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No evidence of adverse cardiac remodeling in former elite endurance athletes

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ABSTRACT

Background: The impact of much higher exercise loads on a previously healthy heart remains controversial. To examine the consequences of decades of strenuous endurance exercise at the highest competition level on heart dimensions and volumes as well as on serum biomarkers of cardiac fibrosis/remodeling.
Methods and results: We compared echocardiographic measurements and serum biomarkers of cardiac fibrosis/remodeling [troponin I, galectin-3, matrix metallopeptidase-2 and 9, N-terminal pro-brain natriuretic peptide, carboxy-terminal propeptide of type I procollagen, and soluble suppressor of tumorigenicity-2 (sST-2)/interleukin(IL)-1R4] in 53 male athletes [11 former professional ('elite') and 42 amateur-level ('sub-elite') cyclists or runners, aged 40–70 years] and 18 aged-matched controls. A subset of 15 subjects (5 controls, 3 sub-elite and 7 elite athletes) also underwent cardiac magnetic resonance imaging (cMRI).
Elite and sub-elite athletes had greater echocardiography-determined left ventricular myocardial mass indexed to body surface area than controls (113 ± 22, 115.2 ± 23.1 and 94.8 ± 21 g/m^2, respectively, $p = 0.008$ for group effect), with similar results for left (50.5 ± 4.4, 48.2 ± 4.3 and 46.4 ± 5.2 mm, $p = 0.008$) and right (38.6 ± 3.8, 41.1 ± 5.5 and 34.7 ± 4.3 mm, $p < 0.001$) ventricular end-diastolic diameter, and cMRI-determined left atrial volume indexed to body surface area (62.7 ± 8.1, 56.4 ± 16.0 and 39.0 ± 14.1 ml/m^2, $p = 0.026$). Two athletes showed a non-coronary pattern of small, fibrotic left ventricular patches detected by late gadolinium enhancement. No group effect was noted for biomarkers.
Conclusions: Regardless of their competition level at a younger age, veteran endurance athletes showed an overall healthy, non-pathological pattern of cardiac remodeling. Nonetheless, the physiopathology of the ventricular fibrotic patches detected warrants further investigation.

1. Introduction

Low to moderate intensity aerobic or endurance exercise (*e.g.*, brisk walking daily for 30–60 min) has well-documented beneficial effects on cardiovascular morbidity and mortality [1,2]. However, the impact of much higher exercise loads (*e.g.*, training for and competing in marathon running events) on a previously healthy heart remain controversial

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[2–5], and some authors warn of the potentially deleterious cardiac effects of long-term strenuous endurance exercise [6–8]. The concept of 'cardiac overuse injury' (or 'over exercise') has been recently reported to group the potential negative effects of strenuous endurance exercise [9].

Middle-aged/older athletes with a lifelong history of training/competition at the highest possible level (*i.e.*, international) are the paradigm for the study of the potential deleterious effects of long-term endurance exercise on heart function. In this study, we aimed to compare morphologic and functional cardiac features as well as biomarkers related to these parameters among former professional and lower level (amateur) endurance athletes (most still active in Masters' competitions), and non-athletic controls.

2. Patients and methods

The study was performed in accordance with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and received institutional review board approval. Written informed consent was obtained from all participants.

2.1. Subjects

Fifty-three elite male endurance athletes (cyclists or runners) and 18 age- and gender-matched controls volunteered to participate in this study (Table 1). Inclusion criteria were as follows: age between 40 and 70 years without major risk factors (hypertension, diabetes, dyslipidemia, smoking), metabolic or cardiovascular disease (CVD), chronic obstructive pulmonary disease, chronic renal or hepatic failure, or cancer. Control subjects had never participated regularly in strenuous endurance exercise (*e.g.*, running, swimming, bicycling) *i.e.*, performing <3 structured weekly training sessions. The athletes group included 11 former professional ('elite') athletes and 42 amateur ('sub-elite') athletes. All professional athletes had previous experience in competition (average 29 ± 9 years), and international-level competition (average 11 ± 4 years). Five of these athletes were professional cyclists and 6 were endurance runners (including a former marathon world champion). Amateur athletes (23 cyclists, 19 endurance runners) had previous experience in national-level competition (24 ± 9 years). With the exception of 4 athletes (2 in each group), all participants were still training and competing regularly in Masters' categories (*e.g.*, running marathons in <3 h or competing in cycling races). The Minnesota Leisure Time Physical Activity Questionnaire [10] was used to determine the exercise habits (type of exercise, weekly frequency, intensity and duration) of each subject during the previous year.

2.2. Blood variables

Blood samples were drawn from an antecubital vein in all participants at 8–9 am (after an overnight fast and refraining from intense exercise for 24+ h) for the analysis of biochemical biomarkers. Glucose, lipids, N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin I, and phosphatase alkaline were determined using standard procedures. Carboxy-terminal extension peptide of type I procollagen (PICP) was measured using an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (Quidel Corporation, San Diego, CA). The minimum detectable concentration for this assay is 0.2 ng/ml and intra- and inter-assay variability are ≤6.3% and

Table 1
Subjects' main characteristics.

	Controls ($n = 18$)	Sub-elite athletes ($n = 42$)	Elite athletes ($n = 11$)	*P*-values				Statistical power (%)*	
				Main effect (group)	Post hoc controls *vs.* sub-elite	Post hoc controls *vs.* elite	Post hoc sub-elite *vs.* elite	Controls *vs.* sub-elite	Controls *vs.* elite
Age (years)	58 ± 5	55 ± 9	54 ± 4	0.086					
Years of high-intensity activity		24 ± 9	29 ± 9						
*Physical activity levels in the last year***									
Hours/week	5.8 ± 2.7	10.6 ± 4.2	10.6 ± 3.1	**0.001**	0.004	0.005	NS	+99%	98.9%
kcal/day	216 ± 60	903 ± 243	923 ± 310	<**0.001**	<0.001	0.006	NS	+99%	+99%
Body mass index (kg/m^2)	25.7 ± 2.3	23.7 ± 2.0	23.0 ± 1.8	<**0.001**	0.004	0.004	NS	89.4%	95.1%
Body fat (%)	22.6 ± 3.0	17.9 ± 5.5	15.4 ± 3.6	<**0.001**	0.003	0.001	NS	98.9%	+99%
SBP (mmHg)	128 ± 14	126 ± 11	125 ± 11	0.849					
DBP (mm Hg)	73 ± 8	72 ± 8	72 ± 5	0.932					
Total cholesterol (mg/dl)	197 ± 33	207 ± 28	196 ± 24	0.318					
LDL- cholesterol (mg/dl)	118 ± 26	125 ± 28	122 ± 21	0.681					
HDL-cholesterol (mg/dl)	63 ± 16	66 ± 16	60 ± 14	0.276					
Triglycerides (mg/dl)	95 ± 41	102 ± 80	93 ± 49	0.678					
Glucose (mg/dl)	88 ± 7	87 ± 8	87 ± 9	0.999					
Electrocardiographic findings, n (%)									
Normal ECG	18 (100%)								
Sinus bradycardia	0	27 (64%)	11 (100%)						
LVH	0	10 (24%)	2 (18%)						
IRBB	0	2 (5%)	1 (9%)						
ERP	0	2 (5%)	0						
First degree AVB	0	2 (5%)	0						
Brugada-like pattern	0	2 (5%)	0						

Data are represented as mean ± standard deviation. Physical activity data were based on the Minnesota Leisure Time Physical Activity Questionnaire (17) and body fat % was measured by bio-electrical impedance analysis. Data not following a normal distribution are in italics. Symbols: * statistical post-hoc power analysis to detect differences between group means with a significance level (α) of 0.05 (2-tailed); ** physical intensity ranged from 3 to 6 metabolic equivalents (METs) in controls and was >6 METs in athletes. Abbreviations: AVB, atrioventricular block; DBP, diastolic blood pressure; ECG, electrocardiogram; ERP, early repolarization; IRBB, incomplete right bundle branch block; LVH, left ventricular hypertrophy; SBP, systolic blood pressure. Significant *P*-values for main (group) effect are in bold.

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≤6.4%, respectively. Serum concentrations of galectin-3, matrix metalloproteinase (MMP)-2 and MMP-9 and soluble suppressor of tumorigenicity-2 (sST-2)/interleukin(IL)-1R4 were also determined using ELISA kits (R&D Systems Inc., Minneapolis, MN). The detection limits for these tests are 0.016 ng/ml (galectin-3), 5.1 pg/ml (sST-2/IL-1R4) 0.033 ng/ml (MMP-2), and 0.156 ng/ml (MMP-9). Maximum intra- and inter-assay variability are 3.8% and 6.3% (galectin-3), 5.6% and 7.1% (sST-2/IL-1R4), 7.0% and 7.0% (MMP-2), and 2.9% and 7.9% (MMP-9).

2.3. Electrocardiography

A standard 12-lead electrocardiography (ECG) with subjects in the supine position after 10 min of rest was performed and analyzed in a blinded fashion by a single experienced cardiologist according to standard clinical criteria [11].

2.4. Echocardiography

All participants underwent transthoracic echocardiography (Philips Medical, Andover, MA) by standard 2-dimensional (2D) and Doppler imaging by a single experienced sonographer. Echocardiographic data were stored digitally and analyzed off-line by this investigator. Left ventricular (LV) volume and ejection fraction (EF) were calculated using the modified biplane technique [12]. LV mass was calculated using the area-length method, and LV geometry was assessed using relative wall thickness [12]. Myocardial tissue velocities were measured off-line on 2D color-coded tissue Doppler images and provided as the average for 3 consecutive cardiac cycles. Body surface area (BSA) was calculated using the Mosteller formula [13]. Measurements are presented as raw data and after BSA indexing when appropriate. Values defining the limits of normal cardiac structure/function were taken from the American Society of Echocardiography/European Association of Echocardiography chamber quantification and diastolic function recommendations [12,14].

2.5. Cardiac magnetic resonance imaging (cMRI)

A resting cMRI was performed in a subset of controls ($n = 5$), amateur athletes [$n = 3$ (1 cyclist)] and professional athletes [$n = 7$ (4 cyclists)]. Images were acquired with a Signa HDx 3.0 T define apparatus (GE Healthcare, Buckinghamshire, United Kingdom). In no subject was cMRI contraindicated. Cine-mode sequences were acquired in the short-taxis, 4 chambers and LV long-axis views; T2-weighted black-blood spin echo was carried out in the 3 typical planes before injection of 0.2 mmol/kg gadolinium-chelate injection, 10–15 min after which high-resolution late gadolinium enhancement (LGE) images in the 3 cardiac planes were acquired. Volumes, mass and function of LV/RV volumes, and LGE were determined using customized analysis software by a single experienced investigator who was blind to the subject's study group. The size of the LGE region was expressed in grams and as %LV mass. All parameters were assessed in a blinded fashion by an experienced researcher using the software Report Card 4.3 (General Electric).

2.6. Statistical analysis

Data were compared across the three groups (controls, former amateur and former professional athletes) by one-way analysis of variance (ANOVA) and the Bonferroni test was used for *post hoc* comparisons or its non-parametric equivalent (Kruskal Wallis test) for those variables that did not follow a normal distribution. Homogeneity of variances was checked using Levene's test and Welch's correction was applied if needed. Because of the small sample size for cMRI data, we used the non-parametric Mann-Whitney *U* test to assess results in controls *versus* all athletes grouped together. All statistical tests were performed using the software package SPSS for Mac 21.00 (IBM Corporation, Armonk, NY, USA). Data are provided as the mean ± SD. Significance was set at $p \leq 0.05$ (two-tailed).

3. Results

The main baseline characteristics of the study subjects are shown in Table 1. Athletes showed significantly higher levels of physical activity and, daily caloric expenditure, and lower body weight and fat composition than non-athletes. No differences were found in glucose or lipid levels between the 3 groups.

No ECG abnormalities were observed in control subjects, whereas several ECG findings were recorded in former athletes (see Table 1).

Echocardiographic results are provided in Table 2. A group effect was found for LV mass and mass index, and for LV and RV diameters, with both groups of athletes showing overall higher values than controls and similar values among themselves. The same was observed when the two athlete groups were considered together. These observations were confirmed by the cMRI results (Table 3). Additional findings were greater LV and RV volumes, along with greater cardiac posterior wall thickness and LA volumes corrected for BSA in athletes than in controls. Also, two sub-elite athletes (20% of all athletes undergoing cMRI) showed small regional myocardial fibrosis areas with a non-coronary pattern by LGE (Fig. 1). Specifically, one athlete showed a regional intra-myocardial fibrosis patch of 1.23 g of mass in the LV lateral wall, while the other athlete showed a small intra-myocardial LGE mass of 0.8 g in the basal segment of the inferolateral LV wall. Non-invasive ischemia induction tests (stress echocardiography) were negative in both athletes.

No group effect was noted for any of the blood biomarkers of cardiac fibrosis/remodeling and results remained essentially unchanged when comparing athletes as a single group *versus* controls (Table 4). Importantly, virtually all individual values fell within normal limits.

4. Discussion

Decades of top level training and participation in endurance sport, either at the most demanding ('elite') competition level (*i.e.*, international events such as 3-week tour races or Olympic Games) or at a lower national (*i.e.*, 'sub-elite') level does not seem to result in major deleterious cardiac consequences. Veteran endurance athletes who have performed regular strenuous endurance exercise over >30 years show a cardiac remodeling pattern characterized by larger LV, RV and LA cavities when compared with non-athletic healthy controls, with the greater LV size matched by an increased LV myocardial mass and with no evidence of permanent major cardiac damage or fibrosis assessed by imaging or blood biomarkers. To the best of our knowledge, this is the first report of RV remodeling using also blood biomarkers in highly competitive veteran athletes. Our study found no evidence of negative chronic consequences of this type of exercise on RV function. Finally, fibrotic, non-ischemic patches were detected in 2 out of the 10 athletes examined by cMRI but were undetectable in control subjects.

4.1. Left-sided heart

In our study, LV end-diastolic diameter (LVEDD) values were <60 mm in all of the athletes (highest individual value = 58 mm), whereas inter-ventricular septum (IVS) thickness at end-diastole was <12 mm in 76% (highest individual value = 15 mm), which is consistent with echocardiographic data reported for other European cohorts [15]. By contrast, the LV mass index was above normal (>115 g/m^2) in 56% of our athletes. Thus, our data are in line with the notion that the athlete's heart is characterized by eccentric LV hypertrophy, *i.e.*, balanced myocardial hypertrophy and ventricular dilation [16]. The finding that diastolic function was not impaired in the athletes with highest LV mass (>250 g; >130 g/m^2) further supports the idea of hypertrophy in

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Table 2
Echocardiographic variables by group.

	Controls ($n = 18$)	Sub-elite athletes ($n = 42$)	Elite athletes ($n = 11$)	*P*-values				Statistical power (%)* and optimal sample size (n)**		
				Main effect (group)	Post hoc controls *vs.* sub-elite	Post hoc controls *vs.*elite	Post hoc sub-elite *vs.* elite	Controls *vs.* sub-elite	Controls *vs.* elite	Sub-elite *vs.* elite
Heart rate (beats/min)	63 ± 8	54 ± 9	58 ± 8	**0.001**	<0.001	NS	NS	97%		
LV mass (g)	179.0 ± 40.2	216.6 ± 47.8	208.2 ± 40.2	**0.016**	0.013	NS	NS	87.9%		
LVMI (g/m^2)	94.8 ± 21.6	115.2 ± 23.1	113 ± 22	**0.008**	0.006	NS	NS	90.7%		
LVEF (%)	68.7 ± 7.2	65.9 ± 6.1	68.1 ± 5.9	0.248						
LVEF Simpson (%)	66.7 ± 5.6	64.9 ± 6.2	64.2 ± 5.1	0.452						
sPAP (mmHg)	23.1 ± 3.7	25.2 ± 4.0	25.2 ± 4.5	0.128						
LVESD (mm)	28.1 ± 5.5	31.6 ± 3.8	29.6 ± 3.7	**0.017**	0.016	NS	NS	69.1% ($n = 104$)		
LVEDD (mm)	46.4 ± 5.2	50.5 ± 4.4	48.2 ± 4.3	**0.008**	0.007	NS	NS	83.3%		
RVOT (mm)	27.1 ± 2.8	30.0 ± 3.3	32.9 ± 3.2	<**0.001**	0.011	<0.001	0.042	+99%	+99%	
IVSs (mm)	16.3 ± 2.8	16.4 ± 2.8	16.7 ± 2.9	0.954						
IVSd (mm)	10.6 ± 1.8	11.2 ± 1.6	10.9 ± 1.2	0.469						
PWTs (mm)	16.6 ± 1.9	17.5 ± 2.3	17.6 ± 3.2	0.358						
PWTd (mm)	10.4 ± 1.4	10.8 ± 1.7	11.5 ± 2.1	0.298						
RWT (cm)	0.45 ± 0.10	0.43 ± 0.09	0.48 ± 0.11	0.277						
RVEDD (mm)	34.7 ± 4.3	38.6 ± 3.8	41.1 ± 5.5	<**0.001**	0.009	<0.001	NS	75.9% ($n = 74$)	83.7%	
TAPSE (mm)	25.9 ± 3.3	26.8 ± 4.0	30.4 ± 4.7	**0.015**	NS	0.016	0.032		14.6% ($n = 22$)	79.5% ($n = 52$)
LVESV (ml)	27.6 ± 8.5	36.2 ± 31.4	33.6 ± 13.0	0.487						
LVEDV (ml)	82.9 ± 22.6	89.3 ± 20.7	91.8 ± 25.3	0.489						
DT (ms)	236.4 ± 56.5	231.1 ± 60.2	223.8 ± 80.2	0.876						
E-wave velocity (cm/s)	0.63 ± 0.10	0.65 ± 0.16	0.63 ± 0.09	0.752						
A-wave velocity (cm/s)	0.55 ± 0.14	0.52 ± 0.12	0.56 ± 0.13	0.556						
E/A ratio	1.20 ± 0.29	1.33 ± 0.44	1.19 ± 0.36	0.404						
S-wave (cm/s)	10.5 ± 2.4	9.8 ± 2.0	10.2 ± 1.6	0.969						
E′-wave velocity (cm/s)	11.2 ± 2.6	13.2 ± 3.9	13.9 ± 3.1	**0.016**	NS	0.006	NS			
A′-wave velocity (cm/s)	10.0 ± 4.1	9.2 ± 2.5	10.1 ± 3.9	0.978						
RV S′-wave velocity (cm/s)	15.0 ± 1.9	14.6 ± 2.2	14.9 ± 3.0	0.803						

Data are represented as mean ± standard deviation. Data not following a normal distribution are in italics. Symbols: *statistical post-hoc power analysis to detect differences between group means with a significance level (α) of 0.05 (2-tailed); **if the statistical post-hoc analysis value was lower than 80%, the estimated optimal sample size to obtain a statistical power ≥ 90% to detect a difference between group means with a significance level (α) of 0.05 (2-tailed) was also calculated.
Abbreviations: DT, E-wave deceleration time; IVSd, inter-ventricular septal thickness in diastole; IVSs, LV inter-ventricular septal wall thickness in systole; LV, left ventricle; LVEF, left ventricle ejection fraction; LVESD, LV end-systolic diameter; LVEDD, LV end-diastolic diameter; LVEDV, LV end- diastolic volume; LVESV, LV end-systolic volume; LVMI, LV mass indexed to body surface area; NS, non-significant; RV, right ventricle; RVEDD, right ventricle end-diastolic diameter; sPAP, systolic pulmonary artery pressure; PWTd: posterior wall thickness, diastole; PWTs: posterior wall thickness, systole; RVOT, right ventricular outflow tract; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion. Significant *P*-values for main (group) effect are in bold.

Table 3
Cardiac magnetic resonance measures by group.

	Controls ($n = 5$)	Sub-elite athletes ($n = 3$)	Elite athletes ($n = 7$)	*P*-value test all athletes *vs.* controls	Statistical power all athletes *vs.* controls
CO (L/min)	5.2 ± 0.7	6.9 ± 2.4	6.1 ± 1.6	0.110	
CI (L/min/m^2)	3.0 ± 0.2	3.8 ± 1.1	3.5 ± 1.0	0.267	
LV mass (g)	114.5 ± 23.7	168.0 ± 27.7	146.9 ± 26.9	**0.027**	**80.8%**
LV mass index (g/m^2)	60.7 ± 10.7	88.1 ± 11.2	81.7 ± 13.9	**0.014**	**95.9%**
LVEF (%)	59.7 ± 7.6	54.2 ± 5.0	60.1 ± 6.5	0.713	
RVEF (%)	61.7 ± 9.2	61.1 ± 9.5	64.2 ± 7.9	0.668	
LVESD (mm)	35.0 ± 2.1	36.7 ± 2.1	40.0 ± 4.9	0.055	
LVEDD (mm)	48.4 ± 3.7	57.0 ± 3.0	56.1 ± 5.2	**0.011**	**92.9%**
IVS (mm)	12.2 ± 1.5	13.3 ± 1.5	12.9 ± 1.5	0.408	
LVESV (ml)	56.7 ± 15.5	88.5 ± 20.1	87.9 ± 23.5	**0.010**	**90.0%**
LVEDV (ml)	139.4 ± 21.4	193.1 ± 26.8	217.9 ± 40.7	**0.003**	**98.7%**
RVESV (ml)	51.7 ± 14.7	73.6 ± 33.6	74.6 ± 24.1	0.086	
RVEDV (ml)	134.8 ± 14.1	183.9 ± 41.8	207.0 ± 34.9	**0.003**	**99.0%**
LVIESV (ml/m^2)	30.7 ± 7.7	48.9 ± 10.3	48.6 ± 10.4	**0.007**	**97.3%**
LVIEDV (ml/m^2)	76.0 ± 9.4	107.2 ± 15.3	121.1 ± 16.8	**0.002**	**99.0%**
RVIESV (ml/m^2)	28.0 ± 7.3	40.6 ± 18.4	41.3 ± 10.6	0.066	
RVIEDV (ml/m^2)	73.0 ± 5.5	102.1 ± 23.8	115.1 ± 12.3	**0.003**	**99.0%**
ILAV (ml/m^2)	39.0 ± 14.1	62.7 ± 8.1	56.4 ± 16.0	**0.026**	
PWTd (mm)	7.2 ± 1.1	9.3 ± 2.1	10.0 ± 1.4	**0.011**	**95.8%**

Data are represented as mean ± standard deviation. Data not following a normal distribution are in italics. Symbol: *statistical post-hoc power analysis to detect differences between group means with a significance level (α) of 0.05 (2-tailed). Abbreviations: CO, cardiac output; CI, cardiac index; LV, left ventricle; ILAV, indexed left atrial volume; IVS, inter-ventricular septum; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; LVIEDV, LV indexed end-diastolic volume; LVIESV, LV indexed end-systolic volume; LVMI, LV Mass indexed to body surface area; PWTd, posterior wall thickness, diastole; RV, right ventricle; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVIEDV, RV indexed end-diastolic volume; RVIESV, RV indexed end-systolic volume. Significant *P*-values are in bold.

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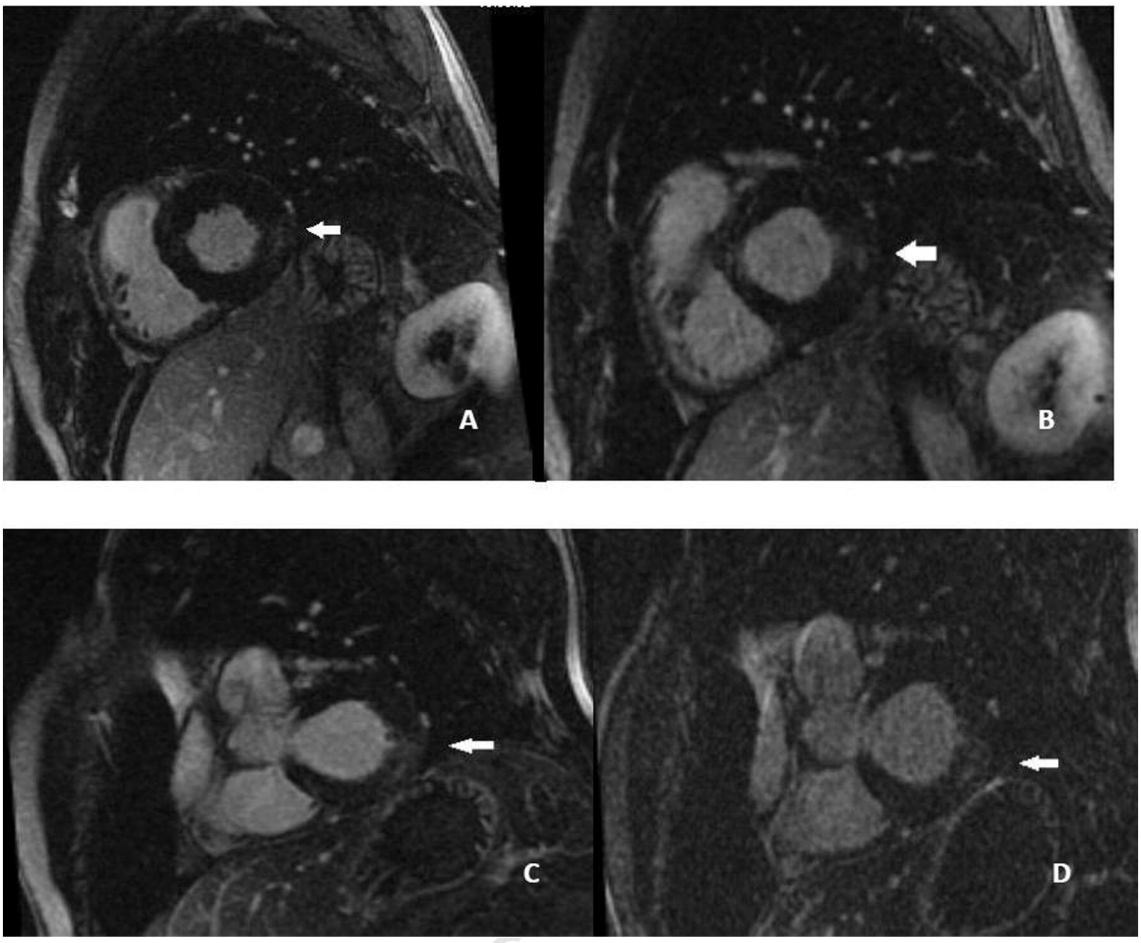

Fig. 1. Late gadolinium enhancement cMRI showing patches in two athletes (arrows). Case 1 (54-year-old marathon runner with 13 years of high-intensity training). Panel A and B. Case 2 (45-year-old cyclist with 15 years of high-intensity training). Panel C and D.

an athlete's heart as a physiological adaptation as opposed to the myocardial hypertrophy found in some heart conditions.

A recent meta-analysis by Iskandar et al. [17] reported that LA dimensions, determined by either LA diameter (echocardiography) or indexed LA volume (cMRI), are increased in elite athletes, particularly in endurance athletes. Our cMRI data concur with the aforementioned findings, indicating that long-term participation in regular endurance exercise increases LA volume, which seems to be an overall physiological adaptation coupled to LV enlargement and volume overload induced by chronic endurance exercise apparently without adverse clinical consequences [17,18].

4.2. Right-sided heart

Intense endurance exercise (*e.g.*, marathon/ultra-marathon running) has been associated with an essentially transient, intensity-dependent reduction in RV systolic function that is often accompanied by a temporary increase in cardiac damage biomarkers (troponin, NT-proBNP) [19]. Accordingly, it has been postulated that repeated episodes of post-exertional RV dysfunction could potentially induce more chronic, eventually irreversible RV damage [20–22]. However, our data indicate normal (or even improved) resting RV systolic function in veteran athletes when compared with controls [23]. Moreover,

Table 4
Serum levels of cardiac damage and fibrosis biomarkers by group.

	Controls ($n = 18$)	Sub-elite athletes ($n = 42$)	Elite athletes ($n = 11$)	*P*-value main effect (group)
NT-proBNP (pg/ml)	50.0 ± 42.3	47.3 ± 37.0	29.9 ± 22.8	0.268
Troponin I (ng/ml)	0.010 ± 0.010	0.010 ± 0.009	0.007 ± 0.004	0.301
PICP (ng/ml)	79.1 ± 18.1	87.4 ± 21.1	96.2 ± 33.1	0.875
Alkaline phosphatase (U/L)	60.7 ± 19.5	60.4 ± 14.4	68.9 ± 26.9	0.897
PICP/alkaline phosphatase	1.37 ± 0.41	1.52 ± 0.45	1.46 ± 0.42	0.130
Galectin-3 (pg/ml)	5.6 ± 1.5	4.8 ± 1.5	5.2 ± 2.1	0.543
MMP-2 (ng/ml)	437 ± 205.1	323.8 ± 42.3	382.8 ± 143.3	0.260
MMP-9 (pg/ml)	374.9 ± 196.9	405.4 ± 163.3	356.6 ± 158.9	0.754
sST-2/IL-1R4 (ng/ml)	31.8 ± 18.0	26.3 ± 11.3	47.8 ± 50.7	0.921

Data are represented as mean ± standard deviation. Note: available n with data for galectin-3, MMP-3, MMP-9 and sST-2/IL-1R4 were 12 (controls), 9 (amateur) and 10 (professionals). Data not following a normal distribution are in italics. Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; PICP, carboxy-terminal propeptide of type I procollagen; MMP2, matrix metallopeptidase 2; MMP9, matrix metallopeptidase 9.

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though several earlier studies have detected greater echocardiography/cMRI-determined RV dimensions in younger amateur athletes than in controls [21,24–26], no previous study has reported RV remodeling in veteran athletes who were highly competitive at a younger age.

Although limited by the small sample size, our cMRI results suggest a trend towards greater RV dilation in former professional athletes, who showed a mean LV end-diastolic volume of 207 ml, roughly one-third larger than normal. Our results also indicate greater RV compared with LV dilation in veteran athletes. This phenomenon may be related to the intensity of exercise performed over the years inducing RV diameter increases without modifying systolic function or increasing biomarkers of myocardial damage, all of which point to a non-pathological nature of RV remodeling. Moreover, such remodeling was independent of RV fibrosis observed on cMRI, though the limitation of this method for discerning LGE in the free wall of the RV owing to the thin walls of this ventricle must be considered [27]. Further, because the pattern of cardiac fibrosis found in athletes is usually mild and diffuse, it may not always be detected by currently available cMRI techniques [22]. La Gerche et al. found LGE in the IVS of 13% of all athletes studied (5 of 39 athletes), who also had greater cumulative exercise exposure and lower RVEF than those with normal cMRI [22]. In our study, no evidence of fibrosis in the IVS was detected in any of the participants. Importantly, in apparent disagreement with previous research using cMRI and in agreement with our findings, Bohm et al. [28] have also recently found no evidence of RV or LV dysfunction at baseline, or of cardiac structural damage, in middle-aged elite endurance athletes (30–60 years) despite the fact that they had been performing strenuous endurance exercise for decades.

4.3. Myocardial fibrosis

Two athletes who underwent cMRI showed small fibrotic patches in the LV detected by LGE that was not attributable to cardiac ischemia. Numerous studies have reported transient increases in biomarkers of cardiac damage (particularly cardiac troponin) following intense endurance exercise [29]. Whether such repeated episodes over the years might induce chronic, essentially irreversible, alterations such as myocardial fibrosis, which in turn would be reflected by LGE, remains speculative. Although LGE could indicate edema, inflammation or ischemia[30,31] or otherwise focal myocardial replacement by fibrosis caused by infection or a genetic abnormality [32], especially in coronary artery disease patients, the pathophysiological significance of this observation in healthy athletes remains unclear. Levine recently suggested that, rather than actual fibrosis, LGE might reflect edema in response to a long high-intensity endurance exercise bout.[33] However, our cMRI evaluations were performed after >24 h of refraining from intense exercise. As recently stated by Bohm et al. [28], an important confounder that might trigger transient cardiac fibrosis or ventricular dysfunction is cardiac infection. Thus, myocarditis induced by previous infection should be ruled out in those athletes showing fibrotic patches on cMRI as exposure to high training loads can induce a certain state of immunosuppression that increases the risk of some infections (*e.g.*, *Epstein-Barr virus* or *Chlamydia pneumonia*), which might cause reversible cardiac inflammation.

We should highlight that the presence of one or more CVD risk factor/s was an exclusion criterion in our study, whereas a certain selection bias towards recruiting older runners with subtle/latent coronary artery disease might have explained the presence of cMRI-detected cardiac fibrosis in some studies [34,35]. Other authors have reported no fibrotic changes in the hearts of highly trained endurance athletes [16,36–39]. Thus, taken together, we believe that the bulk of evidence indicates a low prevalence (at least in the absence of CVD risk factors) of myocardial fibrotic patches in veteran athletes unrelated to underlying myocardial ischemia. Our study is the first to assess myocardial fibrosis by two different techniques, cMRI with LGE and determination of cardiac fibrosis biomarkers in blood. Indeed, we determined new biomarkers of adverse cardiac remodeling due to fibrosis (MMP-2, MMP-9, sST2/IL-1R4 and PICP) [40,41], which complement the information provided by more classic biomarkers (cardiac troponin, NT-proBNP) [40,42]. Our findings are in discordance with those reported by Lindsay and Dunn [41], who found higher serum PICP levels in veteran athletes (mean age 52 ± 1.7 years), with no reported history of high-level competition at younger age. Although these authors suggested biochemical disruption of the collagen balance favoring cardiac fibrosis in their athletes, they provided no evidence by cMRI.

Our study is unique because it includes a number of former elite professional athletes and uses an integrative approach combining the findings of echocardiography, cMRI and specific cardiac remodeling biomarkers. Nonetheless, a number of limitations should be mentioned. First, the small number of the cohort participants, particularly for cMRI studies. However, our results revealed high statistical power for the differences between groups. Second, strain and strain rate tests were not used, limiting the ability to detect subtle functional abnormalities in regional contractility. Finally, as in the vast majority of studies in the field, only male athletes were included in this study and thus no conclusions can be drawn on the long-term effect of endurance exercise in women.

5. Conclusion

The long-term practice of competitive endurance sports (running, cycling) even at the highest competition level produces an overall benign pattern of cardiac remodeling. This pattern is characterized by increased LV, RV, and LA dimensions paralleled by a proportionate increase in LV mass. At least in resting conditions (*i.e.*, with no prior bout of exhaustive exercise), both RV systolic function and cardiac biomarkers seem unaffected by such an athletic lifestyle, corroborating the notion that any alterations detected in these variables are usually transient in nature. The clinical significance and pathophysiology of fibrotic patches showing a non-coronary pattern observed in the cMRI images of some athletes remains to be elucidated.

No major evidence supporting the theory of a certain 'over exercise' effect on the heart was found in this study with individuals practicing the highest loads of competitive endurance exercise over several decades. Our study does not provide scientific evidence to support warnings against healthy people participating in regular competitive endurance exercise.

Conflict of interests

The authors declare no conflicts of interest.

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