Lifelong Physical Activity Regardless of Dose Is Not Associated With Myocardial Fibrosis

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Background—Recent reports have suggested that long-term, intensive physical training may be associated with adverse cardiovascular effects, including the development of myocardial fibrosis. However, the dose–response association of different levels of lifelong physical activity on myocardial fibrosis has not been evaluated.

Methods and Results—Seniors free of major chronic illnesses were recruited from predefined populations based on the consistent documentation of stable physical activity over >25 years and were classified into 4 groups by the number of sessions/week of aerobic activities ≥30 minutes: sedentary (group 1), <2 sessions; casual (group 2), 2 to 3 sessions; committed (group 3), 4 to 5 sessions; and Masters athletes (group 4), 6 to 7 sessions plus regular competitions. All subjects underwent cardiopulmonary exercise testing and cardiac magnetic resonance imaging, including late gadolinium enhancement assessment of fibrosis. Ninety-two subjects (mean age 69 years, 27% women) were enrolled. No significant differences in age or sex were seen between groups. Median peak oxygen uptake was 25 , 26, 32, and 40 mL/kg/min for groups 1, 2, 3, and 4, respectively. Cardiac magnetic resonance imaging demonstrated increasing left ventricular end-diastolic volumes, end-systolic volumes, stroke volumes, and masses with increasing doses of lifelong physical activity. One subject in group 2 had late gadolinium enhancement in a noncoronary distribution, and no subjects in groups 3 and 4 had evidence of late gadolinium enhancement.

Conclusions—A lifelong history of consistent physical activity, regardless of dose ranging from sedentary to competitive marathon running, was not associated with the development of focal myocardial fibrosis. (Circ Cardiovasc Imaging. 2016;9:e005511. DOI: 10.1161/CIRCIMAGING.116.005511.)

Key Words: athlete’s heart • exercise • magnetic resonance imaging • myocardial fibrosis

Although regular physical activity is associated with improvement in cardiovascular physiological parameters and outcomes, recent reports have raised concerns that repeated, long durations of strenuous aerobic exercise over a prolonged period of time may have adverse cardiac effects. Several case reports have shown unexplained cardiomyopathy, malignant arrhythmias, and sudden cardiac death in athletes who trained with high levels (duration and intensity) of endurance exercise over their athletic careers and have postulated that their training resulted in pathological cardiac changes. Additional support for this theory comes from case–control studies that have found a possibly higher prevalence of focal myocardial fibrosis, as demonstrated by late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (cMRI) in marathon runners compared with healthy controls. However, these studies have lacked a systematic, prospectively documented evaluation of lifelong physical activity of study participants and did not thoroughly characterize the participants’ cardiovascular fitness levels by assessing peak oxygen uptake. Moreover, a large proportion of the subjects in these studies were smokers (≥50% in some studies) or had substantial other cardiovascular risk factors, raising the possibility that some may have taken up intensive training as a strategy to compensate for elevated cardiovascular risk.

A systematic, long-term study of lifelong physical activity remains rare, and therefore, the present study was conducted to evaluate the prevalence of focal myocardial fibrosis, assessed by LGE with cMRI, in a cohort of seniors with diverse levels of physical activity, with well-characterized aerobic exercise histories and measures of cardiovascular fitness by cardiopulmonary exercise testing.

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Methods

Subjects
Healthy seniors (aged ≥65 years) were recruited and categorized into the following groups based on their histories of reported number of weekly sessions of aerobic activity lasting at least 30 minutes during the previous 25 years: sedentary (≤1 session/week), casual (2–3 sessions/week), committed (4–5 sessions/week), and Masters athletes (6–7 sessions/week and participating in regular competitions such as marathons and triathlons). This cohort represents the same subjects whose cardiac mechanics (including invasively measured cardiac stiffness) and response to exercise have been reported previously.13,14 All subjects were free of known medical conditions, including obesity, hypertension, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, coronary artery disease, significant valve disease, tobacco use within 10 years, and chronic kidney disease (GFR <45 ml/min/1.73 m²).

Recruitment of participants has previously been described in detail.11 In brief, participants were recruited primarily from the Cooper Center Longitudinal Study (CCLS). The CCLS is a cohort of ≥80,000 individuals in whom physical activity and CV risk factors have been quantified and followed for ≥40 years. At the time of enrollment, 8497 participants had between 3 and 5 serial clinical examinations between 1970 and 2003, with validated questionnaires quantifying aerobic activity during the prior 3-month period.10 Individuals who consistently reported the same level of aerobic activity over several visits spanning at least 20 years underwent further comprehensive exercise history by an experienced exercise physiologist, assisted by family members when possible. If the history obtained by the exercise physiologist was similar to the history from the CCLS questionnaires, the individual underwent additional screening, including medical history and examination by study physicians and nurses, including short-term 7-day Physical Activity Recall Questionnaire and accelerometers. In addition to the CCLS, the sedentary population was enriched with subjects recruited from local senior groups, such as bingo, gardening, and volunteer clubs. Masters athletes were enriched by direct recruitment from the top performers (top 10%–15%) at regional and national endurance events sponsored by US Master’s organizations. Regardless of the source of referral, however, subjects in all 4 physical activity categories were equally well vetted and rigorously screened in regards to their medical history, physical examination, and detailed exercise history for the previous 25 years. For example, for the Masters athletes not recruited through the CCLS, the documentation of exercise history generally came from 2 sources. The first was the athletes’ training logs. Virtually, all of our competitive Masters athletes had detailed training logs documenting their training, some as far back as 50 years. This competitive training was verified by race results, which also had to comprise at least 20 years of competitive racing.

Individuals who were confirmed to be appropriate for their physical activity category then underwent 24-hour ambulatory blood pressure monitoring to ensure absence of hypertension. Resting and exercise stress echocardiography were performed, and individuals with resting wall motion abnormalities or evidence of ischemia were excluded. Thus, this population represents a highly screened cohort optimizing the validity of the dose quantification.

Cardiopulmonary Exercise Stress Testing
Cardiopulmonary exercise stress testing was performed as has been previously described using an individualized, modified Astrand–Saltin incremental treadmill protocol using the Douglas bag technique.16 Blood pressure and heart rate were monitored throughout the test. During the first part of the test, subjects were familiarized with the test, and the starting speed for the treadmill was determined. Gas fractions were analyzed by mass spectrometer, and ventilatory volume was measured by a Tissot spirometer. Peak oxygen uptake (VO₂) was defined as the highest VO₂ uptake measured from at least a 40-s Douglas bag.

Magnetic Resonance Imaging
Rest MRI was performed using a 1.5-Tesla Philips NT MRI. All images were acquired with ECG gating and breathholding. Gradient-echo, cine images of the short axis were obtained using a temporal resolution of ≈40 ms, repetition time of 4 ms, echo time of 2 ms, and flip angle of 55°. Six millimeter slices with skip 4 were obtained from slightly above the mitral annulus to apex. Image resolution was 256×256.

LGE imaging (repetition time 4.4 ms, echo time 1.3 ms, inversion time 225–300 ms) was performed using an inversion recovery pulse sequence 10 to 20 minutes after administration of 0.1 mm/kg of gadolinium.

Endocardial and epicardial contours of short axis were manually traced using Qmass software (Medis, Leiden, the Netherlands). Evidence of LGE was evaluated by a cardiologist with Core Cardiovascular Training Statement level 3 training in CMRI blinded to the exercise training history of the subject. In studies with suspected LGE, a second cardiologist with level 3 MRI training confirmed the findings. Body surface area was determined by the Mosteller method.17

Statistical Analysis
Data are presented as percentages for categorical variables, mean±standard deviation for continuous variables with normal distributions, and median with interquartile range for continuous variables with non-normal distributions. Comparison of differences between groups of continuous variables was done by 1-way analysis of variance or Kruskal–Wallis 1-way analysis of variance rank test and categorical variables by Chi-square or Fisher exact test. P value of <0.05 was considered statistically significant for all analysis.

Results
Ninety-two subjects were evaluated in the study (mean age 69.2 years, 27% women): 25 in the sedentary group, 23 in the casual group, 23 in the committed group, and 21 in the Masters athlete’s group (Table 1). No significant differences in age or sex were noted between groups. BMI was lower among the Masters athletes, although no difference was seen in BSA or lean mass. As noted previously, there was a graded increase in peak VO₂ across the exercise categories (lowest in the sedentary group and highest among the Masters athletes), supporting the validity of the dose quantification.

Left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular (LV) mass were greater in those with histories of higher physical activity (Table 2). No difference was noted in LV ejection fraction. Similar trends were seen for left ventricular end-diastolic index, left ventricular end-systolic index, and LV mass index.

Late gadolinium enhancement was seen in one patient in the casual group that had nonschismic characteristics (Figure 1). No evidence of LGE was noted in the other groups, including Masters athletes (Figure 2).
Discussion

In healthy seniors with well-documented long-term physical activity histories and cardiovascular fitness assessment, increasing levels of lifelong (>25 years) physical activity were not associated with focal areas of myocardial fibrosis, as assessed with LGE by cMRI. LGE in an atypical, nonischemic pattern was seen in only 1 subject in the casual exercise group, and no subjects in the Masters athletes group had LGE, despite a clear demonstration of LV remodeling that is characteristic of the athlete’s heart phenotype and having peak \( V_\text{o}_2 \) measurements confirming an elite level of physical fitness for this age group.

Benefits of Higher Exercise Doses

Compared with a sedentary lifestyle, aerobic exercise has been shown to have several physiological benefits.4 Our group has previously demonstrated that highly trained senior Masters endurance athletes had preserved LV compliance comparable to young, healthy subjects and in contrast to sedentary but healthy elderly subjects, who had decreased compliance.1 Assessment of LV compliance in the same population used in the current study demonstrated that the beneficial effects of exercise on LV compliance was seen only in the more active groups, the Committed (>4 to 5×/week) and Masters athletes groups, suggesting that casual exercise is insufficient to maintain LV compliance.13 Because decreased LV compliance is one of the factors that is thought to play a significant role in the development of heart failure in the elderly, higher levels of regular exercise may have a clinical morbidity and mortality benefit. A recent, large meta-analysis supports this hypothesis, demonstrating that subjects with the highest levels of physical activity, ≥4× the minimal recommended by the 2008 US guidelines, had the lowest incident rate of heart failure.18

Clinical Implications of the Athlete’s Heart Phenotype

Although the majority of observational studies have shown that physical activity and fitness are associated with delayed cardiovascular and total mortality, including studies of elite athletes,2,19–23 some recent reports have suggested that there might a U- or J-shaped relationship between exercise dosage and cardiovascular outcomes, such as atrial fibrillation.24 The development of athlete’s heart in high-performing endurance athletes is a well described phenomenon, which includes an enlarged and compliant left ventricle, and has not been shown to be associated with adverse effects, in contrast to cardiac enlargement associated with pathological processes.25,26 Case reports of endurance athletes experiencing sudden cardiac

| Table 1. Characteristics of Study Population |
|-------------------------------|------------------|-------|-------|-------|--------|
|                                | Group 1          | Group 2 | Group 3 | Group 4 | P Value |
| N                              | 25               | 23     | 23     | 21     |         |
| Age, y                         | 69 (65–71)       | 70 (66–75) | 69 (65–71) | 68 (66–70) | 0.31    |
| Women, %                       | 40.0             | 26.0   | 17.4   | 23.8   | 0.37    |
| BMI, kg/m²                     | 25.9±2.5         | 25.0±2.8 | 24.1±2.7 | 22.5±2.5 | <0.001  |
| BSA, m²                        | 1.88±0.19        | 1.91±0.22 | 1.88±0.18 | 1.79±0.21 | 0.21    |
| Lean mass, kg                  | 51.1±9.6         | 53.7±10.2 | 52.4±9.3 | 50.9±8.1 | 0.73    |
| Peak \( V_\text{o}_2 \), mL/kg/min | 24.2±4.7        | 25.8±5.0 | 32.5±5.3 | 39.8±5.6 | <0.001  |

BMI indicates body mass index; BSA, body surface area; and peak \( V_\text{o}_2 \), peak oxygen uptake.

| Table 2. Cardiac MRI Variables |
|-------------------------------|-------------------|-------|-------|-------|--------|
|                                | Group 1           | Group 2 | Group 3 | Group 4 | P Value |
| LV mass                        | 94.6±22.3         | 100.4±21.8 | 116.5±26.6 | 125.4±29.8 | <0.001  |
| LVEDV (83.4–128.6)             | 108.9 (95.0–131.1) | 115.9 (106.0–146.5) | 143.5 (106.1–163.0) |         |
| LVESV                          | 31.0±11.2         | 36.8±15.7 | 39.9±13.1 | 46.3±14.0 | 0.003   |
| SV (63.0–87.2)                 | 71.5 (66.9–89.9)  | 74.1 (72.3–96.0) | 80.0 (72.3–96.0) | 93.0 (76.5–114.5) | 0.035   |
| LVEF                           | 71.6±5.0          | 69.2±7.1 | 68.5±6.7 | 67.0±5.4 | 0.087   |
| LVMI                           | 49.9±8.1          | 52.1±7.9 | 61.7±11.1 | 69.3±10.9 | <0.001  |
| LVEDVI (59.9±11.8)            | 56.5±11.3         | 59.9±11.8 | 67.1±12.8 | 77.1±13.8 | <0.001  |
| LVESVI (18.9±7.2)             | 16.4±5.1          | 18.9±7.2 | 21.2±6.2 | 25.7±7.0 | <0.001  |
| SVI (40.2±7.0)                | 40.2±6.1          | 41.6±6.1 | 45.9±9.7 | 51.4±8.7 | <0.001  |
| LGE                            | 0                 | 1       | 0       | 0       |         |

LGE indicates late gadolinium enhancement; LV, left ventricular mass; LVMI, left ventricular mass index; LVEDVI, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; SV, stroke volume; and SVI, stroke volume index.
death and ventricular arrhythmias in the setting of an enlarged heart has led several investigators to propose that the long-term effects of high-intensity exercise, particularly in those who engage in ultraendurance competitions over a prolonged time period, may lead to maladaptive cardiac remodeling. A key hypotheses in the development of exercise-induced cardiomyopathy is that recurrent bouts of high-level endurance exercise lead to repeated myocardial injury and subsequent scar formation, which then is the pathological basis of cardiomyopathy and arrhythmogenesis. These investigators have pointed to the elevations in cardiac troponin levels that have been commonly noted in runners post marathon. However, troponin elevation has not been shown to be associated with LGE in this setting, and the degree of troponin release makes it unlikely that it is associated with myocardial necrosis.

Previous Studies Evaluating Myocardial Fibrosis by cMRI LGE

Multiple groups have evaluated for LGE in professional and nonprofessional athletes. Breuckmann et al performed cMRIs on 102 healthy men who had completed ≥5 marathons in the prior 3 years. Although LGE was found in 12 subjects, 5 in a typical ischemic pattern and 7 in an atypical pattern, this was not convincingly greater statistically than what was found in controls. In another analysis of the same cohort, the group reported that the LGE was independently associated with coronary atherosclerosis as assessed by coronary artery calcium scores, which had a higher prevalence than expected in runners than in controls based on Framingham Risk Score. One explanation for this finding is that >50% of the marathon runners had a history of remote tobacco use, which increases the risk of developing coronary artery calcium, but is not included in the Framingham Risk Score, which uses recent tobacco use to estimate risk. In another small study of athletes with long-term follow-up, 6 of 12 men, with 35 to 52 years of training, showed evidence of LGE, 4 in an atypical pattern, 1 probable past myocarditis, and 1 typical ischemic pattern, suggesting that in addition to coronary ischemic disease, previous subclinical myocarditis may also explain the presence of LGE in some of these cases. In contrast, Franzen et al demonstrated that LGE was absent in 20 men triathletes and 20 men middle-aged marathon runners. Similarly, in a recent study of 33 elite male athletes and matched control subjects, with a median age of 47 years, only 1 athlete had LGE localized subepicardial in the LV posteroinferior region. The present study extends these findings by demonstrating a lack of association of focal myocardial necrosis across a significantly older population with longer physical activity histories and encompassing a spectrum of lifelong physical activity histories.

The different prevalence and patterns of LGE reported in these previous studies may reflect differences in the underlying comorbidities and long-term physical activity histories. The present study is the first to evaluate for LGE in a cohort encompassing a wide spectrum of lifelong physical activity levels, with well documented medical histories and prospective assessments of physical activity levels that were then rigorously validated by trained staff and measurements of peak VO2 to confirm cardiovascular fitness levels. This rigorous screening allowed us to better isolate the effect of exercise training per se from the confounding effects of other comorbidities. In fact, the prevalence of LGE in the present cohort was lower than that reported in the general population likely because of the absence of cardiovascular disease risk factors. The lack of association of lifelong high endurance exercise with areas of focal myocardial fibrosis, especially in individuals with youthfully compliant hearts as assessed directly by invasive measures, lends support to the concept that the athlete’s heart is most commonly a reversible physiological adaptation and not a pathological substrate for malignant arrhythmias or a precursor to cardiovascular death. In addition, only one patient in the casual and committed groups had evidence of LGE, still well below the general population prevalence. The low prevalence of LGE seen in these groups counters the argument by some who propose that even non-elite athletes should limit the duration, speed, and distance they exercise because of concerns of cardiac harm.

Figure 1. Late gadolinium image in the short-axis plane of the left ventricle. Small focus of late gadolinium enhancement seen in the intraventricular septum close to the inferior right ventricular insertion point (arrow) in a subject in the casual exercise group.

Figure 2. Late gadolinium images in the short-axis plane of subjects in the Masters athletes group.
Histological Bases and Prognostic Significance of LGE at the RV Insertion Points of the Interventricular Septum in Other Conditions

Another explanation of the differences in prevalence of LGE across studies is that LGE may not represent irreversible fibrosis. Our group has previously shown that an elite ultraendurance athlete who had run and cycled >3000 kilometers over <1-month period had subsequently developed an enlarging area of focal LGE at the right ventricular insertion point along the septum. Of the previous studies reporting LGE in high-volume endurance athletes, the majority of the atypical nonischemic pattern of LGE seem to localize similarly to the interventricular septum at the superior and inferior right ventricular insertion points. Although the pathology of LGE in these cases has not been elucidated, LGE involvement of the interventricular septum at the right ventricular insertion points is also seen in various other conditions. For example, in 1293 patients with hypertrophic cardiomyopathy who underwent cMRI studies, Chan et al demonstrated that 10% had LGE confined exclusively to one or both of the right ventricular insertion points in the interventricular septum. Although the extent of LGE in hypertrophic cardiomyopathy has been shown to be associated with poor prognosis, LGE confined to this particular pattern did not seem to be associated with an increased risk of adverse events, including sudden death. The same group showed that in 20 additional hypertrophic cardiomyopathy hearts with this pattern of LGE who underwent postmortem histopathologic evaluation, the LGE represented replacement fibrosis in only 1 heart, with increased extracellular space because of interstitial fibrosis being seen in the majority of hearts at the right ventricular insertion points.

Another condition where LGE is often seen at the right ventricular insertion points of the interventricular septum is pulmonary hypertension. In a histopathologic case report, Bradlow et al demonstrated that areas of LGE on cMRI corresponded not with a pathological replacement fibrosis or scar, but rather with increased collagen and fat deposition at points where the right and left ventricular muscle fibers interdigitate, termed plexiform fibrosis. The authors hypothesized that in pulmonary hypertension, plexiform fibrosis is the result of increased shear forces related to the hypertrophied right ventricle and the paradoxical motion of the interventricular septum. Perhaps most relevant for LGE seen in athletes, this pattern of LGE is seen not uncommonly in patients with atrial septal defects and then regresses when the defect is closed, suggesting that it might be more likely because of a reversible condition, such as edema, rather than structural fibrosis.

Because during high levels of endurance exercise, the right ventricle is exposed to a disproportionately greater change in loading conditions, remodeling, and function than the left ventricle, a similar mechanism may be the explanation of LGE seen in this population.

Study Limitations

There are several limitations to the present study. Although there were only 21 subjects in the Masters athletes group and LGE may not be present in our sample by chance, this is the largest group of senior athletes with well-documented lifelong histories of competing in high-level endurance training reported to date. Another major weakness of our cross-sectional study design is the inability to adequately account for exercise intensity, duration, or mode of exercise, factors that may have an important impact on the training response. These variables are difficult for subjects to retrospectively quantify over such a long period of time. However, for individuals to place in the top 10% to 15% of Masters competitions, it is likely that the Masters athletes included not only more sessions per week, but also those of greater duration and intensity. Nevertheless, both the fitness and directly measured cardiac compliance of these subjects tracked their exercise frequency closely, supporting this strategy of quantifying long-term exercise habits.

It is also possible that because only seniors were evaluated in this analysis, LGE was not detected in these patients because of survival bias. Moreover, selection of an extrahealthy cohort may have excluded those athletes who do have LGE. However, this strategy was necessary to attempt to assess the isolated effects of exercise level on myocardial LGE while limiting the effects of comorbidities, because several of the previous studies finding LGE in apparently healthy athletes were likely confounded by underlying cardiovascular disease. We also cannot exclude the possibility that an interaction of exercise and cardiovascular comorbidities, such as preexisting coronary artery disease or hypertension, may lead to cardiac fibrosis seen in other studies. Ideally, future studies that prospectively evaluate a large number of athletes with serial cMRI examinations and long-term follow-up would better assess any interaction or confounding between comorbidities and exercise dose and myocardial fibrosis. Finally, although we did not find evidence of focal replacement fibrosis by LGE in the higher physical activity groups, we are not able to evaluate for diffuse fibrosis using newer MRI techniques, such as T1 mapping.

Conclusions

In conclusion, we have demonstrated that increasing levels of lifelong physical activity were not associated with focal myocardial fibrosis, as assessed with LGE by cMRI. Although LGE may occur in some high-level endurance athletes, particularly in the interventricular septum at the right ventricular insertion points, it is unclear if it represents replacement fibrosis or scar, or an exaggeration of the normal local myocardial architecture or edema caused by exercise-induced RV overload and paradoxical septal motion, that have been shown to be transient and reversible in other conditions.

Additional studies are needed to further elucidate the pathological basis of LGE in athletes. Because of the beneficial effects on cardiovascular physiological parameters and outcomes and lack of clear evidence suggesting harm, higher levels of exercise should continue to be encouraged in most individuals, as recommended by the recent statement from the American College of Cardiology’s Sports and Exercise Cardiology Leadership Council.

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Disclosures

None.

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Late gadolinium enhancement by cardiac magnetic resonance imaging has been reported in some middle-aged endurance athletes in several recent cross-sectional studies and case reports, prompting some investigators and editorialists to caution against high levels of aerobic exercise. The majority of these studies have been limited by incomplete characterization of these athletes, including limited accounting of potentially confounding cardiovascular risk factors, and insufficient evaluation of physical activity histories. The current study assessed 92 carefully screened seniors free of cardiovascular disease and categorized them into 4 groups according to well-documented physical activity histories over a period of at least 25 years, including the highest physical activity group consisting of top Masters athletes. Late gadolinium enhancement was not seen in any subject in the 2 highest activity groups and was seen only in one subject with a casual activity history (2–3 days/week). Because of the beneficial impact of physical activity on long-term cardiovascular morbidity and mortality, these findings support individualized exercise prescriptions that promote higher doses of activity and duration. Additional studies are needed to determine the prevalence, histological basis, clinical relevance, and reversibility of late gadolinium enhancement in high-level endurance athletes.
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