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Cardiac Effects of Prolonged Endurance Exercise in Young and Older Athletes

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ABSTRACT

To evaluate the effects of prolonged endurance exercise on the thin-walled chambers of the right ventricle (RV) and left atrium (LA), and heart rate (HR) in young (YA) and older (OA) athletes. Seven YA and seven OA (30 ± 5 and 65 ± 6 years; $\dot{V}O_2$max: 61.5 ± 2.2 and 46.8 ± 4.1 mL/min/kg, respectively) were studied before, during, and after a 15-day cycling journey from Copenhagen (CPH) to Palermo (PMO) (~3000 km). Transthoracic echocardiography (TTE) was performed in both groups, and additional stress echocardiography (SE) in OA. Speckle-tracking echocardiography was applied for RV free-wall strain, LA global peak-atrial longitudinal strain (PALS), and contraction strain (PACS). Assessments were made at baseline (CPH), at arrival (PMO), and for OA six months post-intervention (CPH+6). RV size and function were similar between YA and OA at baseline and remained unchanged at rest post-intervention. In OA, SE revealed decreased RV function during exercise at PMO, normalizing at CPH+6. LA size remained unchanged, but OA showed higher baseline filling pressure (E/e'), PACS, and LA stiffness index with lower PALS than YA. Post-intervention, PALS decreased ($p < 0.01$) while E/e', PACS, and LA stiffness index remained stable. Resting HR increased in OA ($p = 0.002$) but not in YA. $\dot{V}O_2$max was higher in YA and decreased in OA post-intervention ($p = 0.056$). Although RV size and resting function were unaffected, RV exercise-induced dysfunction was observed in OA, potentially due to increased LA stiffness. These findings suggest age-related cardiac fatigue and extended recovery time in OA.

1 | Introduction

Regular, moderate-intensity exercise has well-documented cardiovascular benefits, including reducing cardiovascular disease risk factors and mortality [1]. However, many athletes engage in high-intensity, prolonged physical activity beyond these moderate levels, resulting in cardiac physiological adaptations collectively referred to as "athlete's heart." These adaptations

encompass alterations in electrical conduction, cardiac structure, and function [2]. Importantly, while exercise generally supports cardiac health, there is a U-shaped association between exercise intensity and cardiac mortality, with evidence suggesting that extreme exercise may pose unique risks, especially for older athletes (OA) who are increasingly participating in endurance sports and competitions [3]. Studies indicate that OA, particularly those involved in endurance training, may be at risk of long-term cardiac effects, including increased coronary artery calcium (CAC) scores [4], more complex coronary plaques [5], myocardial fibrosis [6], right ventricular (RV) dysfunction [7], and a higher incidence of atrial fibrillation (AF) [8]. Vigorous endurance exercise exerts a significant volume load on the heart, with the RV often bearing the greatest impact. This volume overload may result in post-exercise dilation and potential impairment of RV function, a condition linked to exercise-induced arrhythmias [9]. Additionally, while left atrial (LA) size increases with exercise, particularly in endurance sports, such enlargement does not always correlate with functional impairment [10]. However, evidence links AF to long-term high-intensity exercise, potentially driven by mechanisms, such as inflammation and fibrosis [11]. Speckle-tracking echocardiography (STE) allows for a noninvasive assessment of LA stiffness as a surrogate marker of fibrosis, showing reliable agreement with invasive measures [12, 13]. Studies in young athletes (YA) indicate that LA enlargement may not correlate with increased stiffness, suggesting a benign nature of remodeling in this population [14, 15].

We have assessed the metabolic and physiological effects of 14 consecutive days of cycling, covering approximately 2700 km, on a cohort of six older men with a mean age of 61 [16]. Following this prolonged exertion, participants exhibited a reduction in cardiorespiratory fitness and enlargement of cardiac chambers, without accompanying changes in functional performance. We hypothesized that this apparent paradox arose from evaluations conducted solely at rest; consequently, we proposed to compare cardiac function during exercise and using advanced modalities such as speckle-tracking echocardiography (STE). We also aimed to determine whether resting heart rate reflected a diminished vagal response post-exercise, indicating prolonged recovery time, and whether this response varied with age.

In summary, prolonged endurance exercise may induce cardiac remodeling, including chamber dilation and transient decreases in RV function. However, these changes appear reversible in young athletes after short-term intensive training. However, there is limited data on the impact of prolonged endurance exercise in older athletes and whether adverse changes occur in this group.

The primary aim of this study was to assess the effects of prolonged endurance exercise on RV systolic function in young and older athletes using echocardiography. Secondary aims included evaluating the impact of exercise on LA stiffness, resting heart rate (HR), and cardiac biomarkers, including STE.

2 | Materials and Methods

This is a prospective, controlled intervention study. Previous publications [17, 18] have addressed data from this study on physical performance, metabolism, and inflammation. The current paper presents novel data focused on cardiac function and remodeling.

2.1 | Study Population

Seven YAs (30 ± 5 years) and seven OAs (65 ± 6 years) participated. The study was performed according to the Declaration of Helsinki and was approved by the Ethical Committee of the Capital Region (H-16049145). All subjects were informed about the safety and risks of participating in the study and gave their written consent.

2.2 | Intervention and Study Protocol

All participants cycled from Copenhagen, Denmark to Palermo, Italy. They spent 15 days and used on average 7.2 and 8.4 h/day (YAs and OAs, respectively). The YAs covered 3087 km and the OAs 2928 km in total. The difference in distance between groups was due to detours and that one stage was shortened for the old group. The cardiac investigations consisted of 5 days of examinations: 1 day before, 1 day during the intervention, and 3 days after cycling to Palermo. Baseline data (noted as CPH) were collected 1 week before the first day of cycling. Furthermore, ECGs were recorded daily for 2 weeks before and throughout the intervention. Additional data were collected on Day 10 from departure (noted as ROME), at arrival (noted as PMO), 24 h (noted as PMO + 1), and 48 h (noted as PMO + 2) after arrival in Palermo. The OA was also re-examined with stress echocardiography (SE) 6 months after returning from Palermo (noted as CPH + 6 months) (Figure 1). Furthermore, the echocardiographic recordings were completed within 4 h of arrival in PMO.

Logistics, transport of extra gear, bike maintenance, and food and beverage preparation before, during, and after cycling were handled by support teams for each group during all 15 days of cycling. The subjects were conscious about eating and drinking enough to ensure adequate energy intake and hydration to maintain exercise capacity for the full distance of the intervention. The two groups departed from Copenhagen 3 days apart, and the entire cycling trip was supervised by accompanying scientific staff who obtained the relevant measures and additional scientific staff at arrival for further testing as described below.

2.3 | Resting Echocardiography (CPH, PMO)

A standard transthoracic echocardiographic examination (TTE) was performed by an experienced sonographer according to the current guidelines using a GE S6 echocardiograph (GE Vingmed Ultrasound AS, Horten, Norway) and stored for offline analysis (EchoPAC version 203; GE Vingmed Ultrasound AS) to obtain parasternal, apical, subxiphoid, and suprasternal views, including M-mode and Doppler imaging options. A focused examination of the right ventricle and left atrium function was also performed. Global systolic RV function was measured according to Lang et al. [19] as right ventricular ejection fraction (RVEF) and RV fractional area change (FAC) in an RV-focused apical four-chamber view. RV longitudinal function (TAPSE) was measured from the tricuspid lateral annulus by

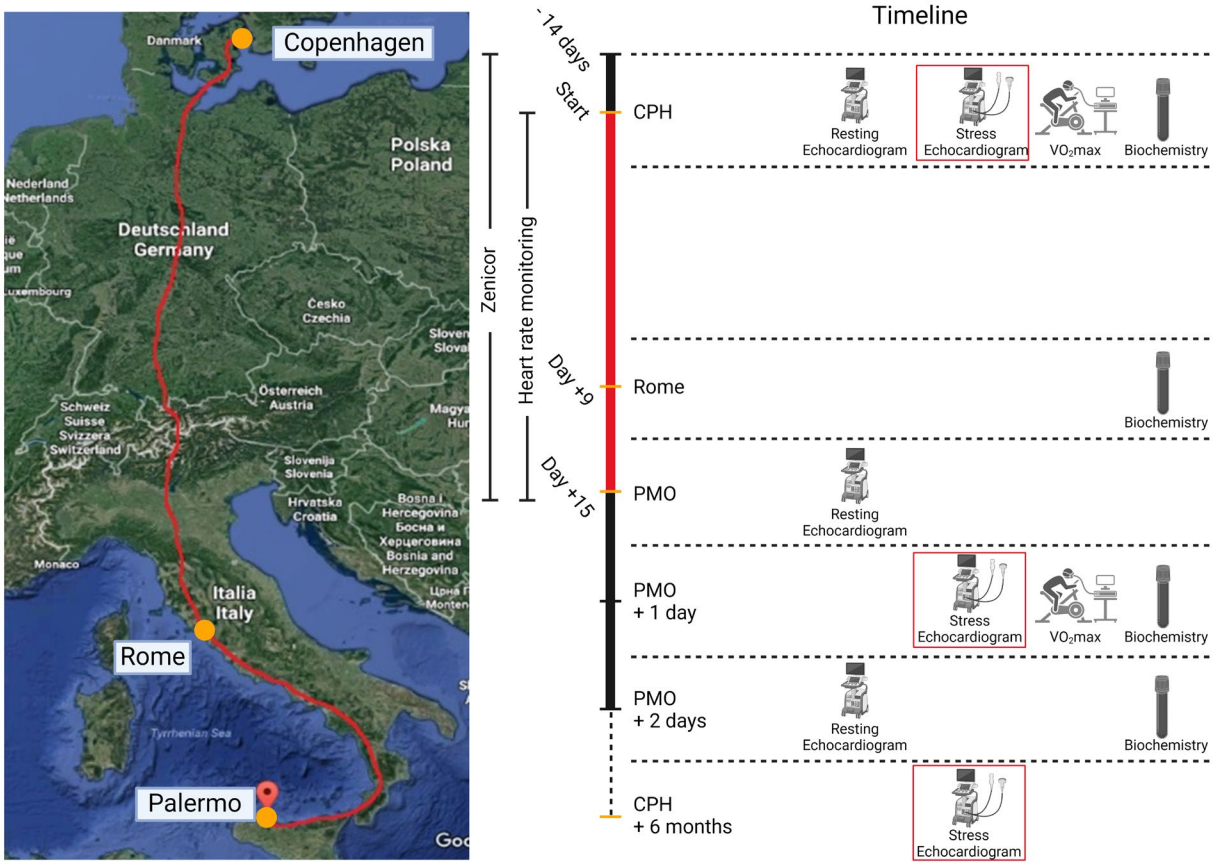

FIGURE 1 | Study design. Seven young and seven old athletes biked ≈3000 km from Copenhagen in Denmark to Palermo in Italy in 15 days. They were investigated at baseline in Copenhagen (CPH) with echocardiography, stress echocardiography, maximal exercise test (VO_2max), and coronary biomarkers (biochemistry). Two weeks before departure and during the 15 days of intervention heart rate and one-lead electrocardiogram were obtained at rest in the morning and evening by Zenicor. In Rome, on day nine (Rome) coronary markers were collected. On the day of arrival in Palermo (PMO) echocardiography was performed. The day after PMO + 1 day stress echocardiography (only in old athletes, marked with a red frame), coronary markers and VO_2max were performed. Two days after arrival in Palermo (PMO + 2 days) echocardiography and coronary biomarkers were performed. Six months after the intervention (CPH + 6 months) stress echocardiography was performed only in old athletes marked with a red frame. Created with Biorender.

M-mode. Pulsed wave (PW) tissue Doppler imaging (TDI) was used to assess the systolic function of the RV, measured in the lateral tricuspid annulus (S′). 2D speckle tracking of RV (only free-wall segments) longitudinal strain ($RV_{FW}LS$) was acquired according to Badano et al. [20]. Left atrial volume (LAV) was measured as mean from biplane 2D apical views (four- and two-chamber) and indexed to body surface area (BSA) as LAVi. LA phasic function was analyzed using 2D-STE [20]. Peak-atrial longitudinal strain (PALS) and peak-atrial contraction strain (PACS) were measured, reflecting the LA reservoir and contraction. LA stiffness index was calculated as (E/e')/PALS [21]. Measurement of time velocity integral of left ventricle outflow tract (TVI LVOT) was used to assess stroke volume (SV) using the equation: SV = (л(LVOTDia/2)2) × TVI LVOT. Relative wall thickness (RWT) (RWT = LVPWD+IVSd/LVEDd) and left ventricular mass (LVmass, g) were calculated according to Lang et al. [19]. The latter is indexed for fat-free mass (FFM) (LVmass index, g/FFM), as were all other morphological measures. Body composition was estimated from the total volume of body water (TBW) calculated from ^2H isotope dilution according to the Maastricht protocol as described earlier [17]. From TBW, the body composition was estimated 7 days before the intervention started and after stage 15 of the intervention. FFM was calculated from TBW ÷ 0.73 [22]. Doppler of the maximal tricuspid regurgitant peak gradient (TRmax PG) was used as an estimate of pulmonary artery systolic pressure (PASP), while the ratio of early diastolic mitral inflow to mitral annular velocity (E/e') was used as an index of LA pressure.

To assess measurement reliability, intraobserver variability was evaluated for key parameters (Right ventricle end-diastolic diameter (RVEDd), proximal right ventricle outflow tract (RVOT), right ventricle free wall longitudinal strain (RVFWLS), left atrium volume (LAV), peak-atrial reservoir strain (PALS) and peak-atrial contraction strain (PACS)). The coefficient of variation (CV) was calculated as (SD/mean) × 100%, based on repeated measurements by the same observer. CVs ranged between 2% and 6%, reflecting acceptable consistency.

2.4 | Stress Echocardiography (CPH, PMO + 2, and CPH + 6 Months)

Stress echocardiography (SE) was performed using two different protocols. The first protocol, conducted pre-intervention

(CPH), involved cycling to exhaustion on an ergometer bike. Measurements were taken at baseline, immediately after maximal exercise (post-max), and during recovery. Following the exercise, each participant was promptly transferred to a supine position on an exam table, where echocardiography was conducted at a heart rate of ~85% of the individual's maximum.

The second protocol was carried out post-intervention (PMO + 2) and at the 6-month follow-up (CPH + 6 months). This protocol involved measurements at baseline, at moderate (60%) and high (85%) exercise intensities relative to maximum heart rate, and during recovery. Testing was performed on a semi-supine ergometer with a left lateral tilt (eBike L ergometer, GE Healthcare, Horten, Norway). All imaging was conducted using a Vivid E9 ultrasound system and analyzed offline with EchoPAC version 113 software (GE Vingmed Ultrasound AS, Horten, Norway).

At each measurement stage, different image sets were acquired, and at least three cardiac cycles were stored for each set during exercise. LV volumes and ejection fraction, RV areas, RV FAC, and TAPSE were analyzed from a single-plane (RV-focused) A4Ch view. Stroke volume was determined by the Doppler velocity time integral method in the LVOT (A5Ch view). PASP was estimated from the maximal trans-tricuspid regurgitant velocity on CW Doppler without adding right atrial pressure. 2D speckle-tracking LV and RV free wall longitudinal strain (SL) was acquired and analyzed from single-plane (RV focused) apical four-chamber gray-scale images (60–90 frames/s).

2.5 | Blood Sampling and Analyses

Venous blood samples were obtained after 15 min of rest (all blood samples). Blood was transferred to EDTA tubes and centrifuged at 4°C for 10 min at 2300 *g*. Values of N-terminal pro-brain-natriuretic peptide (NT-proBNP [International Union of Pure and Applied Chemistry (IUPAC)]-code: NPU21571) increase with age (> 45 years) and are gender-specific. For males, the upper reference limit (URL) despite age is < 10.1 pmol/L.

The catalytic activity of creatine-phospho-kinase (CK) (NPU19656, URL < 280 U/L) and creatine-phospho-kinase-MB-isoenzyme subunit (CK-MB) (NPU57399, URL: < 25 U/L) was measured. High-sensitivity troponin T (TnT) (NPU27501, URL 13.5 pg/mL) was analyzed on plasma samples using the electrochemiluminescence (ECLIA) method on an automated analyzer (Cobas 6000, Roche, Basel, Switzerland).

2.6 | Heart Rate and Rhythm Recordings

Heart rate and rhythm recordings were conducted daily for 14 days before the intervention and throughout the 15 days of the intervention. Each day, participants performed a 30-s, one-lead ECG measurement both in the morning and evening just before bed. All measurements were taken at rest in a seated position. Participants were also instructed to perform additional measurements if they experienced any palpitations. The web-based Zenicor-ECG system (www.zenicor.com) was used for all recordings, which were then transferred to a central database for heart rate and rhythm analysis [23].

2.7 | Statistical Analysis

All data were tested for normal distribution and shown in tables and graphs as mean ± SD or individual data points. An unpaired Student *t*-test was applied to analyze baseline differences between groups. CPH vs. PMO data were analyzed using a Two-way ANOVA analysis of variance. When a significant effect of the intervention or an interaction of group × intervention was present, we conducted a Holm–Sidak post hoc analysis. When missing data were apparent, we used a linear mixed effect model (maximum likelihood and Geisser–greenhouse correction), with intervention and age (intervention × age) as fixed effects type III. Data analysis and graphical work were conducted using Sigmaplot (Systat Software, San Jose, CA, USA), GraphPad Prism 9.0 (GraphPad Software, La Jolla, CA, USA), and SPSS vers. 25 (IBM software). A level of $p < 0.05$ was considered significant.

3 | Results

3.1 | Participants Characteristics

All 14 athletes completed cycling from Copenhagen to Palermo. However, 4 weeks before departure, one OA had an incidence of atrial fibrillation that was electrically converted to sinus rhythm and was on antithrombotic treatment as the only medication among all participants. Characteristics of body composition and physical performance are shown in Table 1. Both groups were well trained, as their VO_2max in OA vs. YA was 143% ± 11% vs. 147% ± 6% of predicted VO_2max according to their age [24]. Although in absolute values, $\dot{V}O_2$max (mL/min/kg) was lower in OAs than in YAs. The OA had trained for a significantly longer time, but the weekly training duration was lower among OA than among YA. All participants were exercising in endurance sports (primarily cycling for the OA). In YA, training consisted of cycling, triathlon, speed skating, and cross-country skiing. Regarding intensity, 5/7 YAs were former elite athletes at a national level, and OA were leisure time master athletes. Despite the difference in age, HR and blood pressure (BP) were identical.

The aim was to equalize the total workload between older (OA) and younger athletes (YA) by having them complete the same routes, with comparable stage distances and altitude gains. The total cycling distance covered was 3087 km for YA, averaging 206 ± 36 km per day, and 2928 km for OA, averaging 195 ± 31 km per day. This ≈5% discrepancy was due to detours because of road closures or work, and one stage was shortened due to extreme weather conditions. The mean cycling time was 7.2 h/day for YA and 8.4 h/day for OA, resulting in average speeds of 28.5 and 23.1 km/h, respectively. On average, exercise intensity was 63% ± 1% (122 ± 2 bpm) of the pre-intervention maximal heart rate (HR_{max}) in the young group and 65% ± 3% (108 ± 5 bpm) in the older group, corresponding to moderate-intensity exercise. However, the prolonged daily exercise duration increased energy expenditure by over 90% in both groups [17], comparable to previously reported

TABLE 1 | Participants characteristics.

	Young athletes (YA) ($n=7$)		Old athletes (OA) ($n=7$)		Two-way ANOVA RM		
	CPH	PMO	CPH	PMO	Main effect: age (p)	Main effect: intervention (p)	Interaction (p)
Body composition and blood pressure							
Age, years	29.9 ± 5.0	—	65.4 ± 5.7	—			
Height, cm	182 ± 5	—	175 ± 9	—			
Body mass, kg	78.0 ± 4.9	76.8 ± 4.8	72.4 ± 10.4	72.3 ± 10.6	0.28	0.20	0.26
BMI, kg/m^2	23.6 ± 0.8	23.2 ± 0.5	23.4 ± 1.2	23.4 ± 1.4	0.94	0.23	0.29
BSA, m2	2.0 ± 0.1	2.0 ± 0.1	1.9 ± 0.2	1.9 ± 0.2	0.14	0.24	0.76
Fat-free mass (FFM), kg	68.5 ± 3.7	69.3 ± 4.2	59.9 ± 9.4	62.8 ± 9.1	0.064	**0.038**	0.21
FFM, % of body mass	88.0 ± 3.8	90.4 ± 4.4	82.6 ± 4.1	86.9 ± 2.8	**0.029**	**0.004**	0.34
Body fat, %	12.0 ± 3.8	9.6 ± 4.4	17.4 ± 4.1	13.1 ± 2.8	**0.029**	**0.004**	0.34
Systolic blood pressure, mmHg	126 ± 8	—	128 ± 7	—	0.628		
Diastolic blood pressure, mmHg	79 ± 8	—	79 ± 6	—	1.000		
Physical performance							
VO_2max, mL/min[a]	4767 ± 336	4898 ± 362	3467 ± 565	3245 ± 822	**< 0.001**	0.45	**0.014**
VO_2max, mL/min/kg[a]	61.5 ± 2.2	63.8 ± 2.9	46.8 ± 4.1	43.5 ± 7.7	**< 0.001**	0.71	**0.01**
% of Predicted VO_2max	147 ± 6	—	143 ± 11	—	0.4742		
Endurance training, h/week	9 ± 4	—	5 ± 1	—	**< 0.001**		
Endurance training, years	12 ± 4	—	25 ± 6	—	**0.025**		

Note: Measurements are divided into young and old athletes at baseline (CPH) and after the intervention (PMO). All measures are reported as means ± standard deviations. Significance for bold values are $p < 0.05$.
Abbreviations: BMI, body mass index; BSA, body surface area; VO_2max: maximal oxygen uptake.
[a]It is noted that only 6 of the OA had a VO_2max test performed.

near-maximal energy expenditure rates observed during the Tour de France [25].

3.2 | Differences in RV Size and Function Before and After the Intervention at Rest

Baseline diastolic measurements of RV size as right ventricular end-diastolic diameter indexed to FFM (RVEDDi) and right ventricular end-diastolic area before indexed to FFM (RVEDAi) were significantly enlarged in OA compared to YA (Table 2), and the ratio of RV: LVratio was significantly higher in OA. RV size and TRmax were unaffected by the intervention in both groups (Table 2). The systolic function of RV measured as TAPSE, S*, RV FAC, and RV_{FW}SL was similar between the two groups and was unchanged after the intervention. The response of the intervention regarding RV function was very heterogeneous in both groups as a response to the intervention, as shown in Figure 2.

3.3 | Differences in LA and LV Size and Function Before and After the Intervention at Rest

LAVi was larger and almost significantly in OA vs. YA when indexed for FFM, but was similar between the groups and unchanged after the intervention, though LAV was increased above reference limits in both groups [12, 26]. LV size did not change after the intervention in any group (Table 2). RWT in YA vs. OA (0.38 ± 0.08 vs. 0.38 ± 0.04, respectively) and left ventricular

TABLE 2 | Resting transthoracic echocardiography before and after the intervention.

	Young athletes ($n=7$)		Old athletes ($n=7$)		Two-way ANOVA RM		
	CPH	PMO	CPH	PMO	Main effect: age (p)	Main effect: intervention (p)	Interaction (p)
Right ventricle							
RVEDD (mm)	33 ± 2	34 ± 2	35 ± 5	37 ± 3	0.17	0.17	0.36
RVEDDi (mm/kg FFM)	0.49 ± 0.03	0.49 ± 0.03	0.60 ± 0.12	0.60 ± 0.08	**0.0152**	0.96	0.87
RVOT (mm)	37 ± 4	40 ± 6	39 ± 6	38 ± 5	0.97	0.33	0.29
RVOTi (mm/kg FFM)	0.55 ± 0.06	0.58 ± 0.11	0.66 ± 0.16	0.62 ± 0.12	0.18	0.96	0.21
RVEDA (cm^2)	24 ± 4	27 ± 7	20 ± 2	19 ± 5	**0.0152**	0.58	0.29
RVEDAi (cm^2/kg FFM)	0.35 ± 0.05	0.38 ± 0.09	0.34 ± 0.09	0.31 ± 0.10	0.24	0.99	0.19
RVESA (cm^2)	13 ± 3	15 ± 5	11 ± 3	11 ± 4	0.08	0.23	0.35
RVESAi (cm^2/kg FFM)	0.19 ± 0.04	0.22 ± 0.06	0.19 ± 0.06	0.18 ± 0.06	0.46	0.62	0.22
RV/LV, ratio	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	**0.0189**	0.23	0.42
TRmax (mmHg)	19 ± 3	21 ± 3	24 ± 4	23 ± 4	0.07	0.56	0.17
Left atrium							
LAV (mL)	74 ± 9	80 ± 12	78 ± 9	80 ± 6	0.51	0.08	0.62
LAVi (mL/kg FFM)	1.1 ± 0.2	1.2 ± 0.2	1.3 ± 0.3	1.3 ± 0.2	0.06	0.54	0.32
Left ventricle							
LVEDD (mm)	55 ± 4	55 ± 3	49 ± 4	50 ± 6	**0.0467**	0.78	0.64
LVEDDi (mm/kg FFM)	0.80 ± 0.05	0.79 ± 0.05	0.83 ± 0.07	0.80 ± 0.06	0.52	**0.0423**	025
LVESD (mm)	39 ± 3	38 ± 3	34 ± 3	36 ± 4	**0.0248**	0.46	0.09
LVESDi (mm/kg FFM)	0.58 ± 0.04	0.55 ± 0.04	0.58 ± 0.08	0.59 ± 0.09	0.55	0.80	0.36
RWT	0.38 ± 0.04	0.37 ± 0.05	0.41 ± 0.05	0.40 ± 0.08	0.23	0.42	0.81
LVmass (g)	221 ± 33	209 ± 23	181 ± 31	179 ± 38	0.0531	0.21	0.34
LVmassi (g/kg FFM)	3.2 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	2.9 ± 0.4	0.38	**0.0188**	0.89
LVEDV (mL)	178 ± 18	173 ± 19	128 ± 129	139 ± 31	**0.0036**	0.63	0.21
LVEDVi (mL/kg FFM)	2.6 ± 0.3	2.5 ± 0.2	2.1 ± 0.4	2.2 ± 0.3	**0.0086**	0.82	0.42
LVESV (mL)	82 ± 14	81 ± 12	58 ± 12	66 ± 19	**0.0178**	0.27	0.19
LVESVi (mL/kg FFM)	1.2 ± 0.2	1.2 ± 0.1	1.0 ± 0.1	1.0 ± 0.2	**0.0338**	0.70	0.36
LVEF (%)	56 ± 5	52 ± 5	57 ± 5	57 ± 4	0.18	0.24	0.24
GLS (%)	−18 ± 2	−17 ± 2	−18 ± 2	−18 ± 2	0.70	0.25	0.62

Note: All measures are reported as means ± standard deviations. Significance for bold values are $p < 0.05$.
Abbreviations: CPH, Copenhagen; E/e', a measure of left ventricle filling pressure; FFM, fatt free mass; LAVi, left atrial volume indexed to FFM; LV GLS, left ventricular global longitudinal strain; LV massi, left ventricle mass indexed to FFM; LVEDDi, left ventricle end-diastolic diameter indexed to FFM; LVEDVi, left ventricular end-diastolic volume indexed to FFM; LVEDVi, left ventricular end-systolic volume indexed to FFM; LVEF, left ventricular ejection fraction; LVESDi, left ventricle end-systolic diameter indexed to FFM; PMO, Palermo; RVEDAi, right ventricle end-diastolic area indexed to FFM; RVEDDi, right ventricle end-diastolic diameter indexed to FFM; RVESAi, right ventricle end-systolic area indexed to FFM; RVOTi, right ventricle outflow tract indexed to BSA; RWT, relative wall thickness; TRmax, maximal tricuspidal regurgitation.

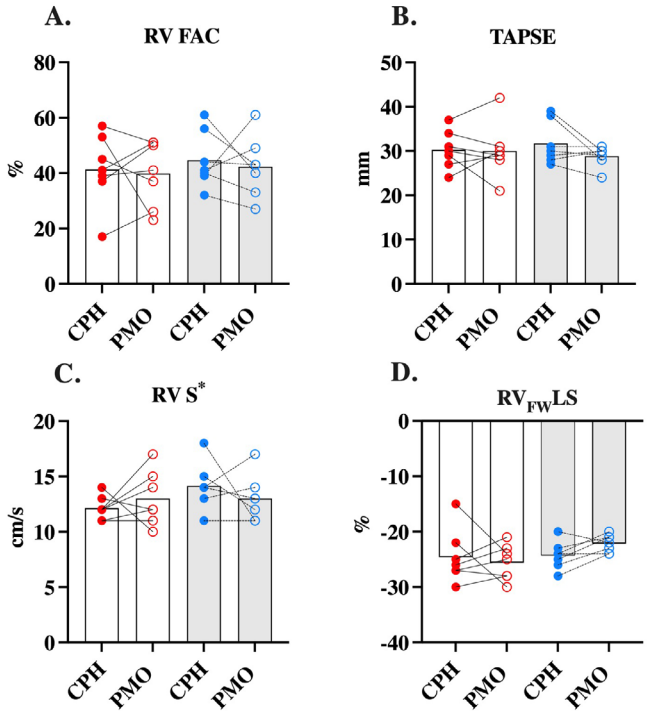

FIGURE 2 | Right ventricle function at rest before (CPH) and after the intervention (PMO). Main finding: no change in RV function after the intervention, although the response is heterogeneous. Individual measurements are red for old athletes and blue for young athletes, with bold dots at CPH and open dots at PMO. Mean values are shown in bars. RV FAC, right ventricle fractional area change; RV S*, right ventricular systolic excursion velocity by tissue Doppler; RV$_{FW}$LS, right ventricle free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

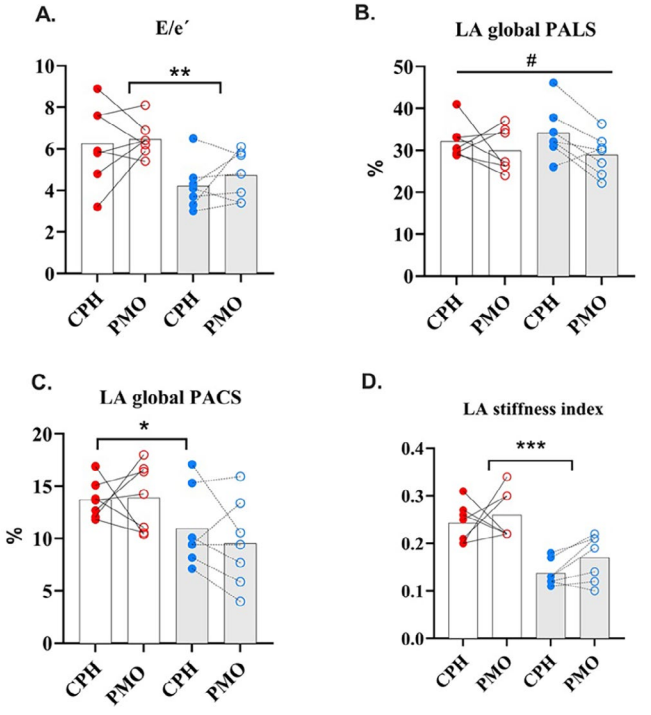

FIGURE 3 | Left atrial function at rest before (CPH) and after the intervention (PMO). Main findings: In OA left ventricular filling pressure (E/e'), LA PACS, and LA stiffness were increased at baseline, and LA PALS decreased in both groups after the intervention. Individual measurements are red for old athletes (OA) and blue for young athletes (YA), with bold dots at CPH and open dots at PMO. Mean values are shown in bars. E/e', early mitral inflow velocity versus mean mitral annular early diastolic velocity; LA global PACS, left atrium global peak-atrial contraction strain; LA global PALS, left atrium global peak-atrial longitudinal strain; LA stiffness index; calculated as: (E/e')/LA global PALS. (A) ** Significant ($p = 0.008$) higher E/e' in OA vs. YA at baseline. (B) # Significant ($p = 0.006$) decrease as an effect of the intervention, independent of age. (C) * Significant ($p < 0.05$) higher LA global PACS in OA vs. YA at baseline. (D) *** A significant ($p < 0.0001$) higher LA stiffness index in OA vs. YA at baseline.

mass (LVM) were similar and within normal limits corresponding to normal LV geometry. However, LV diastolic and systolic volumes were significantly larger in YA than OA (Table 2). Corresponding to stroke volume (SV) 70 ± 20 mL vs. 96 ± 12 mL ($p < 0.05$) and FFM indexed in OA vs. YA, and was unchanged after the intervention, 73 ± 17 mL vs. 92 ± 12 mL in OA vs. YA. LV systolic function, measured as LVEF and global longitudinal strain (GLS), was normal and similar between the two groups (Table 2). Measurements of LV diastolic function were performed with the same mean heart rate in the two groups. LA filling pressure (measured as E/e') was significantly higher in OA compared to YA (6.3 ± 1.9 vs. 4.2 ± 1.1 ratio, $p = 0.008$, OA vs. YA, respectively) (Figure 3A). Correspondingly, LA global PACS (13.7 ± 1.8 vs. 11.0% ± 3.8%, $p < 0.05$, OA vs. YA, respectively) and LA stiffness index (0.24 ± 0.04 vs. 0.14 ± 0.03 ratio, $p < 0.0001$, OA vs. YA, respectively) were significantly higher in OA (Figure 3C,D) and LA global PALS were significantly lower (32.2 ± 4.3 vs. 34.2% ± 6.3%, $p = 0.04$, OA vs. YA, respectively) (Figure 3B).

After the intervention, no LV and LA size change was observed in either group; nor were there any changes in LV systolic function measured as LVEF and GLS (Table 2). LVEDDi and LVmassi increased significantly due to the intervention, but that seems mainly due to changes in FFM.

LA global PALS (Figure 3B) decreased after the intervention ($p = 0.006$); whereas E/e', LA global PACS, and LA stiffness were unchanged.

3.4 | RV and LV Function During Exercise by Stress Echocardiography

RV function was measured in OA at baseline in Copenhagen, after the intervention in Palermo, and again after 6 months. We found a decreased response to exercise (marked as SE in Figure 4) in RV function after the intervention, measured as FAC ($p = 0.01$), RVEF ($p = 0.04$), and TAPSE ($p = 0.009$). However, S' was not significantly attenuated (Figure 4D). The tricuspidal gradient increased during exercise but significantly more in PMO during SE vs. CPH (43 ± 15 vs. 27 ± 10, $p < 0.05$). In contrast to the RV response to exercise, LV function during exercise was unchanged, measured as stroke volume (SV), LVEF, and GLS.

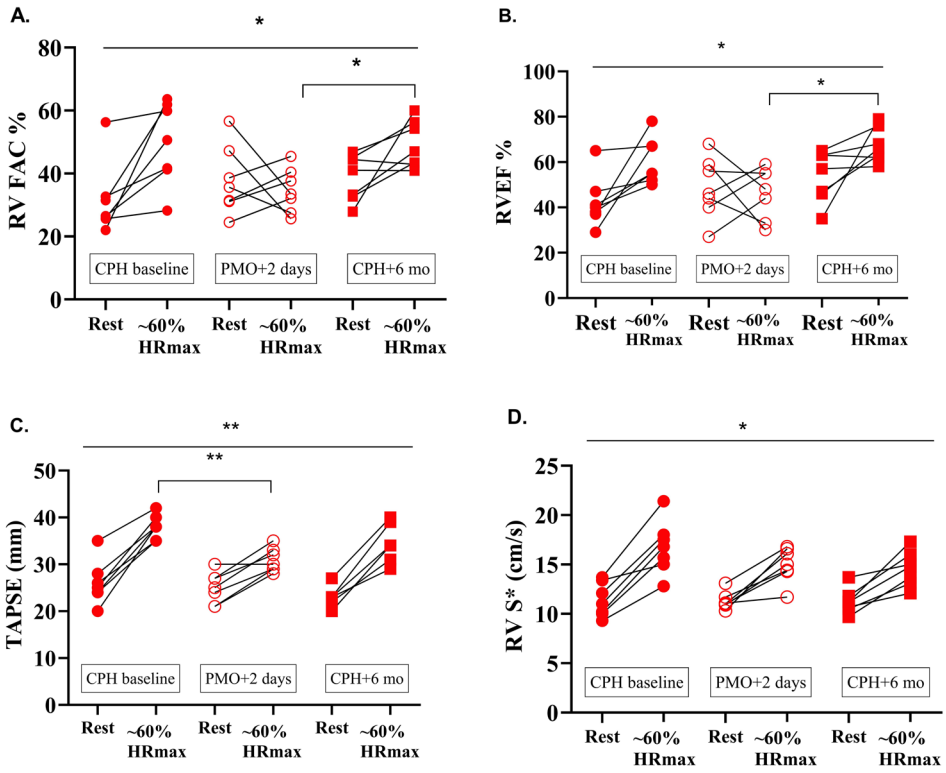

FIGURE 4 | Right ventricle function at rest and during stress echocardiography before (CPH), and after the intervention in Palermo (PMO + 2 days) and 6 months after the intervention in Copenhagen (CPH + 6 months) in old athletes. Main findings: RV function during exercise measured as FAC, RVEF, S* and TAPSE were all reduced after the intervention but regained function when measured 6 months later. Individual measurements include red bold dots in CPH, open red dots in PMO + 2 day, and bold red squares in CPH + 6 months. (A, B) * Significant ($p = 0.0103$) main effect of stress echocardiography exercise (SE submax) vs. baseline and a significantly ($p = 0.0404$) attenuated response to SE in PMO + 2 day vs. CPH + 6 months. (C) ** Significant ($p < 0.0001$) main effect of stress echocardiography exercise (SE submax) vs. baseline and a significantly ($p = 0.0063$) attenuated response to SE in PMO + 2 day vs. CPH baseline. (D) * Significant ($p < 0.0001$) main effect of stress echocardiography exercise (SE submax) vs. baseline. RV FAC, right ventricle fractional area change; RV S*, right ventricular systolic excursion velocity by tissue Doppler; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

3.5 | Heart Rate and Rhythm Measured by Zenicor

Morning resting HR increased significantly during the intervention in OA compared to 14 days before departure (Figure 5A), but it remained unchanged in YA for the same periods (Figure 5B).

Furthermore, one OA had an incidence of self-limited atrial fibrillation the evening before plasma cardiac biomarkers were drawn in Rome. That same OA had a significant increase in NT-proBNP and TnT in Rome; although NT-proBNP increased further in that OA, we found no other incidents of atrial fibrillation, nor after he had returned to Denmark on a one-week event recording.

3.6 | Cardiac Biomarkers

Plasma CK and *CK-MB* concentrations increased as a result of the intervention, but with no effect of age (Figure 6A). *Plasma NT-proBNP* was higher and increased more as a result of the intervention in OA vs. YA (Figure 6C). *Plasma TnT* concentrations were unchanged due to the intervention and age (Figure 6D).

3.7 | Exercise Capacity After 15 Days of Cycling

Maximal oxygen uptake ($\dot{V}O_2$max, mL/min/kg), measured before departure (CPH) and on the day after arrival (PMO + 1), remained unchanged in the young group (YA) but showed a decrease in the older group (OA) ($p = 0.056$, Table 1). When expressed relative to fat-free mass (mL/min/kg FFM), this decrease in OA reached statistical significance ($p = 0.02$). Maximal heart rate remained unchanged in YA (CPH: 195 ± 11 vs. PMO + 2: 196 ± 12 beats/min), but decreased significantly in OA following the intervention (CPH: 168 ± 12 vs. PMO + 1: 156 ± 18 beats/min, $p < 0.0001$) [17].

4 | Discussion

The primary findings of this study were that after 15 days of prolonged endurance exercise, participants experienced: (1) No change in RV systolic function at rest, though RV response was attenuated during exercise in older athletes (OA) post-intervention, with full recovery after 6 months; (2) a reduction in LA reservoir function in both groups post-intervention; and (3) an increase in resting morning heart rate and reduced maximal

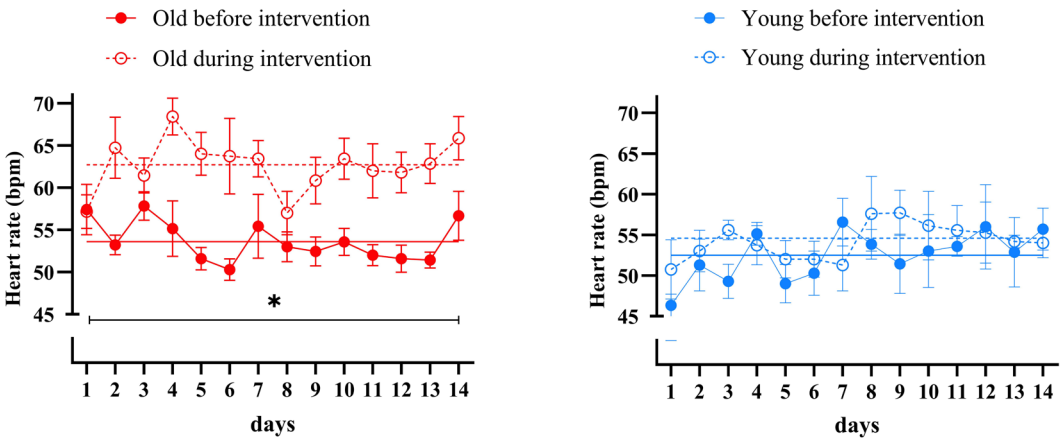

FIGURE 5 | Resting morning heart rate before and after the intervention. Main findings: Resting heart rate increased during the intervention only in the OA. Right: in red old athletes. Left: in blue young athletes. Bold and open dots mark daily mean ± standard deviation morning heart rates 14 days before and during the intervention, respectively. *Significantly ($p < 0.05$) higher morning heart rate in old athletes during vs. before the intervention and significantly ($p < 0.05$) higher heart rate in the old vs. the young athletes during the intervention. The dotted line represents the mean HR during the intervention, and the full line represents the mean HR before the intervention.

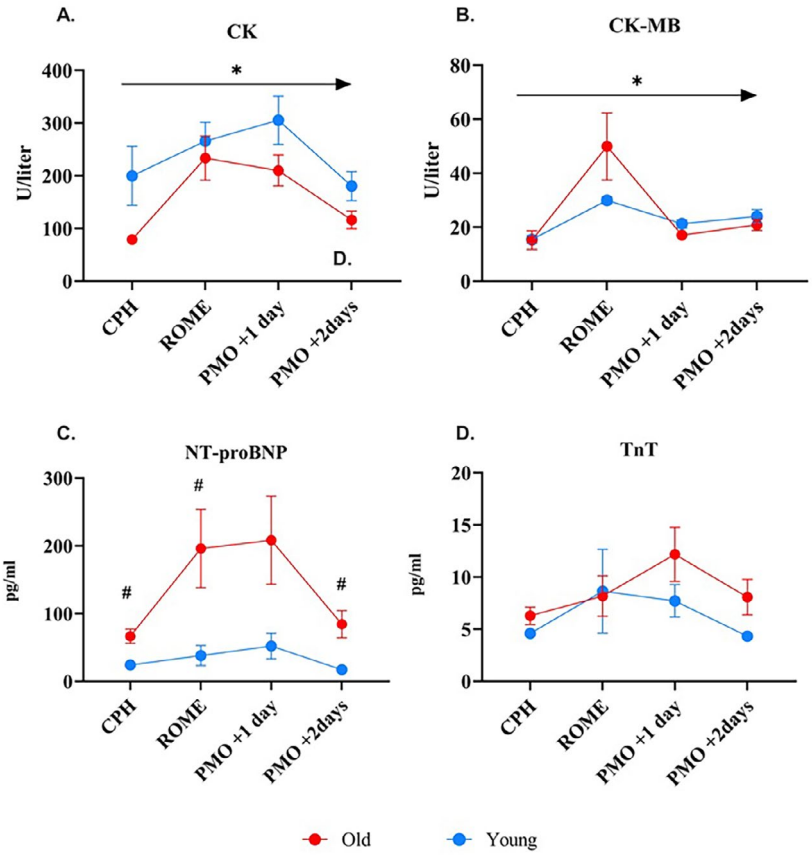

FIGURE 6 | Coronary biomarkers before, during, and after the intervention. Main findings: Cardiac biomarkers increased during the intervention. (A, B) * Significant ($p < 0.0001$) main effect of the intervention. (C) # Significant ($p < 0.05$) effect of age. (D) * Significant ($p < 0.0001$) main effect of stress echocardiography exercise (SE submax) versus baseline. CK, creatine kinase; CK-MB, creatine kinase myocardial band; NT-proBNP, N-terminal pro-b-type natriuretic peptide; TnT; high sensitivity troponin T.

heart rate during exercise in OA. These results suggest that diminished exercise capacity in OA may be due to cardiac fatigue, necessitating a longer recovery period to sustain maximal exercise capacity.

This study uniquely examines the cardiac response to 15 days of prolonged endurance exercise in a group of young and older athletes. The results from this investigation align with findings from a previous study by this group, in which we also found an

acute effect on cardiac biomarkers but unchanged LV and RV function at rest in a small group of OA cycling 2706 km from Copenhagen to North Cape, Norway [16].

With the addition of a control group and improved testing modalities (SE and speckle-tracking echocardiography, STE) this study adds strength to these findings. STE adds significant improvements over standard echocardiographic measures. First, STE adds a less angle-dependent and more reproducible measure of RV and LV function than conventional echocardiography. Additionally, exercise-induced dilatation and limited views of 2D echocardiography may hamper the correct distinction between physiology from pathology, when solely using measures of volume or area of the RV [27]. Lastly, conventional parameters like TAPSE and tricuspid S' velocity represent the displacement degree of the basal segment of the RV-free wall only, whereas STE measures the global function of the RV-free wall from a three-segment model.

The main finding of this study is the observed post-intervention RV fatigue during stress echocardiography. This finding may be attributed to an elevated preload from the intervention, compounded by increased RV afterload, evidenced by a significant rise in TRmax. Furthermore, it is noteworthy that hydration status in the athletes remained stable, as indicated by unchanged creatinine and sodium levels [17].

Additionally, increased LA stiffness, LA contraction function, and reduced LA reservoir function at rest further contribute to this effect. Theoretically, the reduced function of the RV might preserve LV function by unloading, which aligns with the findings of La Gerche et al., who observed that the load of the ventricles during exercise is disproportionate to RV load exceeding LV load [28]. This could explain why LV function during stress echocardiography was preserved. La Gerche et al. further described a post-exercise duration-dependent RV deterioration with greater functional impairment in those who competed at high intensity for the longest time (> 12 h) [29]. Our findings in older athletes following prolonged, moderate-intensity exercise may be explained by the RV's capacity to withstand increased afterload at rest. However, during exercise, the intervention-induced rise in RV preload resulted in functional deterioration.

Despite the athletes' high fitness levels and long-standing exercise history, only modest cardiac remodeling was observed before the intervention. Cardiac morphology exceeded normal limits in athletes primarily regarding LA size and RV:LV ratio, with more pronounced increases in older athletes (OAs). In contrast, LV size was increased in YA vs. OA. This finding is in line with our experience, whereas eccentric LV remodeling in YA is reversible and dependent on loading, as the YA exercised more hours and with a higher intensity than OA before the intervention. LA volume did not increase further post-intervention. LA function showed age-dependent changes pre-intervention, with elevated filling pressures in both LA and LV. Post-intervention, a significant reduction in LA reservoir function was observed across both groups, with an increased LA stiffness index in OAs. Reduced LA functional parameters are associated with a higher likelihood of atrial fibrillation, which may partially account for the increased prevalence of atrial fibrillation in male master athletes. In line with this, one OA experienced atrial fibrillation before the study, while another exhibited a paroxysmal episode during the tour, reflected by elevated NT-ProBNP levels. Intensive endurance exercise is associated with transient increases in circulating cardiac biomarkers, such as troponin, CK-MB/CK, and NT-proBNP. However, these elevations are not necessarily indicative of LV or RV function. NT-proBNP is a peptide hormone with natriuretic and diuretic effects that reduce ventricular load. CK-MB and TnT serve as diagnostic markers in acute coronary syndrome; however, these biomarkers typically do not reflect cardiac disease during intense physical activity. Instead, mechanical stress from exercise may increase membrane permeability, allowing these markers to enter the bloodstream [30]. Previous studies have reported that high-sensitivity troponin concentrations peak approximately 3 h post-exercise. However, sustained troponin elevation following intense exercise has also been linked to undetected obstructive coronary artery disease [31]. As our biomarker measurements occurred 24 h post-exercise (PMO + 1), troponin levels may have increased immediately upon arrival. This potential cumulative effect is supported by lower concentrations measured at the midpoint in Rome compared to levels observed the day after arrival. Troponin increases post-exercise may result from cellular spillover and increased cardiac muscle permeability or may be associated with arrhythmic events, as seen in one athlete who experienced atrial fibrillation and demonstrated significantly elevated troponin levels. The possibility of ischemic heart disease was minimal in this athlete, as normal LV function was observed during exercise in Palermo. In OA, NT-proBNP was expectedly higher than YA, as natriuretic peptides increase with age [32]. The observed increases in CK and NT-proBNP normalized within 2 days, indicating temporary changes rather than permanent cardiac damage.

Heart rate was monitored in both groups throughout the intervention. In addition to an incidence of paroxysmal atrial fibrillation, OA exhibited an increased resting morning heart rate, suggesting heightened sympathetic activity. The mechanism for the increase in resting HR in OA is unclear, as their hydration status (sodium and creatinine concentrations were unchanged after the intervention) and resting stroke volume were unchanged. Still, recovery time in OA was shorter than in YA. Furthermore, maximal heart rate was reduced in OA post-intervention, indicative of central fatigue, a response not observed in YA.

According to the Fick equation, $\dot{V}O_2$max is determined by cardiac output and oxygen extraction. We observed increased stroke volume during submaximal exercise; however, the reduced maximal heart rate and impaired diastolic LV filling in OA attenuated the potential rise in cardiac output, thereby accounting for the observed post-intervention decrease in $\dot{V}O_2$max in this group. Furthermore, we found no difference in peripheral changes in OA and YA after the intervention [17].

5 | Limitations

The modest sample size may have increased the probability of type II statistical errors, and conducting multiple comparisons increases the likelihood of type I errors. Even so, the present field study setting is unique, and a large-scale study could not be conducted due to logistical challenges.

SE data were presented only in OA using two different methods. Using the conventional SE method with physical exercise

to exhaustion and only then in the supine position to record the echocardiographic measures is difficult for athletes, as they resume normal HR quickly. The reason for using this method was that we did not expect to have access to a semi-supine cycling system where recordings could be made during exercise. Fortunately, it was possible, and we therefore chose to use a more advantageous method, considering the difficulties in comparing results from CPH with PMO results. The major limitation would be underestimating the exercise response in Copenhagen before the intervention. However, the response in Copenhagen before the intervention and 6 months later was equal. The method used in Palermo was also used at 6 months follow-up, and comparisons of the three examinations were made at similar heart rates, which are therefore comparable. Baseline SE was also performed in YA with a response equal to that of OA, but as it was not possible for logistical reasons to perform SE in Palermo in YA, these data are not presented.

Using a surrogate marker for LV filling pressure, as E/e' is the best noninvasive and robust measure, making it widely used, although the validation in a population of athletes is limited.

STE imaging has some inherent technical limitations due to the limited temporal resolution of 2D strain, leading to undersampling limitations due to the limited temporal resolution of 2D strain, leading to an underestimation of true peak values. However, this limitation pertains to both groups, and meaningful differences remained demonstrable.

One of the OAs had a paroxysm of atrial fibrillation 4 weeks before departure, and another had an incidence at arrival in Rome for 1 hour. We do not expect any of these incidences to be a confounder of the "isolated" effect of the intervention; more likely, it represents an intrinsic predisposition to get atrial fibrillation, as it is known to be more prevalent in master athletes [8]. Although asymptomatic paroxysms of atrial fibrillation could have been more numerous, as we only recorded heart rhythm twice daily for 30 s.

This study only included males and two age groups. Therefore, we cannot ensure that the reported response to continued exercise can be extrapolated to the general population of athletes.

For logistical reasons, the OA departed 2 days prior to the YA. However, this resulted in minor between-group variations in weather and routing, decreasing comparability. We attempted to ensure that the physical workload was equivalent between the two groups by matching exercise intensity based on heart rate. However, since the participants cycled at different speeds but were required to cover the same distance, the older athletes spent more time cycling. Consequently, they had a shorter recovery period (on average, 1.2 h longer cycling duration). This reduced recovery time may have led to greater accumulated fatigue in the older athletes, potentially affecting their physiological responses and contributing to the observed differences in our results.

6 | Perspectives

This study of highly trained young and master athletes demonstrates that even prolonged endurance exercise is generally well-tolerated, with minimal adverse cardiac effects. However, it also reveals that the chronic impact of exercise with LA enlargement, exacerbated by age-related increases in filling pressures, may progress with prolonged endurance training. This progression is characterized by increased left atrial (LA) stiffness, reduced systolic function, and an elevated risk of atrial fibrillation, as observed in two older athletes (OAs).

Importantly, the findings indicate that an enlarged LA does not inherently indicate impaired LA function. Instead, distinctions can be made using speckle-tracking echocardiography (STE) to assess changes in LA function. Given the prevalence of atrial fibrillation among male master athletes, prospective studies are essential to identify early echocardiographic markers of pathological remodeling and to determine the extent to which chronic remodeling may be reversible.

Furthermore, the observed reduction in right ventricular (RV) function during exercise underscores the need to evaluate athletes under exercise conditions to elucidate mechanisms contributing to reduced exercise capacity and potential signs of cardiac fatigue. Notably, this study suggests that LA dysfunction could significantly influence RV performance during exercise, highlighting the interconnected nature of atrial and ventricular dynamics.

7 | Conclusion

This study shows that prolonged endurance exercise did not change RV size and function at rest. Still, during exercise, RV function was diminished in old athletes, possibly due to reduced LA function. Overall, athletes tolerated the intervention well, but in OA, indications of fatigue, including increased resting heart rate, reduced maximal exercise capacity, and reduced maximal heart rate, were suggestive of an age-dependent increase in recovery time to tolerate this amount of exercise.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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