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Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes

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Wilson M, O'Hanlon R, Prasad S, Deighan A, MacMillan P, Oxborough D, Godfrey R, Smith G, Maceira A, Sharma S, George K, Whyte G. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol* 110: 1622–1626, 2011. First published February 17, 2011; doi:10.1152/japplphysiol.01280.2010.—This study examined the cardiac structure and function of a unique cohort of documented lifelong, competitive endurance veteran athletes (>50 yr). Twelve lifelong veteran male endurance athletes [mean ± SD (range) age: 56 ± 6 yr (50–67)], 20 age-matched veteran controls [60 ± 5 yr; (52–69)], and 17 younger male endurance athletes [31 ± 5 yr (26–40)] without significant comorbidities underwent cardiac magnetic resonance (CMR) imaging to assess cardiac morphology and function, as well as CMR imaging with late gadolinium enhancement (LGE) to assess myocardial fibrosis. Lifelong veteran athletes had smaller left (LV) and right ventricular (RV) end-diastolic and end-systolic volumes ($P < 0.05$), but maintained LV and RV systolic function compared with young athletes. However, veteran athletes had a significantly larger absolute and indexed LV and RV end-diastolic and systolic volumes, intraventricular septum thickness during diastole, posterior wall thickness during diastole, and LV and RV stroke volumes ($P < 0.05$), together with significantly reduced LV and RV ejection fractions ($P < 0.05$), compared with veteran controls. In six (50%) of the veteran athletes, LGE of CMR indicated the presence of myocardial fibrosis (4 veteran athletes with LGE of nonspecific cause, 1 probable previous myocarditis, and 1 probable previous silent myocardial infarction). There was no LGE in the age-matched veteran controls or young athletes. The prevalence of LGE in veteran athletes was not associated with age, height, weight, or body surface area ($P > 0.05$), but was significantly associated with the number of years spent training ($P < 0.001$), number of competitive marathons ($P < 0.001$), and ultraendurance (>50 miles) marathons ($P < 0.007$) completed. An unexpectedly high prevalence of myocardial fibrosis (50%) was observed in healthy, asymptomatic, lifelong veteran male athletes, compared with zero cases in age-matched veteran controls and young athletes. These data suggest a link between lifelong endurance exercise and myocardial fibrosis that requires further investigation.

(ultra)endurance exercise; veteran athlete; cardiac magnetic resonance

AGING IS ASSOCIATED WITH changes to the cardiovascular (CV) system that underpin a reduced functional capacity, although regular endurance exercise training may slow this progressive decline in CV function with age. The benefits of repetitive moderate-intensity exercise as you age are well known, but the consequences of lifelong competitive endurance activity in veteran athletes (>50 yr) is less certain (29).

Compared with age-matched sedentary controls, a higher prevalence of subclinical cardiac disease has been reported in veteran athletes that may increase risks of an exercise-induced cardiac event (15, 20, 26). Several case series and case studies have reported an increased prevalence of supraventricular (16) and complex ventricular arrhythmias (7, 9, 28) in endurance-trained veteran athletes. The etiology and clinical significance of these arrhythmias remain to be fully elucidated, as several forms of idiopathic ventricular arrhythmias have been identified in athletes, which, by definition, originate in hearts without structural abnormalities (1). On the basis of this descriptive data and small number of autopsy reports, some authors have speculated that, in the absence of any other cause, lifelong repetitive bouts of arduous endurance exercise may result in fibrous replacement of the myocardium, resulting in a pathological substrate for the development of arrhythmias (10, 27, 28). Despite such speculation, only limited case evidence exists for exercise-induced myocardial fibrosis in endurance veteran athletes (5, 21, 22).

Furthermore, recent studies examining cardiac structure and function in veteran endurance athletes are limited by recruitment of veteran participants who, while older and endurance trained, were not truly lifelong endurance athletes with poorly documented (ultra)endurance histories (5, 7, 9, 14, 27, 28). Consequently, the impact of lifelong episodes of intense, prolonged exercise, as experienced by veteran endurance athletes, is not fully understood.

Gadolinium-enhanced CV magnetic resonance (CMR) imaging now provides a sensitive tool for detection of myocardial fibrosis. Accordingly, the aim of the present study was to examine the cardiac structure and function of a unique cohort of truly lifelong, competitive veteran endurance athletes (>50 yr) using state-of-the-art CMR imaging.

METHODS

Participants. This study complies with the Declaration of Helsinki, and, following ethical approval from the Brompton, Harefield, and National Heart and Lung Institute research ethics committee, 12 veteran male endurance athletes [mean ± SD (range); age: 57 ± 6 yr (50–67)], 20 age-matched sedentary controls [60 ± 5 yr (52–69)], and 17 young male endurance athletes [31 ± 5 yr (26–40)] were recruited and provided written, informed consent. All subjects self-reported no significant comorbidities, including chronic CV disease [angina, previous myocardial infarction (MI), prior revascularization,

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pulmonary vascular disease, past or current hypertension, diabetes mellitus, and collagen disorders] and pulmonary disease.

Recruitment. Accurate diary recordings of the athlete's full training and competitive histories were collected. The data are unique in as much as all athletes were documented lifelong endurance athletes still competing in intensive endurance events. Veteran athletes were recruited in two ways: *1*) an advertisement placed in the United Kingdom's 100 Marathon running club newsletter, an organization whereby membership is given to the proven completion of a minimum of 100 competitive marathons; and *2*) an advertisement placed in the British Olympic Association's "Olympian" magazine, a quarterly magazine for past and present Olympians. Veteran athletes reported 35–52 yr and young athletes 11–31 yr of continuous training and competition. Six veteran and three young athletes have represented Great Britain in numerous World Championships (total = 35), with one veteran (rowing) and one young athlete (modern pentathlon) medaling at the Olympic Games. Age-matched veteran control participants were recruited via advertisement and word of mouth. Young athletes were recruited through a previous CMR investigation (18), but were also required to provide evidence of lifelong endurance competition. None of the athletes or veteran controls was a current smoker, with only one veteran athlete reporting a smoking history of 15 yr (ceased 10 yr previously). None of the athletes or veteran controls reported diabetes mellitus or had a family history of CV disease or diabetes mellitus. All participants were asked not to run more than a total distance of 20 miles (32 km) in the week leading up to the study, with no training in the immediate 2 days before CV investigations.

CMR. A standard cardiac volume, wall dimension, function, and late gadolinium enhancement (LGE) sequence was performed on a dedicated scanner (Siemens Avanto 1.5-T, Erlangen, Germany), with full myocardial coverage (11). Left (LV) and right ventricular (RV) volumes, mass, and function were quantified using customized analysis software (CMRtools, Cardiovascular Imaging Solutions, London, UK) by a blinded, single experienced investigator. Papillary muscles were included in the mass and excluded from the volume. Wall motion was analyzed based on the 16 segment American Heart Association/American College of Cardiology model (6). Two CMR validated methods to image myocardial inflammation (myocardial inflammation and regional hyperemia) were performed, according to established protocols (18).

Myocardial fibrosis. Imaging for LGE to identify fibrosis was performed 5–10 min after gadolinium contrast injection in identical short-axis planes to cine images using a breath-hold inversion-recovery (fast low-angle shot) gradient echo sequence (24). Inversion times were optimized to null normal myocardium. In all patients, LGE imaging was repeated for each short-axis image in two separate phase-encoding directions to exclude artifact. LGE images were analyzed quantitatively by two independent readers using customized software (MRI-MASS, Medis, Leiden, the Netherlands). In brief, the endocardial and epicardial borders were traced for each short-axis slice. A region of interest averaging 50 mm^2 was defined within the normal, remote myocardium in an area with uniform myocardial suppression free of artifacts. A multipass region-growing algorithm was used to identify the fibrotic boundaries based on the "full-width half-maximum" technique, and myocardial LGE was expressed as present/absent (LGE+/LGE−), as gram mass, and as a percentage of total LV mass (25).

Statistics. Values are presented as means ± SD (range). Three-dimensional cardiac structural indexes were scaled by body surface area (BSA) raised power 1.5. Linear dimensions were scaled by BSA raised 0.5 (2). Statistical analyses comparing veteran athletes, age-matched controls, and young athletes used one-way ANOVA, with a post hoc Bonferroni. To compare athletes and controls presenting with and without LGE, a Mann-Whitney test was used. The critical α-level was set at 0.05, and all analyses were carried out on SPSS software.

RESULTS

Descriptive statistics. There were no significant differences in anthropometric data or blood pressure between all groups (Table 1). There were no significant differences in resting heart rate (56 ± 8 vs. 57 ± 8 beats/min) between veteran and young athletes, while heart rate was higher in veteran controls (67 ± 8 beats/min, $P = 0.002$).

Cardiac morphology and systolic function (CMR). Absolute and indexed left atrial volume and LV mass were not different between groups (Table 2). Veteran athletes had a significantly smaller absolute LV and RV end-diastolic and systolic volumes ($P < 0.05$) than did young athletes. Consequently, absolute and indexed LV stroke volume was smaller in veteran

Table 1. *Participant demographics, including length of endurance career and competitive curriculum vitae*

				P Value	
	Veteran Athletes	Age-matched Controls	Young Athletes	Veteran Athletes vs. Controls	Veteran Athletes vs. Young Athletes
N	12	20	17	NA	NA
Age, yr	57 ± 6 (50–67)	60 ± 5 (52–69)	31 ± 5 (26–40)	0.65	<0.001
Height, m	1.78 ± 0.06 (1.73–1.91)	1.76 ± 0.08 (1.60–1.88)	1.81 ± 0.08 (1.70–1.93)	0.97	1.000
Body mass, kg	77.6 ± 10.1 (65–97)	78.3 ± 9.9 (64–98)	80.0 ± 9.2 (61.8–99)	1.000	1.000
Body surface area, m^2	1.96 ± 0.14 (1.79–2.26)	1.94 ± 0.12 (1.73–2.2)	2.00 ± 0.14 (1.74–2.3)	1.000	1.000
Resting heart rate, beats/min	56 ± 8 (44–69)	67 ± 8 (55–88)	57 ± 8 (48–72)	0.002	1.000
Systolic blood pressure, mmHg	124 ± 7 (110–135)	125 ± 8 (105–140)	124 ± 5 (114–130)	1.000	1.000
Diastolic blood pressure, mmHg	76 ± 9 (65–90)	76 ± 7 (60–85)	77 ± 7 (68–88)	1.000	1.000
Previous or current hypertensive medication, no.	0	0	0	NA	NA
Current smokers, mean years smoking	0 (0)	0 (0)	0 (0)	NA	
Former smokers, mean years smoking	1 (15)	0 (0)	0 (0)	NA	NA
Type 1 or type 2 diabetes mellitus, no.	0	0	0	NA	NA
Family history of type 1 or type 2 diabetes mellitus, no.	0	0	0	NA	NA
Years competitive training	43 ± 6* (35–52)	0 (0)	18 ± 7 (11–31)	<0.001	<0.001
Number of marathons	178 ± 209* (20–650)	0 (0)	2 ± 3 (0–10)	<0.001	<0.001
Number of ultramarathons	65 ± 91* (0–257)	0 (0)	0 ± 1 (0–3)	<0.001	<0.001
Number of ironman triathlons	4 ± 12 (0–39)	0 (0)	1 ± 3 (0–10)	0.63	0.24

Values are means ± SD (range) or frequency (years). NA, not applicable.

Table 2. *Cardiac magnetic resonance data indexes of left atrial, left and right ventricular volumes, mass, and systolic function*

	Veteran Athletes		Age-matched Controls		Young Athletes		*P* Value	
	Absolute	Absolute BSA	Absolute	Absolute BSA	Absolute	Absolute BSA	Veteran Athletes vs. Control	Veteran Athletes vs. Young Athletes
LAEDV, ml	70 ± 13 (52–92)	25.7 ± 5.6 (24.6–34)	78 ± 12 (54–101)	26.6 ± 3.5 (18–32)	72 ± 21 (43–117)	25.5 ± 6.8 (22.6–35.3)	0.567	1.000
LVEDV, ml	182 ± 28 (142–232)	66.8 ± 11.3 (52–81)	143 ± 18 (100–170)	52.8 ± 6.6 (36–65)	211 ± 35 (162–272)	74.7 ± 9.6 (57–88)	<0.001	0.018
LVESV, ml	63 ± 16 (42–90)	23 ± 6.4 (16–35)	42 ± 9 (25–61)	15.5 ± 3.4 (19–23)	76 ± 18 (47–111)	26.8 ± 5.6 (16–39)	<0.001	0.049
IVSd, mm	11 ± 1 (9–13)	7.8 ± 0.9 (6.6–9.5)	10 ± 2 (7–13)	6.9 ± 1.0 (5.1–9.4)	10 ± 1 (9–12)	7.4 ± 0.5 (6.6–8.5)	0.049	1.000
PWd, mm	10 ± 1 (8–11)	6.9 ± 0.9 (5.8–8.2)	8 ± 1 (7–10)	5.9 ± 0.6 (7–7)	10 ± 1 (9–12)	7.3 ± 0.5 (6.5–8.5)	<0.001	0.113
LV length, mm	88 ± 6 (78–97)	63 ± 4.5 (56.8–70)	93 ± 6 (84–102)	96.0 ± 5.8 (85–104)	97 ± 7 (89–112)	69.1 ± 3.1 (62.4–73.9)	0.088	<0.001
LV mass, g	148 ± 16 (120–167)	54.6 ± 6.7 (45–66)	147 ± 23 (108–180)	54.2 ± 7.1 (44–71)	151 ± 23 (119–210)	53.3 ± 5.2 (43–64)	1.000	1.000
RVEDV, ml	181 ± 24 (150–227)	66.6 ± 9.4 (56–88)	146 ± 19 (113–187)	54.2 ± 7.2 (41–66)	215 ± 37 (143–276)	72.1 ± 21.5 (58–92)	0.003	0.008
RVESV, ml	63 ± 15 (45–96)	23 ± 6.4 (18–37)	42 ± 13 (25–69)	15.8 ± 4.7 (8–25)	82 ± 22 (41–114)	26.8 ± 5.6 (18–42)	0.005	0.011
LVSV, ml	119 ± 18 (101–163)	43.8 ± 6.9 (36–56)	101 ± 11 (75–1,115)	37.3 ± 4.1 (27–46)	136 ± 21 (104–183)	47.9 ± 5.4 (36–55)	0.014	0.036
RVSV, ml	119 ± 16 (102–174)	43.7 ± 6.4 (36–54)	104 ± 12 (77–124)	38.4 ± 4.0 (28–48)	133 ± 21 (97–154)	44.5 ± 12.6 (36–45)	0.047	0.093
LVEF, %	66 ± 5 (55–71)		71 ± 4 (64–78)		65 ± 4 (56–74)		0.008	1.000
RVEF, %	66 ± 5 (58–75)		72 ± 6 (63–82)		62 ± 6 (53–73)		0.03	0.22

Values are means ± SD (range). BSA, body surface area; LAEDV, left atrium end-diastolic volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; IVSd, intraventricular septum during diastole; PWd, posterior wall thickness during diastole; LV length, left ventricular length; LV mass, left ventricular mass; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; LVSV, left ventricular stroke volume; RVSV, right ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction.

athletes ($P < 0.05$) than young athletes, although both LV and RV ejection fractions were preserved. Veteran athletes had a significantly larger absolute and indexed LV and RV end-diastolic and systolic volumes, intraventricular septum during diastole, posterior wall thickness during diastole, and LV and RV stroke volumes ($P < 0.05$), together with significantly reduced LV and RV ejection fractions ($P < 0.05$) compared with veteran controls.

Short-tau inversion recovery and LGE. None of the athletes or veteran controls demonstrated focal or global myocardial edema on short-tau inversion recovery imaging. Myocardial recent gadolinium enhancement pre- and post-contrast ratio was <45% in all athletes and veteran controls, and none reached the recent gadolinium enhancement threshold of myocardium/skeletal muscle ratio of >4.0. No LGE was observed in age-matched veteran controls or young athletes. In contrast, six lifelong veteran endurance athletes (50% of cohort) demonstrated LGE (Table 3). The presence of LGE was not associated with age, height, weight, or BSA ($P > 0.05$), but was significantly associated with the number of years spent training ($P < 0.001$), number of competitive marathons ($P < 0.001$), and ultraendurance (>50 miles) marathons ($P < 0.007$) completed.

Regardless of positive or negative LGE scores, all 12 veteran athletes underwent perfusion imaging. Normal perfusion scores were noted in 11 veteran athletes, with only 1 veteran athlete (LGE positive; suspect dual infarct) demonstrating a significant nonviable myocardium perfusion defect (Fig. 1). The athlete volunteered for coronary angiography, which revealed normal and "unobstructed" coronary arteries (defined as smooth contours with no focal reduction). The athlete did not present with symptoms, a personal or family history of CV disease, obesity, hypertension, hypercholesterolemia, or diabetes mellitus, and did not demonstrate Q waves, ST segment depression, or T wave inversion, indicative of a previous MI, on a resting or exercise 12-lead ECG.

DISCUSSION

The impact of lifelong, intense endurance exercise in veteran athletes on myocardial structure and function is poorly understood. While aging resulted in some morphological and functional differences, these were partially attenuated, compared with sedentary veteran controls. Uniquely, six (50%) veteran athletes demonstrated LGE indicative of myocardial fibrosis, with the presence of LGE associated with the number of years spent training, number of marathons, and ultraendurance (>50 miles) marathons completed.

Cardiac structure and function in the veteran athlete. Current data suggest that LV wall thickness and LV mass are maintained by lifelong endurance exercise. This supports previous data reporting a maintained LV mass, despite a significant age-related reduction in cardiomyocyte number associated with hypertrophy of remaining cells and an increase in interstitial tissue (19). Few studies have reported LV and RV volumes of current endurance veteran athletes (>50 yr) compared with young athletes. The examination by Miki et al. (13) of nine veteran cyclists 2 yr postretirement demonstrated a reduction in LV dimension ($P < 0.001$) with no change in LV wall thickness, while Sandstede et al. (23) reported a reduction in both absolute and normalized LV and RV end-diastolic and

Table 3. *Location and extent of LGE in veteran athletes*

Participant No.	Age, yr	Percentage of Total LGE Mass, g	LGE Pattern	Perfusion Defect	Interpretation	Location
1	67	18.9	CAD	Yes	Probable dual infarction	Septal and lateral wall
2	50	8	Non-CAD	No	Probable myocarditis	Epicardial lateral wall
3	66	3	Non-CAD	No	Nonspecific	Basal and midinsertion point
4	60	3	Non-CAD	No	Nonspecific	Inferior insertion point mid and apical
5	50	1	Non-CAD	No	Nonspecific	Insertion point inferior mid/apical
6	51	1	Non-CAD	No	Nonspecific	Inferior insertion point

LGE; late gadolinium enhancement, CAD; coronary artery disease.

systolic volumes, with preservation of LV and RV mass in veteran sedentary men compared with young sedentary men (59 ± 8 vs. 32 ± 7 yr). The present study also supports the preservation of LV and RV ejection fraction in lifelong endurance veteran athletes (4, 8, 12, 17).

Presence of fibrosis. While there was no evidence of edema in any of the athletes or controls studied, LGE on CMR representing myocardial fibrosis was noted in six (50%) of the lifelong veteran endurance athletes. A recent CMR study (5) examined 102 healthy asymptomatic veteran male marathon runners also reported an unexpectedly high prevalence of LGE (12%), although it was not significantly different from that of age-matched control participants (4%, $P = 0.07$). The higher presence of fibrosis in the present study (50 vs. 12%) may represent a difference in study populations. The athletes examined in the present study are a truly lifelong endurance group who have been exposed to many more repeated bouts of intense (ultra)endurance exercise. Second, 51.9% ($n = 56$) of the veteran athletes used by Mohlenkamp et al. (14) and Breuckmann et al. (5) were reported to be previous smokers, with a further 4.6% current smokers. In the present study, only one veteran athlete (not presenting with LGE) reported a previous smoking history of 15 yr, with all age-matched control participants reporting to be lifelong nonsmokers. This is important, as LGE may be the sole result of coronary artery disease (CAD) and associated endothelial dysfunction (29). Finally, Mohlenkamp et al. (14) observed higher calcium scores in veteran athletes presenting with LGE than those without LGE, which may also be partially attributed to higher smoking prevalence rates. In agreement with Mohlenkamp et al. (14) and Breuckmann et al. (5), the present study observed a strong association between the presence of LGE and the number of marathons or ultraendurance marathons (>50 miles per event) previously completed.

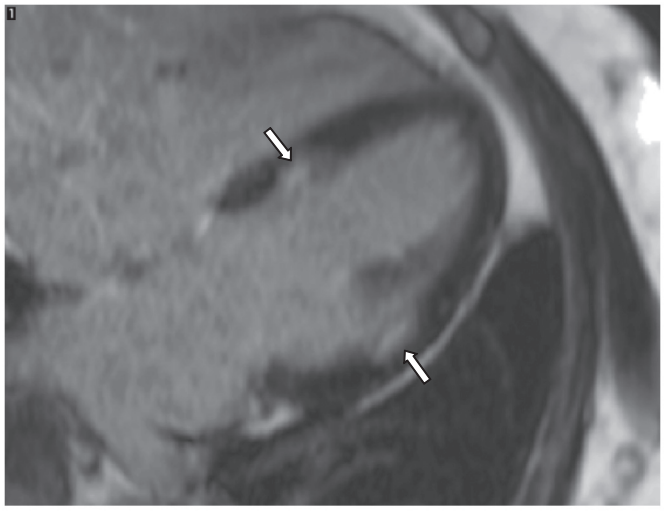

Fig. 1. Late enhancement study, following gadolinium-contrast agent, demonstrating localized infarction in both the septal and lateral walls (arrows).

Breuckmann et al. (5) differentiated subendocardial regions of LGE, typical of MI (CAD) pattern ($n = 5$), from regions of a predominantly, midmyocardial patchy pattern of LGE (non-CAD) pattern ($n = 7$). Similarly, we found one veteran athlete with a CAD pattern of fibrosis (Table 3, Fig. 1), although, interestingly, coronary angiography revealed unobstructed coronary arteries. This athlete presented with a perfusion defect, similar to those athletes with a CAD fibrosis pattern and similar to those reported by Breuckmann et al. (5). However, no perfusion defect was noted in the other five veteran athletes presenting with LGE, including the athlete with a fibrotic pattern concomitant with a previous episode of myocarditis. In four athletes in the present study (33%), as well as those with nonspecific fibrosis in the study by Breuckmann et al. (5), the cause(s) and consequence(s) of the myocardial fibrosis are currently unknown.

The case for a direct effect of exercise in promoting myocardial fibrosis is limited but has (re)gained some popularity in recent years. Case studies, such as the report of focal fibrosis in the papillary muscle of a highly trained endurance athlete (22), have been widely reported. Whyte et al. (27) documented idiopathic interstitial myocardial fibrosis at postmortem in the heart of an athlete who died suddenly during marathon running. The deceased had been running for 20 yr, having completed multiple marathons, with a personal best time of 2 h 30 min. At autopsy, the weight of the heart was 480 g (above that expected for a 75-kg male: upper limit of 431 g), with widespread replacement fibrosis, particularly in the lateral and posterior ventricular walls, as well as interstitial fibrosis in the inner layer of the myocardium. Premortem, the athlete was healthy and free from CV disease, and there was no documented evidence of diseases associated with widespread myocardial fibrosis. Clinical experimental data are still limited and do not reflect cause and effect. However, Benito et al. (3) recently observed collagen deposition and a significant increase in messenger RNA and protein expression of fibrosis markers after long-term intensive exercise training, together with changes in ventricular function and increased arrhythmia inducibility in male Wistar rats conditioned to run vigorously for 16 wk compared with time-matched sedentary control rats. Importantly, the authors documented that the cessation of endurance training was able to arrest and even reverse this pathological process.

Limitations and future research. Like many studies of this type, the numbers of veteran athletes are small (largely because this is a small and unique population), and generalization is difficult. Echocardiography was not performed on the age-matched control group; thus the evaluation of lifelong endurance exercise upon diastolic function is not permitted. Future studies employing large cohorts of lifelong veteran male and female athletes are warranted to enhance our understanding of the impact of long-term endurance exercise on cardiac structure and function.

Conclusion. Lifelong veteran endurance athletes demonstrated smaller LV and RV end-diastolic and end-systolic volumes, with maintenance of left atrial end-diastolic volume, LV and RV systolic function, and LV mass, compared with young endurance athletes. Veteran athletes had significantly larger absolute and indexed LV and RV end-diastolic and systolic volumes, intraventricular septum thickness during diastole, posterior wall thickness during diastole, and LV and RV stroke volumes ($P < 0.05$), together with significantly reduced LV and RV ejection fractions ($P < 0.05$) compared with veteran controls. Of note, 6 (50%) of the veteran athletes examined using CMR demonstrated LGE indicative of myocardial fibrosis compared with the absence of LGE in 20 age-matched controls and 17 young endurance athletes. The presence of LGE in veteran athletes was significantly associated with the number of years spent training, number of competitive marathons, and ultraendurance (>50 miles) marathons completed, supporting a link between lifelong endurance exercise and myocardial fibrosis, which requires further study.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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