MAYO CLINIC

REVIEW

Myocardial Fibrosis in Athletes

Freek R. van de Schoor, MD; Vincent L. Aengevaeren, MD; Maria T.E. Hopman, MD, PhD; David L. Oxborough, PhD; Keith P. George, PhD; Paul D. Thompson, MD; and Thijs M.H. Eijsvogels, PhD

Abstract

Myocardial fibrosis (MF) is a common phenomenon in the late stages of diverse cardiac diseases and is a predictive factor for sudden cardiac death. Myocardial fibrosis detected by magnetic resonance imaging 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 of the PubMed and MEDLINE databases up to June 2016. Key Medical Subject Headings terms and keywords pertaining to MF and exercise (training) were included. Articles were included if they represented primary MF data in athletes. We identified 65 athletes with MF from 19 case studies/series and 14 athletic population studies. Myocardial fibrosis 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.

 ■ Mayo Clin Proc. 2016;■■(■):1-15

Cardiac remodeling is a common adaptation in trained athletes that consists of increased left ventricular (LV) and right ventricular (RV) dimensions and atrial cavity size and is 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 imaging (CMR) using late gadolinium enhancement (LGE).[5-11] Myocardial fibrosis 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] Myocardial fibrosis leads to increased myocardial stiffness,[14] which increases LV end-diastolic and left atrial pressures. In animal models and patient studies, MF 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 to identify predictors and the potential mechanism(s) of MF development and its clinical implications.

From the Department of Physiology, Radboud University Medical Center, Nijmegen, The Netherlands (F.R.S., V.L.A., M.T.E.H., T.M.H.E.); Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK (D.L.O., K.P.G., T.M.H.E.); and Division of Cardiology, Hartford Hospital, Hartford, CT (P.D.T., T.M.H.E.).

METHODS

MF Assessment

Myocardial fibrosis can be determined by microscopic examination of tissue samples or by CMR. Myocardial tissue is obtained in vivo by transvenous endomyocardial biopsy of the RV. Fibrillar collagen can then be quantified under polarized light after Picrosirius red[24] or Masson trichrome[25] staining. Using

ARTICLE HIGHLIGHTS

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

CMR to assess LGE, a sign of MF, is preferred for assessment of focal MF because it is readily available, is noninvasive, 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 biopsy or CMR. The literature was searched using the PubMed and MEDLINE databases up to June 1, 2016. Key Medical Subject Headings terms and keywords were included pertaining to MF (*delayed [gadolinium] enhancement, pathological late gadolinium enhancement, myocardial late gadolinium enhancement, abnormal late gadolinium enhancement, fibrosis, myocardium, myocardial fibrosis, papillary muscles/pathology, ventricular dysplasia,* and *ventricular torsion*) and exercise training (*exercise, athletes, sports, sport, motor activity, marathon, triathlon, bicycling, swimming, physical endurance, marathon running, sports medicine,* and *exercise-induced*).

Selection of Studies

The selection process consisted of review of the titles, abstracts, and full texts of articles by two authors (F.R.S. and T.M.H.E.), who later met to reach mutual consensus. The inclusion criteria were (1) fibrosis established by validated techniques and (2) a study population consisting 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 underlying (genetic) cardiovascular disease, such as hypertrophic cardiomyopathy or arrhythmogenic RV cardiomyopathy.

RESULTS

The 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).

MF Reported in Case Studies/Series

Case reports/series included 35 athletes (Table 1) participating in a wide range of sports: orienteering,[33] powerlifting,[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 a soccer player.[28] Athletes ranged in age from 13 to 73 years at MF diagnosis, and 76% of the population was male. Although the sex and age of 6 athletes was not reported,[35,41] most athletes with MF were young (20 of 35 were aged $\leq$30 years). In 12 athletes (34%), the biopsies were performed postmortem.

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; 7 studies confirmed the presence of MF in athletes, and 7 studies did not. Overall, 89% of the population was male, and MF was reported in 30 of the 509 athletes (5.9%). Interestingly, lifetime exercise exposure (1-100 completed marathons) and age (26-72 years) varied substantially across participants, but most reports occurred in long-term endurance athletes.

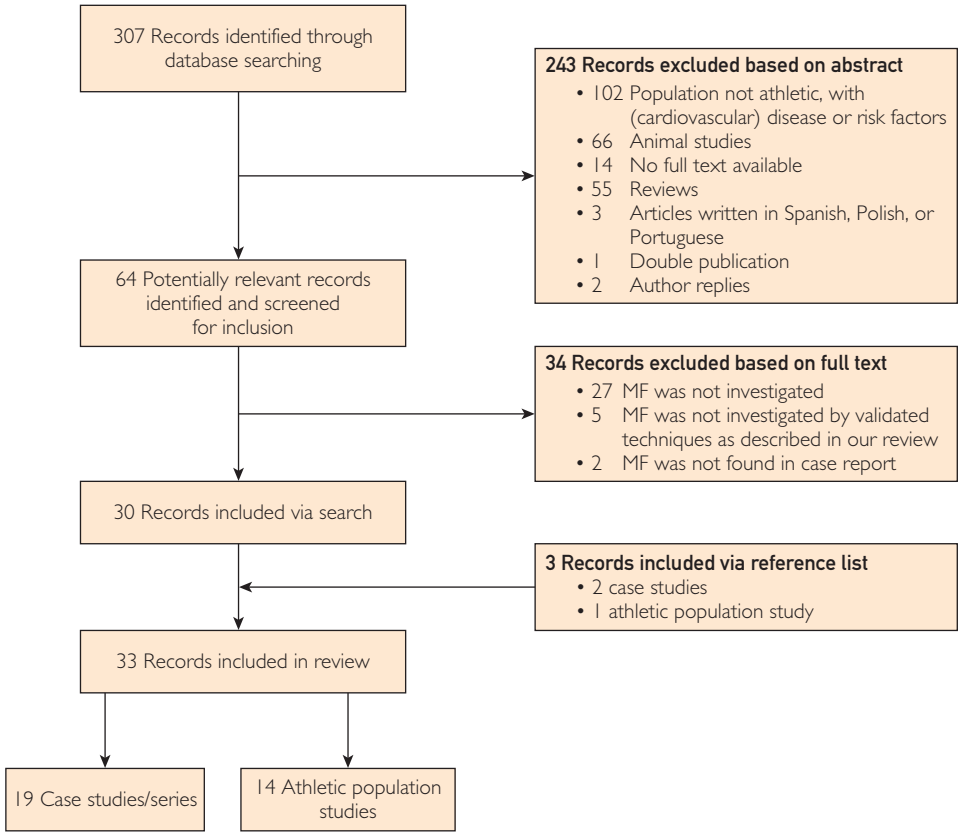

FIGURE 1. Flowchart of the search strategy to determine the prevalence of myocardial fibrosis (MF) in athletes. The following Medical Subject Headings keywords were used in the literature search: *delayed enhancement, pathological late gadolinium enhancement, myocardial late gadolinium enhancement, abnormal late gadolinium enhancement, fibrosis, myocardium, myocardial fibrosis, papillary muscles/pathology, ventricular dysplasia, ventricular torsion, exercise, athletes, sports, sport, motor activity, marathon, triathlon, bicycling, swimming, physical endurance, marathon running, sports medicine,* and *exercise-induced*.

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 nonspecific LGE pattern, and the remaining athletes demonstrated an ischemic (n=7, 20%), myocarditic (n=7, 20%), or hypertrophic (n=1, 3%) MF pattern; the pattern was not specified in 6 athletes (17%) (Figure 2).

Findings from the CMR studies confirm the variation in MF patterns (Table 2). Most athletes with MF (12 of 30, 40%) show a nonspecific 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 (n=3, 10%) and mechanical overload (n=7, 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[6] reported that MF was confined to the interventricular septum, frequently where the RV attaches to the septum (the hinge points). Overall, a significant proportion of MF in athletes is found in the septum (19 of 65, 29%)[5,6,34,41–43] and RV insertion points (12 of 65, 19%).[5,6,8,42]

TABLE 1. Characteristics of Case Series and Reports of Myocardial Fibrosis (MF) in Athletes

Reference, year	Type of athlete	Years of exercise/hours of sport per week/number of marathons	Age (y)	Sex	Description of MF	Mode of diagnosis
Thiene et al,[28] 1983	Soccer player (n=1)	Not specified	24	Male	Patchy fibrosis, scattered myofibrillar degeneration with contraction bands, and initial polymorphonuclear neutrophil infiltration	Biopsy (postmortem)
Bharati et al,[29] 1988	Runner (n=1)	Trained on a regular basis	47	Male	Myocardial disarray, fibrosis, fatty infiltration, mononuclear 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 (postmortem)
Rowe,[30] 1991	Marathon runner (n=1)	Completed 524 marathons, most in <4 h Also cross-country ski and canoe races, triathlons, and ultramarathons	62	Male	Focal fibrosis of the LV papillary muscles consistent with remote ischemia	Biopsy (post-mortem)
Zeppilli et al,[31] 1994	Basketball player (n=1) Soccer players (n=2) Volleyball player (n=1) Water-skier (n=1)	Not specified	17-23	60% male	Fibrosis prevailing in the RV with occasional focus of cellular necrosis (basketball player) Focal nonspecific fibrosis (soccer player) Diffuse, nonspecific fibrosis (soccer player) Myocarditis with fibrosis largely prevailing in the RV (volleyball player) Mild focal increase of the interstitial fibrous tissue, suggesting active myocarditis (water-skier)	Biopsy (minor arrhythmias or echocardiographic abnormalities)
Kindermann et al,[32] 1998	Endurance athlete (n=1)	Weekly 10 h of endurance training, including 50 km of running and 1-2 h of mountain biking	32	Male	Focal fibrosis	Biopsy (drop of performance)
Larsson et al,[33] 1999	Orienteers (n=2)	One participant was ranked in the national elite class	27, 28	100% male	Myocarditis healed, fibrosis, hypertrophy Hypertrophy, fibrosis	Biopsy (postmortem)

Continued on next page

TABLE 1. Continued

Reference, year	Type of athlete	Years of exercise/hours of sport per week/number of marathons	Age (y)	Sex	Description of MF	Mode of diagnosis
Lesauskaite and Valanciute,[34] 1998	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 the posterior wall of the LV and interventricular septum Foci of connective tissue in the LV and interventricular septum	Biopsy (postmortem)
Heidbüchel et al,[35] 2003	Endurance athletes (n=3)	≥3 x 2 h/wk for ≥5 y	Not specified	Not specified	Fibrosis (with fat in 1 patient)	Biopsy (ventricular arrhythmias)
Murty et al,[36] 2008	Not specified (n=1)	Not specified	16	Male	There were wide swaths of MF 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 (postmortem)
Ottaviani et al,[37] 2008	Soccer player (n=1)	Not specified	13	Male	The lateral wall of the LV presented an area of MF, characterized by replacement of the necrotic fibers by dense collagenous scarring	Biopsy (postmortem)
Lakhan and Harle,[38] 2008	Powerlifter (n=1)	Participated regularly in aerobic activity and traveled frequently	73	Female	Widespread interstitial MF in the RV and LV, mostly prevalent in the endomyocardium and affecting 25% of the myocardium	Biopsy (postmortem)
Whyte et al,[39] 2009	Marathon runner (n=1)	Running for 20 y, completed multiple marathons, personal best 2 h and 30 min	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 (postmortem)

Continued on next page

TABLE 1. Continued

Reference, year	Type of athlete	Years of exercise/hours of sport per week/number of marathons	Age (y)	Sex	Description of MF	Mode of diagnosis
Harper and Mottram,[40] 2009	Triathlete (n=1)	Averaged 10-15 events per year Former world champion	32	Female	Patchy interstitial fibrosis in the RV	Biopsy (exercise-induced recurrent ventricular tachycardia)
La Gerche et al,[41] 2010	Endurance athletes (n=3)	≥3 h/wk of sport with a moderate to intense dynamic component, competitively or recreationally for ≥5 y	Not specified	Not specified	Septal fibrosis	Biopsy (RV arrhythmias)
Bhella et al,[42] 2010	Runner (n=1)	After running 1460 km and ascending >2600 m the run was ended; in support of the event, after a 3-d rest, the individual cycled an additional 1580 km in 9 d 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 et al,[43] 2010	Competitive high school athlete (n=1)	Not specified	14	Female	Extensive areas of interstitial fibrosis involving the posterior LV wall, the interventricular septum, and the papillary muscles	Biopsy (postmortem)
Pressler et al,[44] 2011	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 et al,[45] 2012	Cyclist (n=1)	23,000 km per year for 14 y	30	Male	Focal fibrosis of the LV and intracardiac dimensions consistent with physiologic remodeling	Biopsy (palpitations)
Schnell et al,[46] 2016	Cyclists (n=5) Football player (n=1) Basketball player (n=1)	≥6 h/wk for ≥5 y	19-32	86% male	LGE predominantly in the lateral wall; mean ± SD size of 20.3±7.7 g Subepicardial (cyclist, football player, basketball player) Transmural patches (cyclist) Intramural patches (cyclists) Likely to reflect chronic scarring	CMR (pathologic T-wave inversions on ECG (n=4) or ventricular arrhythmias (n=3)

CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; LGE = late gadolinium enhancement; LV = left ventricle; RV = right ventricle.

TABLE 2. Prevalence and Patterns of Myocardial Fibrosis (MF) in Athletic Populations Using CMR[a,b]

Reference, year	Study population	Exercise exposure	Age (y), mean ± SD	Sex	Prevalence of MF (%)	Pattern/location of MF
Wilson et al,[5] 2011	Lifelong veteran endurance athletes (n=12) Veteran sedentary controls (n=20) Young endurance athletes (n=17)	Mean ± SD of 43±6 y of competitive exercise training No exercise training Mean ± SD of 18±7 y of competitive exercise training	57±6 60±5 31±5	100% male	50 0 0	1. Septal and lateral wall 2. Epicardial lateral wall 3. Basal and mid insertion point 4. Inferior insertion point mid and apical 5. Insertion point inferior mid/apical 6. Inferior insertion point
La Gerche et al,[6] 2012	Marathon runners (n=7) Endurance triathletes (n=11) Alpine cyclists (n=9) Ultra-triathletes (n=13)	>10 h of intense training per week Finished in the first 25% of the field in a recent endurance event	37±8	90% male	12.8	Interventricular septum, frequently in the vicinity of the RV attachment
Breuckmann et al,[7] 2009	Marathon runners (n=102) Sedentary controls (n=102)	≥5 marathons in ≤3 y No exercise training	57±6	100% male	Athletes, 12 Controls, 4	Athletes: 42% involving the subendocardial layer and partial transmural spreading; 58% atypical patchy to streaky subepicardial to midmyocardial hyperenhancement, which may represent interstitial fibrosis or myocardial fiber disarray for various potential reasons Controls: 50% CAD pattern; 50% non-CAD pattern
Mordi et al,[8] 2016	Aerobic exercise (n=21), predominantly running	>6 h/wk of intensive aerobic exercise at amateur level	46±11	100% male	9.5	Small amounts of LGE at RV insertion points
Karlstedt et al,[9] 2012	Marathon runners (n=25)	Mean ± SD of 47±7 miles/wk ≥3 marathons in the past 2 y	55±4	84% male	8	Anterior wall of the LV myocardium in subendocardial distribution before running the marathon, with concomitant evidence of obstructive LAD artery disease
Erz et al,[10] 2013	Runners (n=23) Triathletes (n=16) Cyclists (n=5) Speed skater (n=1)	7 h/wk for ≥2 y	40±9	100% male	2.2	Posterolateral wall of the LV, indicative of nonischemic scarring; most likely due to former myocarditis

Continued on next page

TABLE 2. Continued

Reference, year	Study population	Exercise exposure	Age (y), mean ± SD	Sex	Prevalence of MF (%)	Pattern/location of MF
Mangold et al,[11] 2013	Long-distance runners (n=39) Cyclists (n=8) Triathletes (n=34) Handball players (n=13) Speed skater (n=1)	Mean ± SD of 13.1±4.2 h/wk for ≥2 y	35±11	77% male	2.1 (2 cyclists)	Spot-shaped pattern consistent with a nonischemic, postinflammation Disseminated and intramural myocardial hyperenhancement
Mousavi et al,[19] 2009	Moderately trained marathon runners (n=10) Highly trained marathon runners (n=4)	Mean ± SD of 26±8 miles/wk Mean ± SD of 53±12 miles/wk	33±6	57% male	0	Not applicable
Hanssen et al,[20] 2011	Marathon runners (n=28)	Mean ± SD training mileage of 43±17 km/wk in the 10 wk before the marathon; median ± SD finish time was 245±55 min	41±5	100% male	0	Not applicable
Trivax et al,[21] 2010	Marathon runners (n=25)	Previous 6 mo: mean ± SD of 30.2±11.4 miles/wk Past 5 y: mean ± SD of 17.0±11.8 miles/wk	39±9	52% female	0	Not applicable
Gaudreault et al,[22] 2013	Marathon runners (n=20)	Mean ± SD of 8.1±2.3 h/wk Mean ± SD of 9±8 marathons in a mean ± SD of 14±5 y	45±8	70% male	0	Not applicable
O'Hanlon et al,[23] 2010	Marathon runners (n=17)	7 h/wk	34±7	100% male	0	Not applicable
Heidbüchel et al,[35] 2003	Endurance athletes (n=28)	≥3 × 2 h/wk for ≥5 y	Not specified	Not specified	0	Not applicable
Scharhag et al,[47] 2006	Mountain bike marathon cyclists (n=15) Marathon runners (n=5)	Training history in endurance exercise of a mean ± SD of 7±3 y and trained a mean ± SD of 9±4 h/wk	36±7	100% male	0	Not applicable

[a]CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; LAD = left anterior descending; LGE = late gadolinium enhancement; LV = left ventricle; RV = right ventricle.
[b]Studies are arranged from highest to lowest MF prevalence.

Some have speculated that the distention of the RV 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 LV 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[7] reinforced the heterogeneity of the percentage of LGE-positive myocardium (range, 0.5%-17.8%) in German marathon runners. Also, these authors found that the median percentage of MF was comparable between runners with a subendocardial LGE pattern (0.9%), runners with a nonspecific pattern (1.2%), and physically inactive controls (2.2%). Last, the mean ± SD volume of the LGE region in the study by Schnell et al[46] was 20.3±7.7 g, which was the equivalent of 12%±4.8% of the LV mass.

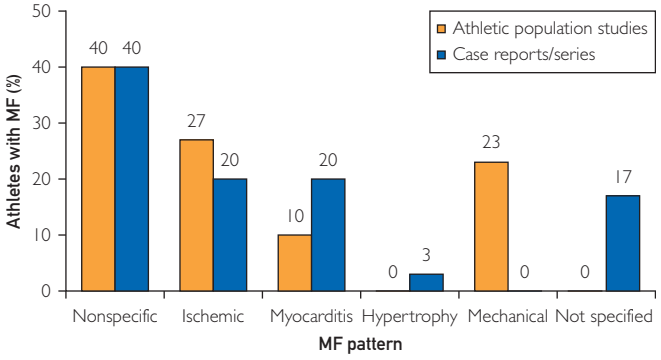

FIGURE 2. The prevalence of the pattern of myocardial fibrosis (MF) found in athletes in case reports/series and athletic population studies.

DISCUSSION

The present review reveals that the phenotype of MF in athletes demonstrates large variance in patterns, location, and quantification. Nonetheless, a nonspecific LGE pattern, location in the RV or septum, and representing 1% to 3% of the myocardium seem to be the most common descriptors used for MF typically found in athletes by magnetic resonance imaging. 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 vs 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[7] found that MF was more prevalent in athletes (n=102) than in controls (n=102) (12% vs 4%; *P*=.077). Wilson et al[5] observed MF in 6 of 12 lifelong veteran endurance athletes but not in any of 20 sedentary peers. Although both studies reported a higher prevalence of MF in athletes vs physically inactive controls, the presence of MF in these control groups was lower compared with recent observations in the general population. In a large American cohort study of nonathletes (mean ± SD age, 68±9 years), MF was found in 146 of 1840 participants (7.9%).[48] Population studies from Iceland (n=936)[49] and Sweden (n=248)[50] report an even 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

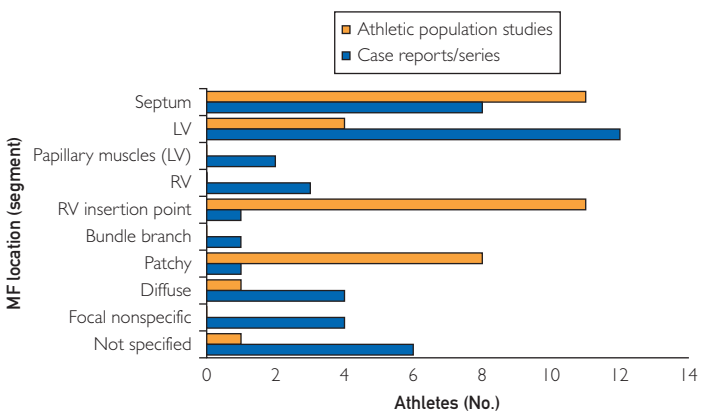

FIGURE 3. The frequency of the location of myocardial fibrosis (MF) reported in case studies/series and athletic population studies. In 10 athletes (5 in case series[29,34,39,43] and 5 in an athletic population study[6]), MF was present at multiple locations of the heart. LV = left ventricle; RV = right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

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 vs Diffuse MF

The 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 may limit the generalizability of these findings. Nevertheless, 2 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 was observed between athletes (n=21, ≥6 h/wk of exercise training) and controls (n=21).[8] In contrast, significantly higher native T1 values of the LV and interventricular septum were found in Turkish athletes (≥6 h/wk intense exercise training) compared with age- and sex-matched controls (<3 h/wk moderate exercise). Moreover, athletes reporting at least 5 years of exercise training had higher T1 values, indicating more diffuse fibrosis compared with athletes exercising for less than 5 years ($P<.05$).[51] These findings suggest a higher prevalence of diffuse MF in Turkish athletes vs controls. Apart from the age difference between Scottish (mean ± SD age, 46±11 years) and Turkish (mean ± SD age, 25±3 years) athletes, 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 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[6] reported that athletes with LGE had participated in endurance exercise longer (mean ± SD, 20±16 years) than athletes without MF (mean ± SD, 8±6 years; $P=.043$). Similarly, Wilson et al[5] reported that LGE was related to the years of training ($P<.001$) and the number of completed competitive marathons ($P<.001$) or ultra-endurance marathons (>50 miles) ($P=.007$). Möhlenkamp et al[53] reported an association between the number of completed marathons and LGE ($P=.02$). Evidence from case reports/series confirms that athletes diagnosed as having MF demonstrate high doses of exercise for many years (Table 1). For example, an athlete trained 10 h/wk, including 50 km of running and 1 to 2 hours of mountain biking,[32] while another athlete cycled an average of 23,000 km/y 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[5] found that the prevalence of MF was the highest (50%) in veteran endurance athletes (mean ± SD age, 57±6 years) who had been involved in lifelong competitive training for a mean ± SD of 43±6 years. Studies including predominantly younger participants or less-trained individuals generally fail to find MF.[19-23]

Potential Mechanisms of MF Development

Evidence of MF in athletic populations is exclusively based on observational studies, which do not provide insight into potential underlying mechanisms. However, we summarize the available evidence for 4 different pathways based on patient characteristics, location and patterns of MF, and identified predictors.

Genetic Predisposition. Ten case reports describe the presence of MF in 28 young athletes (≤30 years old). 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] In hypertrophic cardiomyopathy, LGE varies from very limited to large, confluent, infarct-like patches occupying significant proportions of the LV,[56] and it localizes preferentially to the most hypertrophied regions of the ventricle.[54] Furthermore,

Mayo Clin Proc. ■ XXX 2016;■■(■):1-15 ■ http://dx.doi.org/10.1016/j.mayocp.2016.07.012
www.mayoclinicproceedings.org

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 in individuals with the same genetic defect that little, if any, relationship can be established between mutations and phenotype, clinical course, and patient outcome. Similarly, genetic factors may contribute to the variability of MF presentations in athletes.

Silent Myocarditis. The results of 5 biopsy studies and 3 CMR-LGE studies suggest that myocarditis is responsible for LGE and that this is probably true in some (n=10) but not all (n=65) athletes. Late gadolinium enhancement has high specificity for the detection of injury in myocarditis but variable sensitivity to detect active or chronic inflammation.[59] This might be due to limited areas of necrotic myocytes that cannot be visualized because of limited pixel size in CMR images compared with 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, and 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] Several animal studies found that exercise itself may cause myocarditis and lead to the development of MF.[62-64] In a rat model of exercise training, MF disappeared 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 dilatation or fibrosis.[66] A mouse model found that physical activity during a "silent" myocarditis may exaggerate damage to the heart.[67] Mice were infected with coxsackievirus to induce myocarditis and then were divided into 4 groups: group 1 received immunosuppression with daily doses of cyclosporine and an antithymocyte monoclonal antibody, group 2 performed daily swimming exericise, group 3 received both interventions, and group 4 served as controls. After 21 days, mortality rates were highest in the exercise-only group (group 2).[67] Hence, it is possible that continued exercise training accelerates myocardial damage and MF during a silent myocarditis.

Pulmonary Artery Pressure Overload. The volume of LGE is typically small and confined to the septum or RV insertion points in 48% of athletes diagnosed as having MF by magnetic resonance imaging 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] Late gadolinium enhancement 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 RV and LV 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% vs 4% for the RV and LV, respectively.[71] The thinner wall of the RV may facilitate the progression from increased wall stress to cardiomyocyte damage more than in the LV. Although echocardiography studies show that acute exercise-induced changes in RV structure and function fully recover within days,[6] chronic structural changes from repetitive prolonged exercise are possible. Therefore, MF in athletes may result from long-term endurance exercise training and competition and the associated repetitive exercise-induced elevations in pulmonary artery pressures.

Repetitive Microdamage. Cardiac troponin I and T are the standard biomarkers used to serologically identify myocardial damage. Many studies have reported 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 microdamage to cardiomyocytes. Accordingly, repetitive exposure to high-intensity endurance exercise—induced cardiac microdamage, evidenced by minor troponin level elevations, could lead to MF development after 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. Three of 12 German marathon runners with LGE (25%) required revascularization during a mean ± SD of 21±3 months of follow-up compared with 1 of 90 runners (1%) without LGE ($P<.001$).[7] Half of the runners with MF, however, had an LGE pattern suggestive of ischemic myocardial injury. The increased risk of MF on adverse outcomes persisted during a mean ± SD of 74±12 months of follow-up.[79] Runners with coronary events had a higher prevalence of LGE (57%) compared with peers without coronary events (8%; $P=.003$), despite comparable mean ± SD 10-year Framingham Risk Scores (7.9%± 2.3% vs 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 vs 26; $P=.0046$),[53] demonstrating that the increased incidence of cardiovascular events in some runners with LGE is due to atherosclerosis and previous infarction. Other studies in other patients do not support atherosclerosis and previous 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 previous infarction or those with evidence of active myocardial inflammation should be pharmacologically treated to reduce their risk of an acute cardiac event and to treat their myocarditis, respectively.

The prognostic significance of nonspecific 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. Myocardial fibrosis detected by LGE in cardiac studies of asymptomatic athletes performed 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] most available evidence suggests 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 (ie, 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 previous infarction and seems 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 RV and the septum. This pattern seems more common in long-term endurance athletes and may represent the effect of repetitive myocardial microtrauma or repetitive dilatation of the RV with exercise. Athletes with underlying cardiovascular disease should receive pharmacological treatment to reduce the risk of secondary events. The significance of nonspecific MF is largely unknown, and future studies investigating the functional and clinical consequences of MF in athletes are warranted.

Abbreviations and Acronyms: **CAD** = coronary artery disease; **CMR** = cardiac magnetic resonance imaging; **ECG** = electrocardiogram; **LAD** = left anterior descending; **LGE** = late gadolinium enhancement; **LV** = left ventricle; **MF** = myocardial fibrosis; **RV** = right ventricle

Grant Support: This study was supported by Marie Sklodowska-Curie Fellowship grant 655502 (T.M.H.E)

from the European Commission; Rubicon grant 825.12.016 from the Netherlands Organisation for Scientific Research (T.M.H.E.); and a grant from the Radboud Institute for Health Sciences (V.L.A).

Potential Competing Interests: Dr Thompson has received research grants from Aventis, Regeneron, Sanofi, and Pfizer; has served as a consultant for Aventis, Regeneron, Merck, Genomas, Abbvie, Sanofi, and Pfizer; has received speaker honoraria from Regeneron, Sanofi, Amgen, Aventis, and Merck; and owns stock in General Electric, JA Wiley Publishing, Johnson & Johnson, Abbvie, Abbott, Medtronic, and Cryolife.

Correspondence: Address to Thijs M.H. Eijsvogels, PhD, Department of Physiology (392), Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands (Thijs.Eijsvogels@radboudumc.nl).

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(3):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(23):1727-1733.
3. Eijsvogels TM, Fernandez AB, Thompson PD. Are there deleterious cardiac effects of acute and chronic endurance exercise? *Physiol Rev*. 2016;96(1):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(3):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(6):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(8):998-1006.
7. Breuckmann F, Möhlenkamp S, Nassenstein K, et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. *Radiology*. 2009;251(1):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*. 2016;17(7):797-803.
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(2):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(12):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 Fail Rev*. 2005;10(1):71-78.
13. Hill JA, Olson EN. Cardiac plasticity. *N Engl J Med*. 2008;358(13):1370-1380.
14. Sugihara N, Genda A, Shimizu M, et al. Diastolic dysfunction and its relation to myocardial fibrosis in essential hypertension [in Japanese]. *J Cardiol*. 1988;18(2):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(19):1574-1580.
16. Diez J. Mechanisms of cardiac fibrosis in hypertension. *J Clin Hypertens (Greenwich)*. 2007;9(7):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(10):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(10):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(10):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(4):143-152.
21. Trivax JE, Franklin BA, Goldstein JA, et al. Acute cardiac effects of marathon running. *J Appl Physiol (1985)*. 2010;108(5):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(10):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. *J Histochem Cytochem*. 2014;62(10):751-758.
25. Roberts WC, Siegel RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol*. 1987;60(16):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(8):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(13):932-937.
28. Thiene G, Pennelli N, Rossi L. Cardiac conduction system abnormalities as a possible cause of sudden death in young athletes. *Hum Pathol*. 1983;14(8):704-709.
29. Bharati S, Dreifus LS, Chopskie E, Lev M. Conduction system in a trained jogger with sudden death. *Chest*. 1988;93(2):348-351.
30. Rowe WJ. A world record marathon runner with silent ischemia without coronary atherosclerosis. *Chest*. 1991;99(5):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(2):373-380.
32. Kindermann W, Janzen I, Urhausen A, Schieffer HJ. Heart enlargement in an athlete: a diagnostic challenge [in German]. *Z Kardiol*. 1998;87(2):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(3):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(2):157-161.
35. Heidbüchel 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(16):1473-1480.

36. Murty OP, Mun KS, Hussin H. Silent bony calcification of coronaries in an adolescent: an unusual case. *J Forensic Leg Med*. 2008;15(1):37-41.
37. Ottaviani G, Lavezzi AM, Matturri L. Sudden unexpected death in young athletes. *Am J Forensic Med Pathol*. 2008;29(4):337-339.
38. Lakhan SE, Harle L. Cardiac fibrosis in the elderly, normotensive athlete: case report and review of the literature. *Diagn Pathol*. 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 [published online February 2, 2009]. *BMJ Case Rep*. 2009. http://dx.doi.org/10.1136/bcr.08.2008.0758.
40. Harper RW, Mottram PM. Exercise-induced right ventricular dysplasia/cardiomyopathy: an emerging condition distinct from arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Lung Circ*. 2009;18(3):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(16):1268-1274.
42. Bhella PS, Kelly JP, Peshock R, Levine BD. Delayed enhancement of the intraventricular septum following an extraordinary endurance exercise [published online December 2, 2010]. *BMJ Case Rep*. 2010. http://dx.doi.org/10.1136/bcr.06.2010.3096.
43. Sivridis E, Pavlidis P, Stamos C, Giatromanolaki A. Sudden death after myocardial infarction in a high-school athlete. *J Forensic Sci*. 2010;55(5):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(1):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(2):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(2):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. *Eur J Cardiovasc Prev Rehabil*. 2006;13(3):388-397.
48. Turkbey EB, Nacif MS, Guo M, et al. Prevalence and correlates of myocardial scar in a US cohort. *JAMA*. 2015;314(18):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(9):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(4):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;32(6):975-981.
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(3):423-432.
53. Möhlenkamp 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(15):1903-1910.
54. Olivotto I, Girolami F, Nistri S, et al. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. *J Cardiovasc Transl Res*. 2009;2(4):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(1):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(7):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(3):199-204.
58. Marian AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol*. 2008;23(3):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(17):1475-1487.
60. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. *Am J Cardiovasc Pathol*. 1987;1(1):3-14.
61. Cooper LT Jr. Myocarditis. *N Engl J Med*. 2009;360(15):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(1):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(5):1749-1755.
65. McCarthy RE III, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med*. 2000;342(10):690-695.
66. Kallwellis-Opara A, Dorner A, Poller WC, et al. Autoimmunological features in inflammatory cardiomyopathy. *Clin Res Cardiol*. 2007;96(7):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. *J Lab Clin Med*. 1990;115(4):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(19):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(16):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(16):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(6):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(3):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(4):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(1):e3-e4.
75. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol*. 2006;48(10):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(16):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. *Eur J Heart Fail*. 2009;11(10):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(23):2733-2743.
79. Möhlenkamp 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(1):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(9):1171-1175.
81. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ; Million Women Study Collaborators. 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(8):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(5):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(6):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(5):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(6):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(3):276-283.