BENEFITS OF LIFELONG EXERCISE TRAINING ON LEFT VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION

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ABSTRACT

BACKGROUND. Endurance exercise training induces cardio-protective effects, but athletes are not exempted from a myocardial infarction (MI). Evidence from animal studies suggests that exercise training attenuates pathological left ventricular (LV) remodelling following MI. We tested the hypothesis that lifelong exercise training is related to an attenuated pathological LV remodelling after MI as evidenced by a better LV systolic function in veteran athletes compared to sedentary peers.

DESIGN. Cross-sectional study

METHODS. Sixty-five males (60±6 years) were included and allocated to four groups based on lifelong exercise training volumes: 1) athletes (ATH, n=18), 2) post-MI athletes (ATH+MI, n=20), 3) sedentary controls (SED, n=13), and 4) post-MI controls (SED+MI, n=14). Athletes were lifelong (≥20 years) highly physically active (≥30 MET-hours/week), whereas sedentary controls did not meet the exercise guidelines (<10 MET-hours/week) for the past 20 years. LV systolic function, diastolic function, and wall strain were measured using echocardiography.

RESULTS. Cardiac enzyme markers (creatine-kinase, creatinine, aspartate transaminase, and lactate dehydrogenase) following MI and infarct location did not differ between ATH+MI and SED+MI. LV ejection fraction was significantly higher in ATH (61%±4), ATH+MI (58%±4), and SED (57%±6) compared to SED+MI (51%±7; P<0.01). LV circumferential strain was superior in ATH (-19% [-21% to -17%], ATH+MI (-16% [-20% to -12%]), and SED [-15% [-18% to -14%] compared to SED+MI (-13% [-15% to -8%], P<0.01). Diastolic function parameters did not differ across groups.

CONCLUSION. These findings suggest that lifelong exercise training may preserve LV systolic function and possibly attenuates or minimizes the deleterious effects of pathological post-MI LV remodelling in veteran athletes.

Keywords: coronary artery disease; physical activity; echocardiography; secondary prevention

INTRODUCTION

Regular exercise training leads to a favourable cardiovascular risk factor profile,[1] improves cardiovascular function,[2, 3] and lowers the risk for cardiovascular disease.[4, 5] Despite the cardio-protective effects of exercise training, athletes are not exempted from acute coronary syndromes or myocardial infarction.[6]

After a myocardial infarction, the pathological LV remodelling starts within hours.[7, 8] This process is characterized by LV wall thinning, LV wall dilatation, reduced ejection fraction, and scar formation [7, 8] and eventually leads to impaired LV function. Preventing or reversing these maladaptations is of utmost importance to recover and maintain LV function. Animal studies demonstrated that exercise training before a myocardial infarction attenuates pathological LV remodelling.[9] Trained rats had less cardiac damage after ligation of the left anterior descending artery and fewer changes in cardiomyocyte function.[9] These results suggest that a physically active lifestyle before a myocardial infarction may attenuate pathological LV remodelling. Confirmation of these findings in humans is lacking.

The primary aim of the study was to determine whether lifelong exercise training is related to an attenuated pathological left ventricular remodelling after myocardial infarction. For this purpose, we collected echocardiographic images in veteran athletes with and without a myocardial infarction and sedentary controls with and without a myocardial infarction. We hypothesized that veteran athletes will have a better LV systolic function compared to their sedentary peers after a myocardial infarction.

METHODS

PARTICIPANTS

Sixty-five male participants were included and stratified into four groups based on their lifelong physical activity patterns and cardiac medical history: 1) veteran athletes (ATH, n=18), 2) veteran post-MI athletes (ATH+MI, n=20), 3) sedentary controls (SED, n=13), and 4) sedentary post-MI controls (SED+MI, n=14). To ensure that pathological LV remodelling was stabilized,[7] post-MI participants with a myocardial infarction diagnosis >6 months before the start of the study were included. Participants were recruited via local newspapers, internet advertisement, and the *Nijmegen Exercise Study*.[5] Individuals that expressed interest in study participation were screened by telephone and received a questionnaire regarding their exercise history. Individuals that were more than 20 years physically active and performed regular endurance exercise for ≥30 MET-hours per week were assigned to the athlete group. Individuals that did not exceed the recommended exercise dose of the World Health Organisation (<10 MET-hours/week) with habitual physical activities over the past 20 years, were assigned to the sedentary control group.[10] Individuals that could not be assigned to the athlete or sedentary group were excluded from further study participation. Smokers and diabetics were not included in the study. Additional exclusion criteria for the asymptomatic veteran athletes and sedentary controls was the use of cardiovascular medication (e.g., antihypertensives, lipid-lowering medications). The Local Ethical Committee of the region Arnhem-Nijmegen approved the study and all participants gave written consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

STUDY DESIGN

Individuals that expressed interest in the study were first screened via telephone and completed a questionnaire regarding their lifelong exercise history. Participants visited our laboratory on two days during this cross-sectional study. On day 1, participants were medically screened for eligibility, followed

by an incremental maximal cycling test. On day 2, participants underwent a comprehensive assessment of LV function using transthoracic echocardiography.

MEASUREMENTS

MEDICAL SCREENING

A physician screened the participants by taking a detailed medical history, physical examination, and 12-lead electrocardiogram. Blood samples were obtained, under fasting conditions, from an antecubital vein for the analysis of total cholesterol, HDL, LDL, triglycerides, glucose, and HbA1c.

LIFELONG PHYSICAL ACTIVITY PATTERNS

Lifelong physical activity patterns were queried via an exercise history questionnaire, distinguishing five age-periods: I) 20-29 years, II) 30-39 years, III) 40-49 years, IV) 50-59 years, and V) >60 years. Each category consisted of three queries: 1) type of activity (*e.g.*, running, cycling, etc., or nothing), 2) exercise time (hours) per activity per week, and (3) self-perceived intensity (light, moderate, or vigorous) per activity. The corresponding metabolic equivalent of task (MET) score per exercise activity was determined,[11] and exercise dose (MET-hours/week) was calculated by multiplying exercise time with MET scores. Average exercise dose was calculated over the last 20 years. For post-MI participants, exercise dose before and after the myocardial infarction diagnosis were calculated.

INCREMENTAL MAXIMAL CYCLING TEST

Cardiorespiratory fitness (VO_2peak, mLO_2/min/kg) was assessed via an incremental maximal cycling test. Participants cycled with 60-80 rotations per minute while the workload increased with 20 Watt/min for athletes and 10 Watt/min for post-MI controls. Heart rate (12 lead-electrocardiogram), oxygen uptake (VO_2 [ml/min]), carbon dioxide output (VCO_2 [ml/min]), and respiratory exchange ratio (RER) were continuously measured (CPET, Cosmed v9.1b, Italy).[12] The anaerobic threshold was defined as a RER above 1.0.[12] Participants were verbally encouraged to stimulate maximal exercise performance. Lactate concentration (mmol/L) was measured via a capillary blood sample taken one-and-a-half minute after exercise cessation (Arkray, type LT-1730, Japan).

CARDIAC MEDICAL HISTORY

Myocardial infarction characteristics were extracted from medical health records from the hospitals at which the patients were admitted. Specifically, clinical diagnosis of the myocardial infarction, cardiac enzyme levels (troponin-I, creatine kinase [CK], creatinine [CREAT], aspartate transaminase [ASAT], and lactate dehydrogenase [LDH]), treatment strategy, and secondary events were identified and used for data analyses.

ECHOCARDIOGRAPHY

Participants abstained from exercise 24 hours before the echocardiography assessment. Two-dimensional Doppler and four-dimensional images were obtained by a single experienced cardiologist using an ultrasound system (Vivid E9, General Electric Healthcare, Norway) equipped with a M5-S and V4 probe. All measurements were performed according to the American Society of Echocardiography (ASE) guidelines [13] with the participant in the left lateral recumbent position. Images were taken at end-expiratory breath hold, carefully avoiding Valsalva manoeuvre. A continuous three-lead electrocardiogram registration was used to detect end-diastole time points (onset of QRS). Data were transferred to a workstation for offline analysis (EchoPac PC version 113, General Electric Healthcare, Norway). Data analysis of the echocardiographic images was performed by an independent, blinded expert.

Left ventricular systolic function

LV ejection fraction (LVEF) was calculated from the LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) using Simpson's biplane method. Based on ASE guidelines, a LVEF below 52% was defined as an impaired LVEF.[13] Stroke volume was calculated by multiplying the time velocity integral and cross-sectional area of the LV outflow tract. Cardiac output was calculated by multiplying stroke volume with heart rate. Cardiac index was calculated by dividing cardiac output by body surface area. Body surface area was calculated using DuBois' formula (equation 1).

$$0.007184 * (body\ mass\ (kg)^{0.425}) * (height\ (m)^{0.725}) \quad \text{Equation 1}$$

Pulsed-wave tissue Doppler imaging measurements of peak systolic annular tissue velocities were obtained at the septal and lateral mitral annulus from apical 4-chamber images and an average of both sites is presented.

Left ventricular wall strain

Via the apical window, a 4D full volume R-wave 6 beat gated dataset of the LV was acquired. Volume-rate was kept >30 Hz. The dataset was post-processed using 4D automated LV quantification tool available in EchoPac to determine LV wall strain. From 4D images, endocardial border detection process was initialized by manual alignment of the apex and mitral valves in a long-axis view at both end-diastolic and end-systolic phase. The endocardial border was automatically generated throughout the cardiac cycle. The proposed contour was evaluated via short-axis cut-planes of the 3D volume at base, mid, and apex of the LV and cut-planes of the apical 4-, 3-, and 2-chamber views. Only major deviations of the expected endocardial borders were operator corrected. Papillary muscles and major trabeculae were included in the LV cavity. The epicardial border was automatically generated by the software, which created a 3D region of interest of the LV wall. Speckle tracking was applied to determine global longitudinal, circumferential, area, and radial strain.

Left ventricular diastolic function

Diastolic function was assessed with LV inflow pulsed-wave Doppler measurements at the mitral leaflet tips, including peak flow velocity of the early rapid filling wave (E-wave), peak flow velocity of the late filling wave due to atrial contraction (A-wave) and E/A ratio. Using pulsed-wave tissue Doppler, the tissue velocity of the septal and lateral mitral annulus was registered. From these tracings, peak early mitral annular tissue velocity (e'-wave), and peak late mitral annular tissue velocity during atrial contraction (a'-wave) were measured. The ratio of E-wave and e' (E/e') was calculated.

STATISTICAL ANALYSIS

Data is reported as mean±standard deviation or median (interquartile range [IQR]). Categorical data were analysed using the *Fisher's exact* test. Parameters were checked for normality using a *Shapiro-Wilk* test. Skewed variables were $\log_e$-transformed before analyses. Data that could not be transformed into Gaussian distribution were analysed using nonparametric tests. An *independent Student's t* or *Mann-Whitney-U* test were used to analyse cardiac enzyme levels between ATH+MI and SED+MI, when appropriate. ANOVA with a *Tukey post hoc* or *Kruskal-Wallis* test were performed to determine differences between groups, when appropriate. Statistical analyses were performed using SPSS 21.0 software (IBM Corp., Armonk, N.Y., USA).

RESULTS

PARTICIPANT CHARACTERISTICS

Participant characteristics of the four study groups are summarized in Table 1. Average exercise time and dose were significantly higher in ATH and ATH+MI compared to SED and SED+MI (Supplement Figure 1). Exercise time and dose before compared to after myocardial infarction increased in the ATH+MI, but did not change in SED+MI. ATH and ATH+MI performed most of the time moderate intensity exercise (65%), followed by vigorous intensity exercise (33%) and light intensity exercise (2%). VO_2peak differed across groups, with ATH demonstrating the highest VO_2peak uptake (48.0±8.9 mL/min/kg), followed by ATH+MI (40.9±5.5 mL/min/kg), SED (31.6±4.8 mL/min/kg) and SED+MI (29.7±6.5 mL/min/kg, $p<0.01$). VO_2peak did not differ between SED and SED+MI (Table 1).

[insert Table 1]

MEDICAL HISTORY AND MEDICATION USAGE

No differences were observed between ATH+MI and SED+MI for time between myocardial infarction diagnosis and study participation, cardiac enzyme levels (Troponin-I, CK, CREAT, ASAT, and LDH), and infarct location (Table 2). Percutaneous Coronary Intervention (PCI) treatment was applied in 94% of the post-MI patients and prevalence did not differ between both post-MI groups (Table 2). None of the participants received coronary artery bypass grafting surgery. 71% of the post-MI participants completed a cardiac rehabilitation program and this did not differ between both post-MI groups (Table 2). Four post-MI controls needed an elective PCI and one of them reported a recurrent myocardial infarction, whereas none of the post-MI athletes needed an elective PCI or reported a recurrent myocardial infarction. Apart from ACE-inhibitors, medication use did not differ between post-MI groups (Table 2).

[insert Table 2]

ECHOCARDIOGRAPHY

LEFT VENTRICULAR SYSTOLIC FUNCTION

Due to a low-quality echocardiogram, LVESV, and LVEDV of two ATH and two ATH+MI could not be determined and were not included in the statistical analyses. LVESV was significantly lower in ATH (38 mL [32 to 50]) and SED (39 mL [32 to 44]) compared to SED+MI (50 mL [44 to 69]) ($P < 0.01$), but did not differ compared to ATH+MI (47 mL [42 to 52], $P > 0.10$). LVEF was significantly higher in ATH (61% [57 to 62]), ATH+MI (59% [56 to 60]), and SED (58% [52 to 63]) compared to SED+MI (51% [47 to 55], $P < 0.01$, Figure 1). Two (10%) ATH+MI *versus* eight (57%) SED+MI demonstrated an impaired LVEF ($P < 0.01$). Stroke volume was significantly higher in ATH (83 mL [73 to 102] compared to SED (71 mL [60 to 79]) and SED+MI (68 mL [57 to 82], $P < 0.05$), but stroke volume did not differ between ATH+MI (82 mL [68 to 97]) and ATH, SED, and SED+MI ($P > 0.10$). Cardiac output, cardiac index, and peak systolic annular tissue velocity did not differ across groups (Table 3).

[insert Figure 1]

[insert Table 3]

LEFT VENTRICULAR WALL STRAIN

LV longitudinal strain did not differ between ATH+MI (-13% [-18 to -10]), SED (-12% [-15 to -11]), and SED+MI (-11% [-15 to -6], $P > 0.05$), but LV longitudinal strain was superior (*i.e.*, more negative strain) in ATH (-16% [-18 to -14]) compared to SED+MI (Figure 2¸$P < 0.05$). LV circumferential strain was superior in ATH (-19% [-21 to -17], ATH+MI (-16% [-20 to -12]), and SED [-15% [-18 to -14] compared to SED+MI (-13% [-15 to -8], $P < 0.01$). LV area strain was superior in ATH (-31% [-34 to -26]) and ATH+MI (-26% [-33 to -21]) compared to SED+MI (-20% [-26 to -13], $P < 0.05$), whereas LV area strain did not differ between SED (-26% [-29 to -22]) and the other three groups (Figure 2, $P > 0.05$). LV radial strain did not differ between ATH+MI (37% [30 to 52]), SED (38% [31 to 45]), and SED+MI (33% [24 to 38], $P > 0.05$), but LV radial strain was superior in ATH (47% [38 to 55]) compared to SED+MI (Figure 2, $P < 0.01$). LV longitudinal, circumferential, area, and radial strain did

not differ between ATH and ATH+MI ($P > 0.10$). LV circumferential strain was superior in SED compared to SED+MI ($P < 0.05$).

[insert Figure 2]

LEFT VENTRICULAR DIASTOLIC FUNCTION

All diastolic function parameters (i.e. LVEDV, E-wave, A-wave, E/A ratio, e' LV, a' LV, and E/e' ratio) did not differ across groups (Table 3).

DISCUSSION

The major finding of this study is that ATH+MI had a better ejection fraction and a superior global LV wall strain compared to SED+MI. Ejection fraction and LV wall strain are important parameters for LV systolic function.[13] We found no differences in LV function between ATH and ATH+MI, whereas ejection fraction and circumferential strain differed between SED and SED+MI. These findings suggest that lifelong exercise training may protect against the deleterious effects of a myocardial infarction and/or minimizes the effects of pathological LV remodelling after a myocardial infarction.

The magnitude of pathological LV remodelling is dependent on the severity of the myocardial infarction,[14] clinical treatment (PCI),[15] medication use,[16] and lifestyle changes following diagnosis.[16] We found no difference in cardiac enzyme levels, PCI treatment, infarct location, and medication (except ACE-inhibitors) between both post-MI groups, suggesting that myocardial infarction size was comparable between ATH+MI and SED+MI. A potential explanation for the difference in ACE-inhibitors may relate to the physically active lifestyle of the ATH-MI. Physical activity is related to a favourable blood pressure, [17] which may have enabled ATH-MI to reduce their medication. Interestingly, ATH+MI reported an increase in activity levels after the myocardial infarction compared to before, whereas the SED+MI did not change their physical activity behaviour. These findings suggest

that ATH+MI and SED+MI did not differ in clinical characteristics, while their habitual exercise levels were significantly different.

Before the myocardial infarction, ATH+MI were highly physically active (49 [35-84] MET-hours/week), whereas SED+MI were inactive (1 [0-4] MET-hours/week). Several studies support the hypothesis that exercise training induces preconditioning effects against ischemia and reperfusion,[18, 19] which subsequently protects the myocardium against damage produced by ischemia and reperfusion.[9] A reduction of the induced cardiac damage due to a myocardial infarction will promote the healing process of the infarcted area.[9] Indeed, evidence from animal studies suggests that exercise training before a myocardial infarction attenuates LV remodelling [9] and improves cardiac function [9] after myocardial infarction. Findings from our study support this hypothesis as LV function (i.e. LV ejection fraction, global circumferential and area strain) was superior in ATH+MI compared to SED+MI. Our results are indicative that lifelong exercise training may improve infarct healing after myocardial infarction.

An alternative explanation for the better LV systolic function in ATH+MI *versus* SED+MI may relate to their activity patterns after the myocardial infarction. Most cardiovascular professional societies recommend post-MI patients to participate in a cardiac rehabilitation program, and advise post-MI patients to remain physically active at a low-to-moderate endurance intensity level [16] to improve functional capacity and reduce (cardiovascular) mortality. [20 21] An early start of cardiac rehabilitation and prolonged exercise training (>12 weeks) is associated with larger improvements in LV remodelling.[22] In the present study, ATH+MI continued and even increased their high-level physical activity patterns after MI, whereas SED+MI maintained their sedentary lifestyle. The VO_2peak of our study population reinforces these observations; ATH+MI (40.9±5.5 mL/min/kg) showed a substantially higher VO_2peak uptake compared to SED+MI (29.8±6.1 mL/min/kg). The physically active lifestyle after the myocardial infarction may have contributed to the better LV systolic function in ATH+MI compared to SED+MI. In fact, these observations may represent optimal cardiac rehabilitation, as LV function of ATH+MI was not different from their non-MI peers.

In the current study, it is impossible to distinguish the independent effects of exercise training before and after the myocardial infarction on LV function. To gain more information about post-infarction cardiac function and lifelong exercise training, we correlated the training of the different age periods with ejection fraction and the strain parameters. Overall, we observed that higher levels of physical activity were related to improved LV function, which is in line with the reported results of this study (supplement Table 1). The combination of exercise training before and after myocardial infarction may be superior to exercise training before or after myocardial infarction only. One animal study suggests that the combination of exercise training before and after myocardial infarction improves LV remodelling by reducing the inflammatory response and scar thinning process.[23] Another animal study demonstrated that the combination of exercise training before and after myocardial infarction improved infarct healing and post-MI survival compared to no exercise training.[9] However, ameliorating effects on LV remodelling observed in mice that either exercised before or after myocardial infarction were lost in mice that exercised before *and* after myocardial infarction.[9] Absence of exercise benefits on LV remodelling in this combination group most likely relate to a very early start of post-MI exercise training accompanied with a high exercise intensity (~7 km/day in the first week post-MI) in this particular study.[9] Indeed, there is evidence that vigorous post-MI exercise may cause further deterioration of the injured heart.[24] This negative effect seems to be dependent on the severity of the myocardial infarction and timing of the exercise training.[25] Additional research is warranted to assess the relation between exercise before and after the myocardial infarction in relation to LV remodelling in humans.

In contrast to LV systolic function, we did not observe statistical differences in diastolic function between ATH+MI and SED+MI. A potential explanation could relate to the fact that not all post-MI patients develop diastolic dysfunction after a myocardial infarction.[26] Specific treatment to improve diastolic function following a myocardial infarction is not available.[27] Potentially the long period between myocardial infarction and study participation (Q_{50}: 6 years [Q_{25}: 3 to Q_{75}: 10]), and adequate cardiac medication use may have contributed to the null findings of diastolic function between groups. Alternatively, aging has been associated with a progressive decline in diastolic function.[28, 29] Aging may

lead to an impaired diastolic relaxation pattern [28, 29] and lifelong exercise training can only partially minimize the age-related decline.[28] Sub analysis of our results, revealed that indeed a higher age was associated with a significantly lower E/A ratio ($r=-0.35$; $P < 0.01$) and a higher E/e' ratio ($r=0.42$; $P < 0.01$). These findings indicate that the inclusion of an older study population affected our results on diastolic function. Collectively, the possibility that not all post-MI patients develop diastolic dysfunction after a myocardial infarction and the influence of ageing on diastolic function, could have resulted into the null findings in diastolic function in the present study.

CLINICAL IMPLICATIONS

In an event when exercise training *'fails'* to prevent a myocardial infarction, our data suggest that veteran athletes may restore and/or maintain their LV systolic function after a myocardial infarction. Additional benefits are improved secondary prevention, since none of the ATH+MI had an elective PCI or recurrent myocardial infarction. The information of the current study that exercise training improves LV remodelling after myocardial infarction might be another reason to motivate sedentary post-MI patients or individuals at risk for cardiovascular disease to change their lifestyle and enjoy exercise training to improve cardiovascular health.

Limitations

Presence of recall bias regarding exercise history of the participants is a potential study limitation. To minimize this error, we did not elucidate our study hypothesis to the study participants.[30] Moreover, the time span of exercise history was similar between the three groups and it is likely that recall bias was similar across groups. This study was cross-sectional by design and is subject to the inherent limitations of that approach. It is likely that over the last 20 years, lifestyle habits have changed, and this might have influenced the risk for a myocardial infarction (*e.g.*, smoking or dietary habits). To avoid such concerns, a longitudinal study design is preferred, but such a study would take too much time for observations and tests. Ethical concerns would emerge during a longitudinal study design, because individuals clearly at risk for myocardial infarction will receive preventative measures. These

individuals may not endure a myocardial infarction and will have no cardiac damage. Consequently, it would be impossible to study the protective effects of lifelong exercise training against pathological LV remodelling after the myocardial infarction. Therefore, we used the cross-sectional approach, coupled with great effort to minimize bias. We could not retrieve information about other clinical markers (e.g. LVEF) than the reported cardiac enzyme markers, which may have limited the comparison of infarct size between post-MI groups. Although previous studies demonstrated that the cardiac enzyme markers reported in this study are related to infarct size,[31-33] LVEF directly after the myocardial infarction would have improved the comparison between post-MI groups. Unfortunately, these values could not be provided by the different hospitals of the patients that were included in the present study. Finally, it is important to keep in mind that of these results were generated from a relative small study population and future work needs to confirm our findings in a large sample size. Nonetheless, we believe that this study is a first step to confirm animal data that demonstrate that exercise may attenuate the deleterious effects of MI

CONCLUSIONS

ATH+MI had a better LV systolic function compared to SED+MI and a similar LV systolic function compared to ATH. SED+MI had a lower LVEF and circumferential wall strain compared to SED. These findings suggest that lifelong exercise training may protect against the deleterious effects of a myocardial infarction and/or minimizes the effects of pathological LV remodelling after a myocardial infarction in veteran athletes.

Conflicts of interest

The authors MM, GS, AvD, and MH declare that they have no conflict of interest that are directly relevant to the content of this manuscript. TE was financially supported by a European Commission Horizon 2020 grant [Marie Sklodowska-Curie Fellowship 655502].

Authorship

MM, TE, AD, MH contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, and/or interpretation of data for the work. MM and TE drafted the manuscript. GS, AD, MH critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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FIGURE LEGENDS

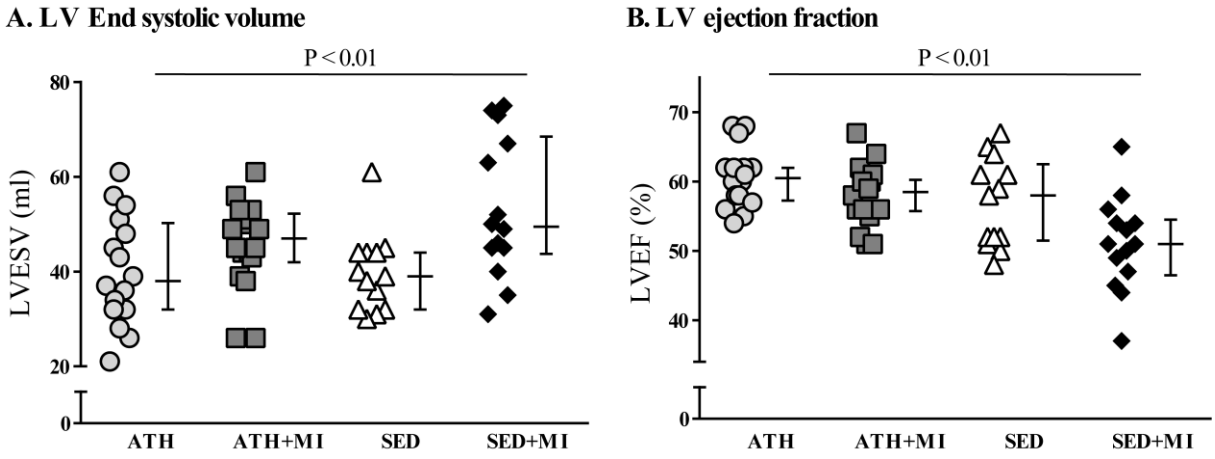

Figure. 1 Individual and average values of A) left ventricular end systolic volume (LVESV) and B) left ventricular ejection fraction (LVEF) of the veteran athletes (ATH, circles), veteran post-MI athletes (ATH+MI, squares), sedentary controls (SED, triangles), and sedentary post-MI controls (SED+MI, diamonds). LVESV was significantly lower in ATH and SED compared to SED+MI ($P < 0.01$), but did not differ compared to ATH+MI ($P > 0.10$). LVEF was significantly higher in ATH, ATH+MI, and SED compared to SED+MI ($P < 0.01$). Group averages are reported as median and interquartile range.

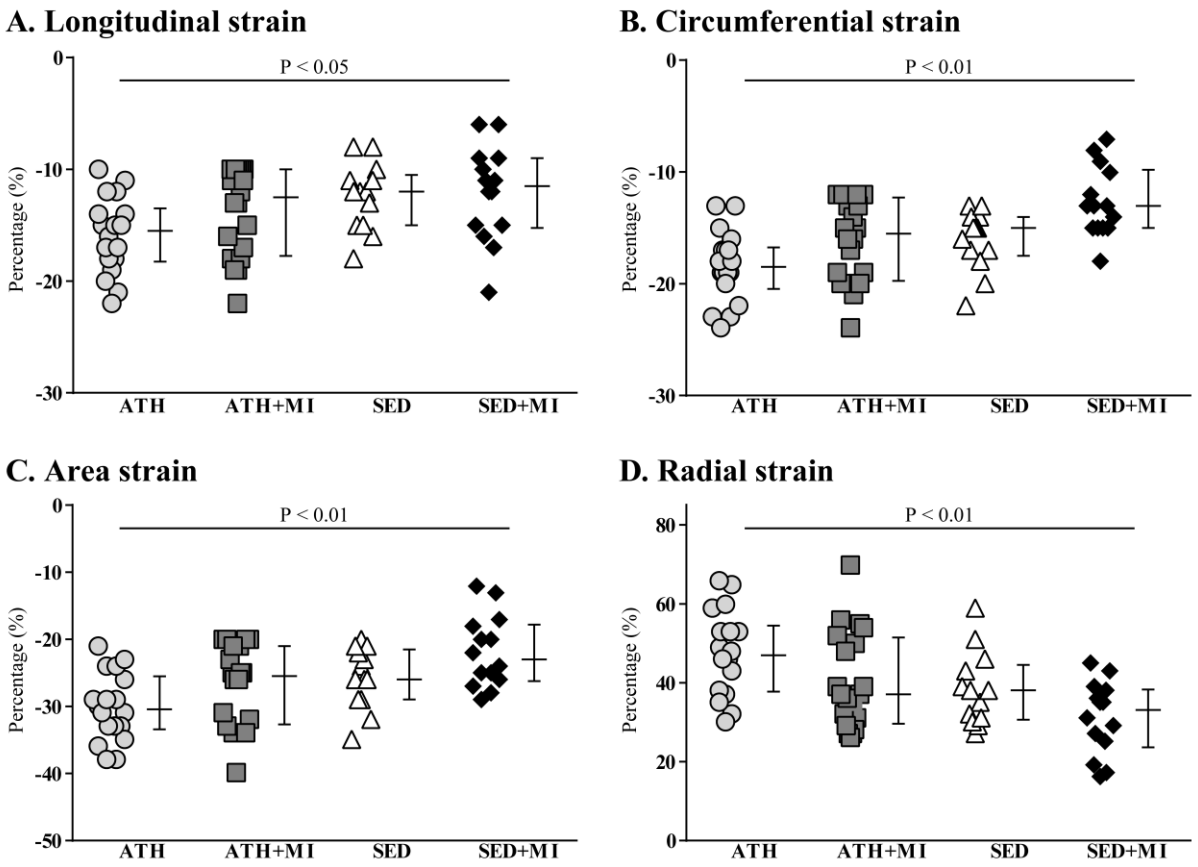

Figure. 2 Individual and average values of A) LV longitudinal strain, B) circumferential strain, C) area strain, and D) radial strain of the of the veteran athletes (ATH, circles), veteran post-MI athletes (ATH+MI, squares), sedentary controls (SED, triangles), and sedentary post-MI controls (SED+MI, diamonds). LV longitudinal strain did not differ between ATH+MI, SED, and SED+MI, but LV longitudinal strain was superior (*i.e.*, more negative strain) in ATH compared to SED+MI. LV circumferential strain was superior in ATH, ATH+MI, and SED compared to SED+MI. LV area strain was superior in ATH and ATH+MI compared to SED+MI, whereas LV area strain did not differ between SED and the other three groups. LV radial strain did not differ between ATH+MI, SED, and SED+MI, but LV radial strain was superior in ATH compared to SED+MI. Group averages are reported as median and interquartile range.

Table 1. Participants' characteristics of the veteran athletes (ATH, *n*=18), veteran post-MI athletes (ATH+MI, *n*=20), sedentary controls (SED, *n*=13) and sedentary post-MI controls (SED+MI, *n*=14). P-value refers to a one-way ANOVA, (*) Kruskal-Wallis test, or (¥) Mann-Whitney-U test.

	ATH	**ATH+MI**	**SED**	**SED+MI**	*p*
n	18	20	13	14	
CHARACTERISTICS					
Age (years)	61±7	60±6	58±7	61±6	0.67
Height (cm)	178±8	176±5	181±5	176±5	0.09
Body mass (kg)	74±8	77±7	88±9 [1,2]	83±14	<0.01
Body Mass Index (kg/m^2) *	23.3 (20.6-25.3)	24.5 (23.9-26.0)	26.9 (25.4-27.4) [1]	26.6 (22.5-28.8) [1]	<0.01
Body Surface Area (m^2)	1.91±0.13	1.93±0.11	2.09±0.10 [1,2]	1.99±0.18	<0.01
Mean arterial pressure (mmHg) *	98 (89-108)	95 (93-100)	105 (94-109)	92 (89-97)	0.14
Diastolic blood pressure (mmHg)	82 (76-90)	77 (74-81)	88 (82-92)	77 (73-82)	0.06
Systolic blood pressure (mmHg)	130 (120-142)	131 (126-142)	137 (124-145)	124 (118-132)	0.22
Resting heart rate (beats/min) *	50 (48-55)	57 (53-62)	61 (54-71) [1]	59 (56-60) [1]	<0.01
Ever smoked (yes *n*)	10 (56%)	12 (60%)	11 (85%)	10 (71%)	0.34
Positive family history (yes *n*)	9 (50%)	15 (75%)	6 (46%)	11 (79%)	0.13
LIFELONG PHYSICAL ACTIVITY PATTERNS					
Exercise time					
Average (hours/week) *	7.1 (5.8-11.9)	5.7 (4.9-9.4)	0.1 (0.0-0.9) [1,2]	0.1 (0.0-0.4) [1,2]	<0.001
Pre-MI (hours/week) ¥		5.7 (4.6-8.6)		0.2 (0.1-1.1)	<0.001
Post-MI (hours/week) ¥		6.2 (5.3-10.3)		0.0 (0.0-0.6)	<0.001
Exercise dose					
Average (MET-hours/week) *	60 (47-110)	51 (40-93)	1 (0-6) [1,2]	0 (0-3) [1,2]	<0.001
Pre-MI (MET-hours/week) ¥		49 (35-84)		1 (0-4)	<0.001
Post-MI (MET-hours/week) ¥		56 (43-93)		0 (0-4)	<0.001
INCREMENTAL MAXIMAL CYCLING TEST					
VO_2peak (mL/min/kg)	48.0±8.9	40.9±5.5 [1]	31.6±4.8 [1,2]	29.7±6.5 [1,2]	<0.01
%VO_2peak predicted (%)	164±22	143±16 [1]	115±19 [1,2]	111±22 [1,2]	<0.01
Power Output (Watt)	319±58	274±40 [1]	213±48 [1,2]	188±43 [1,2]	<0.01
Maximal heart rate (beats/min)	165±13	164±15	168±15	147±20 [1,2,3]	<0.01
Anaerobic threshold (Watt)	224±63	200±44	145±41 [1,2]	134±56 [1,2]	<0.01
Respiratory Exchange Ratio (VCO_2 / VO_2)	1.14±0.06	1.12±0.08	1.10±0.07	1.11±0.10	0.56
Lactate (mmol/L) *	11.6 (8.9-12.3)	10.5 (9.2-11.2)	11.3 (10.8-12.4)	11.4 (9.9-12.4)	0.28
FASTING BLOOD LEVELS					
HbA1c (mmol/mol) *	35.5 (34.4-39.4)	36.6 (35.5-37.7)	37.2 (35.5-38.8)	37.7 (36.1-39.4)	0.18
Cholesterol (mmol/L)	5.4±0.8	4.5±0.9 [1]	6.0±0.9 [2]	4.2±0.7 [1,3]	<0.01
HDL (mmol/L)	1.8±0.3	1.6±0.4	1.4±0.3 [1]	1.4±0.2 [1]	<0.01
LDL (mmol/L)	3.3±0.8	2.6±0.8 [1]	4.1±0.7 [1,2]	2.3±0.6 [1,3]	<0.01
Triglycerides (mmol/L) *	0.9 (0.7-1.3)	0.9 (0.8-1.1)	1.3 (1.0-2.2) [1]	1.2 (0.9-1.9)	<0.01
Glucose (mmol/L) *	4.6 (4.3-5.0)	4.6 (4.5-5.0)	4.7 (4.4-5.0)	4.7 (4.3-5.0)	0.79

MET: Metabolic Equivalent of Task; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: low-density lipoprotein.

[1]Significant different from ATH; [2]Significant different from ATH+MI; [3]Significant different from SED.

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Table 2. Cardiac medical history data of the veteran post-MI athletes (ATH+MI, *n*=20) and sedentary post-MI controls (SED+MI, *n*=14). P-value refers to a (¥) *Mann-Whitney U* or *Fisher's exact* test (two-sided).

		ATH+MI		**SED+MI**	***p*-value**
Post-MI time (years)		5 (3-10)		7 (4-10)	0.73
ENZYME MARKERS*					
Troponin-I (µg/L) (median [IQR]) ¥	n=10	7.5 (1.1-24.2)	n=7	17.9 (4.2-100.0)	0.23
CK (u/L) (median [IQR]) ¥	*n*=17	775 (251-2029)	*n*=14	522 (399-2222)	0.45
CREAT (umol/L) (median [IQR]) ¥	*n*=14	87 (78-103)	*n*=13	89 (71-97)	0.49
AST (u/L) (median [IQR]) ¥	*n*=14	38 (26-135)	*n*=12	75 (35-117)	0.44
LDH (u/L) (median [IQR]) ¥	*n*=13	407 (335-638)	*n*=11	382 (176-520)	0.14
INFARCT LOCATION					
Anterior (n)		7 (35%)		8 (57%)	0.30
Inferior (n)		7 (35%)		5 (36%)	1.00
Non-STEMI (n)		6 (30%)		1 (7%)	0.20
TREATMENT*					
PCI (n [%])		18 (95%)		12 (92%)	1.00
Thrombolytic therapy (n [%])		1 (5%)		1 (8%)	
CARDIAC REHABILITATION					
Cardiac rehabilitation (n [%])		13 (65%)		11 (79%)	0.47
POST-MI INCIDENTS					
Elective PCI (n)		0 (0%)		4 (29%)	0.022
Recurrent myocardial infarction (n)		0 (0%)		1 (7%)	0.41
MEDICATION					
Anticoagulant (n)		19 (95%)		14 (100%)	1.00
Anti-platelet (n)		18 (90%)		12 (86%)	1.00
Vitamin K antagonist (n)		1 (5%)		2 (14%)	0.56
Antihypertensives (n)		14 (70%)		13 (93%)	0.20
ACE-inhibitor (n)		5 (25%)		9 (64%)	0.035
AT2-antagonist (n)		3 (15%)		3 (21%)	0.67
Beta-blocker (n)		8 (40%)		10 (71%)	0.09
Diuretic (n)		1 (5%)		3 (21%)	0.28
CCB (n)		1 (5%)		0 (0%)	1.00
Antihyperlipidemic agents (n)		16 (80%)		14 (100%)	0.13
Statins (n)		16 (80%)		14 (100%)	0.13

*Based on a sub sample; hospital data were not available

MI: myocardial infarction; PCI: Percutaneous coronary intervention; CK: Creatine kinase; CREAT: Creatinine; ASAT: Aspartate transaminase; LDH: Lactate dehydrogenase; NON-STEMI: non-ST elevation myocardial infarction; ACE: angiotensin converting enzyme; AT: angiotensin; CCB: calcium channel blocker.

Table 3. Left ventricular systolic and diastolic function of the veteran athletes (ATH, *n*=18), veteran post-MI athletes (ATH+MI, *n*=20), sedentary controls (SED, *n*=13) and sedentary post-MI controls (SED+MI, *n*=14). P-value refers to a one-way ANOVA or (*) Kruskal-Wallis test.

	ATH	**ATH+MI**	**SED**	**SED+MI**	*p*
SYSTOLIC FUNCTION					
Stroke volume (mL) *	83 (73-102)	82 (68-97)	71 (60-79) [1]	68 (57-82) [1]	0.045
Cardiac output (L/min) *	4.3 (3.7-5.8)	4.7 (3.9-5.5)	4.4 (4.1-6.1)	3.6 (3.4-5.1)	0.45
Cardiac index (L/min/m^2)	2.1 (1.9-2.7)	2.4 (2.1-2.8)	2.2 (1.9-2.8)	1.9 (1.7-2.8)	0.33
s' velocity (cm/s)	9.3±1.9	8.8±1.7	9.0±1.4	8.4±2.0	0.52
DIASTOLIC FUNCTION					
LVEDV (mL)	101±24	109±18	92±15	107±22	0.14
E (m/s)	63.0±11.9	62.9±16.3	62.7±15.7	68.9±15.0	0.61
A (m/s)	58 (46-71)	59 (52-75)	69 (54-81)	70 (64-81)	0.07
E/A ratio	1.10 (0.86-1.29)	0.95 (0.80-1.27)	0.92 (0.71-1.18)	0.92 (0.80-1.05)	0.51
e' LV (cm/s)	11.7 (9.7-13.3)	9.3 (8.0-10.5)	9.0 (7.3-10.5)	10.3 (7.5-12.1)	0.10
a' LV (cm/s)	11.3±2.5	10.4±1.7	11.2±2.0	10.4±1.2	0.41
E/e'	5.9 (5.0-6.5)	6.4 (5.6-8.5)	7.5 (6.1-8.7)	6.7 (6.2-7.8)	0.11

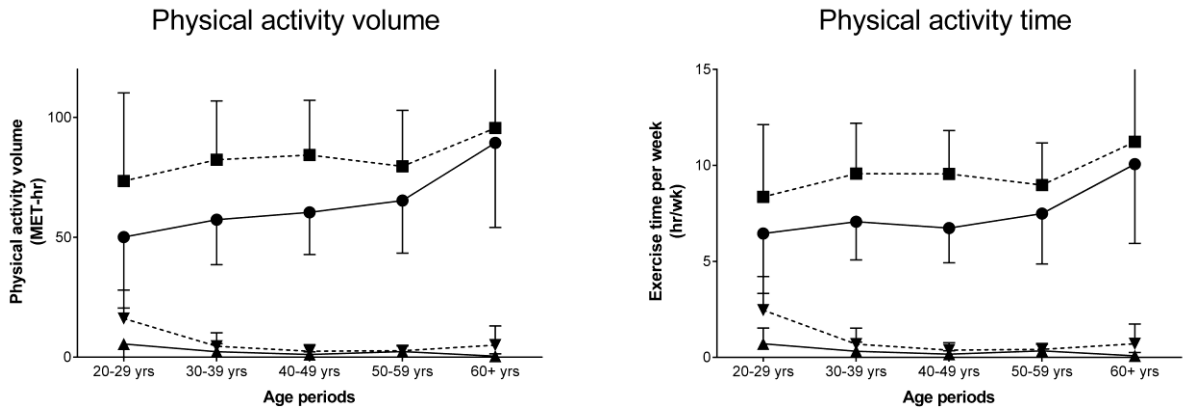
s' velocity: peak systolic annular tissue velocity; LVEDV: left ventricular end-diastolic volume; E: peak flow velocity of the early rapid filling wave at the mitral leaflet tips; A: peak flow velocity of the late filling wave at the mitral leaflet tips; e' LV: peak annular tissue velocity during early filling; a': peak annular tissue velocity during late diastolic atrial contraction; E/e': ratio of peak E velocity with e'. [1]Significant different from ATH.

Supplementary Table 1. Correlation analysis between physical activity dose of the five different age periods and cardiac function parameters.

Parameter		**EF%**	**GLS**	**GCS**	**AS**	**GRS**
P1 20-29 yrs	*r*	0.33**	-0.24	-0.30*	-0.28*	0.25*
	n	61	65	65	65	65
P2 30-39 yrs	*r*	0.41**	-0.34**	-0.36**	-0.36**	0.33**
	n	61	65	65	65	65
P3 40-49 yrs	*r*	0.44**	-0.39**	-0.37**	-0.40**	0.36**
	n	61	65	65	65	65
P4 50-59 yrs	*r*	0.51**	-0.42**	-0.34**	-0.41**	0.39**
	n	59	62	62	62	62
P5 60+ yrs	*r*	0.42**	-0.37*	-0.30	-0.36*	0.32*
	n	38	38	38	38	38

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).



Supplementary Figure 1. Physical activity dose of the different age periods for ATH, ATH-MI, SED, and SED-MI. Athletes were more physically active throughout their life than the sedentary group and tended to increase their physical activity across their life. The sedentary groups tended to decrease their physical activity after their 30s.