: the role of hypoperfusion. *Am J Forensic Med Pathol.* 1998;19:157-161.

35. Heidbuchel H, Hoogsteen J, Fagard R, et al. High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. *Eur Heart J.* 2003;24:1473-1480.

36. Murty OP, Mun KS, Hussin H. Silent bony calcification of coronaries in an adolescent--an unusual case. *Journal of forensic and legal medicine.* 2008;15:37-41.

37. Ottaviani G, Lavezzi AM, Matturri L. Sudden unexpected death in young athletes. *The American journal of forensic medicine and pathology.* 2008;29:337-339.

38. Lakhan SE, Harle L. Cardiac fibrosis in the elderly, normotensive athlete: case report and review of the literature. *Diagnostic pathology.* 2008;3:12.

39. Whyte G, Sheppard M, George K, et al. Post-mortem evidence of idiopathic left ventricular hypertrophy and idiopathic interstitial myocardial fibrosis: is exercise the cause? *BMJ Case Rep.* 2009;2009.

40. Harper RW, Mottram PM. Exercise-induced right ventricular dysplasia/cardiomyopathy--an emerging condition distinct from arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart, lung & circulation.* 2009;18:233-235.

41. La Gerche A, Robberecht C, Kuiperi C, et al. Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin. *Heart.* 2010;96:1268-1274.

42. Bhella PS, Kelly JP, Peshock R, Levine BD. Delayed enhancement of the intraventricular septum following an extraordinary endurance exercise. *BMJ Case Rep.* 2010;2010.

43. Sivridis E, Pavlidis P, Stamos C, Giatromanolaki A. Sudden death after myocardial infarction in a high-school athlete. *Journal of forensic sciences.* 2010;55:1378-1379.

44. Pressler A, Schmid A, Freiberger V, Scherr J, Uder M, Halle M. Myocarditis, myocardial fibrosis and eligibility for competitive sports. *Int J Cardiol.* 2011;152:131-132.

45. Poussel M, Djaballah K, Laroppe J, Brembilla-Perrot B, Marie PY, Chenuel B. Left ventricle fibrosis associated with nonsustained ventricular tachycardia in an elite athlete: is exercise responsible? A case report. *J Athl Train.* 2012;47:224-227.

46. Schnell F, Claessen G, La Gerche A, et al. Subepicardial delayed gadolinium enhancement in asymptomatic athletes: let sleeping dogs lie? *Br J Sports Med.* 2016;50:111-117.

47. Scharhag J, Urhausen A, Schneider G, et al. Reproducibility and clinical significance of exercise-induced increases in cardiac troponins and N-terminal pro brain natriuretic peptide in endurance athletes. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology.* 2006;13:388-397.

48. Turkbey EB, Nacif MS, Guo M, et al. Prevalence and Correlates of Myocardial Scar in a US Cohort. *JAMA.* 2015;314:1945-1954.

49. Schelbert EB, Cao JJ, Sigurdsson S, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *JAMA.* 2012;308:890-896.

50. Barbier CE, Bjerner T, Johansson L, Lind L, Ahlstrom H. Myocardial scars more frequent than expected: magnetic resonance imaging detects potential risk group. *J Am Coll Cardiol.* 2006;48:765-771.

51. Gormeli CA, Gormeli G, Yagmur J, et al. Assessment of myocardial changes in athletes with native T1 mapping and cardiac functional evaluation using 3 T MRI. *Int J Cardiovasc Imaging.* 2016.

52. Piehler KM, Wong TC, Puntil KS, et al. Free-breathing, motion-corrected late gadolinium enhancement is robust and extends risk stratification to vulnerable patients. *Circ Cardiovasc Imaging.* 2013;6:423-432.

53. Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J.* 2008;29:1903-1910.

54. Olivotto I, Girolami F, Nistri S, et al. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. *Journal of cardiovascular translational research.* 2009;2:349-367.

55. Rubinshtein R, Glockner JF, Ommen SR, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail.* 2010;3:51-58.

56. Olivotto I, Maron MS, Autore C, et al. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2008;52:559-566.

57. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA.* 1996;276:199-204.

58. Marian AJ. Genetic determinants of cardiac hypertrophy. *Current opinion in cardiology.* 2008;23:199-205.

59. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol.* 2009;53:1475-1487.

60. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol.* 1987;1:3-14.

61. Cooper LT, Jr. Myocarditis. *N Engl J Med.* 2009;360:1526-1538.

62. Benito B, Gay-Jordi G, Serrano-Mollar A, et al. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation.* 2011;123:13-22.

63. Aschar-Sobbi R, Izaddoustdar F, Korogyi AS, et al. Increased atrial arrhythmia susceptibility induced by intense endurance exercise in mice requires TNFalpha. *Nat Commun.* 2015;6:6018.

64. Chen Y, Serfass RC, Mackey-Bojack SM, Kelly KL, Titus JL, Apple FS. Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise. *J Appl Physiol (1985).* 2000;88:1749-1755.

65. McCarthy RE, 3rd, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med.* 2000;342:690-695.

66. Kallwellis-Opara A, Dorner A, Poller WC, et al. Autoimmunological features in inflammatory cardiomyopathy. *Clinical research in cardiology : official journal of the German Cardiac Society.* 2007;96:469-480.

67. Cabinian AE, Kiel RJ, Smith F, Ho KL, Khatib R, Reyes MP. Modification of exercise-aggravated coxsackievirus B3 murine myocarditis by T lymphocyte suppression in an inbred model. *The Journal of laboratory and clinical medicine.* 1990;115:454-462.

68. Blyth KG, Groenning BA, Martin TN, et al. Contrast enhanced-cardiovascular magnetic resonance imaging in patients with pulmonary hypertension. *Eur Heart J.* 2005;26:1993-1999.

69. McCann GP, Beek AM, Vonk-Noordegraaf A, van Rossum AC. Delayed contrast-enhanced magnetic resonance imaging in pulmonary arterial hypertension. *Circulation.* 2005;112:e268.

70. Babu-Narayan SV, Goktekin O, Moon JC, et al. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. *Circulation.* 2005;111:2091-2098.

71. La Gerche A, Heidbuchel H, Burns AT, et al. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Med Sci Sports Exerc.* 2011;43:974-981.

72. Shave R, Baggish A, George K, et al. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol.* 2010;56:169-176.

73. Eijsvogels TM, Januzzi JL, Taylor BA, et al. Impact of statin use on exercise-induced cardiac troponin elevations. *Am J Cardiol.* 2014;114:624-628.

74. Eijsvogels TM, Hoogerwerf MD, Oudegeest-Sander MH, Hopman MT, Thijssen DH. The impact of exercise intensity on cardiac troponin I release. *Int J Cardiol.* 2014;171:e3-4.

75. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol.* 2006;48:1977-1985.

76. Bello D, Shah DJ, Farah GM, et al. Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing beta-blocker therapy. *Circulation.* 2003;108:1945-1953.

77. Kwon DH, Halley CM, Popovic ZB, et al. Gender differences in survival in patients with severe left ventricular dysfunction despite similar extent of myocardial scar measured on cardiac magnetic resonance. *European journal of heart failure.* 2009;11:937-944.

78. Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation.* 2006;113:2733-2743.

79. Mohlenkamp S, Leineweber K, Lehmann N, et al. Coronary atherosclerosis burden, but not transient troponin elevation, predicts long-term outcome in recreational marathon runners. *Basic Res Cardiol.* 2014;109:391.

80. O'Keefe JH, Franklin B, Lavie CJ. Exercising for health and longevity vs peak performance: different regimens for different goals. *Mayo Clin Proc.* 2014;89:1171-1175.

81. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ, Million Women Study C. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation.* 2015;131:721-729.

82. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. *J Am Coll Cardiol.* 2015;65:411-419.

83. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175:959-967.

84. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol.* 2014;64:472-481.
85. Maessen MF, Verbeek AL, Bakker EA, Thompson PD, Hopman MT, Eijsvogels TM. Lifelong Exercise Patterns and Cardiovascular Health. *Mayo Clin Proc.* 2016;91:745-754.
86. Farahmand BY, Ahlbom A, Ekblom O, et al. Mortality amongst participants in Vasaloppet: a classical long-distance ski race in Sweden. *J Intern Med.* 2003;253:276-283.

FIGURE LEGENDS

Figure 1: Flow chart of search strategy to determine the prevalence of fibrosis amongst athletes. The following MeSH keywords were employed in the literature search: delayed enhancement, pathological late gadolinium enhancement, myocardial late gadolinium enhancement, abnormal late gadolinium enhancement, fibrosis, myocardium, myocardial fibrosis, papillary muscles/pathology, ventricular dysplasia, ventricular torsion, and exercise, athletes, sports, sport, motor activity, marathon, triathlon, bicycling, swimming, physical endurance, marathon running, sports medicine, exercise-induced. N indicates number of studies.

Figure 2. The prevalence of the pattern of myocardial fibrosis found in athletes in case reports/series (blue bars) and cardiac magnetic resonance imaging (CMR) studies (orange bars). MF = myocardial fibrosis.

Figure 3. The frequency of the location of myocardial fibrosis reported in case studies/series (blue bars) and athletic population studies (orange bars). In 10 athletes fibrosis was present at multiple locations of the heart (n=5 in case series [29, 34, 39, 43] and n=5 in an athletic population study [6]). RV = right ventricle. LV = left ventricle.