Age matters: differences in exercise-induced cardiovascular remodeling in young and middle aged healthy sedentary individuals.

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Abstract

Aims: Remodeling of the cardiovascular system (including heart and vasculature) is a dynamic process influenced by multiple physiological and pathological factors. We sought to understand whether remodeling in response to a stimulus, exercise training, altered with healthy ageing.

Methods: 237 untrained healthy male and female subjects volunteering for their first-time marathon were recruited. At baseline and after 6 months of unsupervised training, race completers underwent tests including 1.5T cardiac magnetic resonance, brachial and non-invasive central blood pressure (BP) assessment. For analysis, runners were divided by age into under or over 35 years (U35, O35).

Results: Injury and completion rates were similar among groups. 138 runners (U35: n=71, females=49%; O35: n=67, females=51%) completed the race. On average, U35 were faster by 37 minutes (12%). Training induced a small increase in left ventricle (LV) mass in both groups (3g/m², p<0.001), but U35 also increased ventricular cavity sizes (LV end-diastolic volume [EDV]i +3%; LV end-systolic volume [ESV]i +8%; right ventricle [RV] EDVi +4%, RVESVi +5%; p<0.01 for all). Systemic aortic compliance fell in the whole sample by 7% (p=0.020) and, especially in O35, also systemic vascular resistance (-4% in the whole sample, p=0.04) and blood pressure (systolic/diastolic, whole sample: brachial -4/-3 mmHg, central -4/-2 mmHg, all p <0.001; O35: brachial -6/-3 mmHg, central -6/-4 mmHg, all p<0.001).

Conclusion: Medium-term, unsupervised physical training in healthy sedentary individuals induces measurable remodeling of both heart and vasculature. This amount is age dependent, with predominant cardiac remodeling when younger and predominant vascular when older.

Keywords:
1) Physical training; 2) Cardiac remodeling; 3) Vascular remodeling; 4) Healthy ageing;
Introduction

“Cardiac plasticity” is the ability of the myocardium to undergo reversible structural and functional changes via “remodeling”, a process that appears evolved to optimize performance.[1] It starts at the molecular level and leads to changes in myocytes, but also affects the extracellular compartments,[2]–[6] translating into changes in wall thickness, chambers volumes and ventricular function which can, in some cases, double the size of the heart.[1] Similar plasticity is found in the vascular tree where macroscopically measurable changes in large vessels occur, including intima-media thickness, media-to-lumen ratio and elastic properties.[7]

The overall cardiovascular phenotype at any given time is determined by age, sex, [8] environmental factors (for example sedentary vs athletic), disease and genetics.[9][10], [11] Our knowledge of their relative contributions is incomplete. Ageing-related cardiac changes include a reduction in myocyte numbers (30% fall from second to seventh decade)[3],[2] with hypertrophy of remaining cells in addition to alterations in contractile proteins and collagen, leading to a stiffer heart.[6], [12] Vascular changes include reduced capillary density, altered collagen and elastin, and an increase in vascular stiffness, with increased peripheral resistance.[7] The two compartments interact directly via vascular coupling (volume and pressure loading) and through paracrine and neurohumoral control.[13], [14]

These changes may be reversible and plastic, but current knowledge is incomplete. Physiological exercise can explore the system: intense physical exercise leads to the “athlete’s heart”, while moderate training has been associated with increased capillarity, enlargement of conduit vessels [15] and delayed age-related increase in cardiac stiffening.[16]

Society is currently changing with 1) demographic ageing, with 22% of people expected to be over 65 by 2040;[17] 2) activity changes, i.e. increasingly sedentary lifestyles for some and increasing recreational running in others;[18] 3) altering emergent disease profiles, e.g. heart failure with preserved ejection fraction (HFpEF).[19] Accordingly, we wished to explore the relationship between healthy ageing and differences in cardiovascular adaptation in response to a stimulus, here moderate, unsupervised, medium-term aerobic exercise.

Methods
This was a prospective observational study, evaluating first-time marathon runners of both sexes, unaware of pre-existing cardiovascular conditions and not on medications, sedentary. Exclusion criteria included cardiovascular disease uncovered during preliminary investigations and contraindication to cardiac magnetic resonance (CMR). The study was advertised by email over 2 consecutive years to novice marathon runners, identified through the database records of the Virgin Money London Marathon, and on social media. Interested runners contacted a dedicated call center and were given an appointment for eligibility assessment and recruitment.

The study protocol has already been described [20]–[23]. Briefly, it included:

1) Cardiopulmonary exercise test (CPET) using a semi-recumbent tilting cycle ergometer (Schiller ERG 911 BP/LS, Schiller, Switzerland) and a dedicated metabolic cart (Quark CPET, COSMED, Rome, Italy).[24]

2) Allometry and bioimpedance (BC-418, Tanita, USA).

3) Cardiac magnetic resonance (CMR) (1.5T Aera, Siemens Medical Solution, Erlangen, Germany), performed accordingly to international guidelines,[25] including parametric T1 mapping and extracellular volume (ECV), pulse wave velocity (PWV) measured with phase-contrast MR imaging and late gadolinium enhancement (LGE) images.[26] Image analysis was performed by 3experienced operators. See Table S2 for intra- and inter- operator reproducibility data.

4) Brachial and non-invasive central- blood pressure (BP) assessment and wave analysis using a Cardioscope II BP+ device (USCOM, Sydney, NSW, Australia).[27]

5) Hematocrit and serum creatinine.

Systemic vascular resistance (SVR) and systemic arterial compliance (SAC) were also calculated as follows:

\[
SVR = \frac{MAP}{CO} \times 80
\]

\[
SAC = \frac{SV}{SBP - DBP}
\]

Where SVR: systemic vascular resistance; MAP: mean arterial pressure; CO: cardiac output; SAC: systemic arterial compliance, SBP: systolic BP; DBP: diastolic BP.
All measurements were carried out before training started, 6 months before the marathon, and repeated between 1 and 3 weeks after the race, to avoid the acute effects of the race. It was recommended that participants followed the race organisers’ “Beginner’s Training Plan” (see Appendix 1), but alternative training plans were allowed. The calculation of synthetic ECV [28] was preferred because haematocrit, needed in order to calculate normal ECV, was unavailable at follow-up in 35 subjects due to the cyberattack that affected NHS and the hospital laboratory immediately before the study dates. All procedures were in accordance with the principles of the Helsinki declaration, all participants gave written informed consent, and the study was approved by the London-Queen Square National Research Ethics Service Committee(15/LO/0086).

Statistical analysis
Quantitative variables are expressed as mean±standard deviation (SD) or (range) and categorical variables as an absolute number with percentage in parentheses. Only the subjects who completed the study were included in the analysis. To assess the cardiovascular effects of aerobic exercises in different age group, we used linear mixed-effects models accounting for repeated measurements with an unstructured covariance matrix, fitting the models by maximizing the restricted log-likelihood followed by a posteriori contrasts when applicable. False Discovery Rate algorithm was used for multiple post-hoc comparisons. The variables were transformed to handle possible violations of the hypothesis of normality of the residuals. For analysis of the age effect, we split recruited runners into two groups, “under 35” (U35) and “over 35” (O35), when a runner is ≤35 or ≥35 years respectively, accordingly to the classification of “young” versus “master” athlete. Linear regression analysis was also performed (results in Appendix 2). An α level of 0.05 was used for all hypothesis tests; analyses were performed using R Core Team software (2018), Vienna, Austria.
Results

Study population

Two hundred and thirty-seven runners were recruited. Among them 166 (70%) completed the race, 52 (22%) interrupted their training following musculoskeletal injury, 19 (8%) did not compete for other reasons. Among the race completers, 27 did not attend for follow-up, 1 was excluded after being diagnosed with hypertension. The final cohort consisted of 138 subjects who underwent evaluations at 180±10 days before the London Marathon and 16±8 days after (Figure 1). Baseline mean age was 37±10years (range 21-69y.o.), 51% were females (mean age 37±10years, 47% <35y), 49% were males (mean age 37±11years, 54% <35years). Reported median hours of training per week were 1.9.

See Table 1 for full details.

Baseline characteristics

We did not find any significant difference in the baseline characteristics between the subjects who completed the study or dropped out. Race finishers were similar in age and gender (U35: n=71, mean age 29±4y, females=49%; O35: n=67, mean age 46±7y, females=51%). The prevalence of former smokers was lower in U35 than in O35 (10% vs 32% respectively, p =0.002). No differences were observed for ethnicity and blood tests results. See Table 1 and 2.

Marathon completion rate and injury rate during training did not differ between age groups (Figure 1). Mean race time (HH:MM) was 4:44 (range: 2:57-7:57) in the whole cohort. U35 were faster (mean race time in U35: 4:38 [range 2:56–6:51] against 5:15 [range 3:27–7:57] in O35).

All participants achieved an RER of 1.1 or greater at the baseline CPET. Age predicted peak oxygen uptake was 109±17%, without significant differences between groups, although absolute physical performance was superior in U35 than in O35 for peak oxygen uptake (+5.6 ml/kg/min, p<0.001), maximal reached power (+13W, p=0.012) and exercise time (+166 seconds, p<0.001).

Mean height, weight, body surface area (BSA) did not differ between groups. On average, body mass index (BMI) was high-normal (24.4, range 16.7-35.2), and lower in U35 than O35 (U35: 23.6±0.3; O35: 25.1±0.4, p=0.009).
Average biventricular chambers size and LV mass indexed for BSA were normal in the whole sample.[29] All volumes and mass were higher in U35 than in O35 (LV EDVi: +8ml/m²; LV ESVi: +5ml/m², RV EDVi and ESVi: +10ml/m²; LV mass +6gr/m²; p<0.001 for all). Native T1 values and synthetic ECV were within the normal range and not different between groups.[26] There was basal infero-lateral mid-myocardial non-ischemic LGE in one male subject in the O35, both before and after training (unchanged).

Average BP was normal in the whole sample, but lower in U35 than in O35 by 5/3mmHg for brachial SBP/DBP (p=0.02/0.03 respectively) and by 6/3mmHg for central SBP/DBP (p=0.004 for cSBP and p=0.03 for cDBP). Arterial PWV in the whole aorta was 6±15m/s, lower in U35 than O35 by 1.4m/sec (p <0.001).[20] Similarly, SVR were on average 1135dyn·s/cm⁵, significantly lower in U35 than in O35 by 173dyn·s/cm⁵ (p <0.001). Finally, SAC of the whole sample was 3.0 ±8 ml/m², higher in U35 than in O35 (+0.3 ml/m², p=0.001).

See Table 2 and Table S1.

**Follow up**

**Cardiopulmonary exercise testing**

After training, there were small increases in overall fitness. Mild improvement was observed in peak oxygen uptake (+1ml/kg/min, p=0.035). Exercise time increased on average by 21seconds (p=0.010) and peak power by 4W (p=0.002). Subgroup analysis showed these changes in the U35 only (exercise time: +6%, peak power: +5%, peak VO₂ +3%; p<0.01, p<0.01 and p<0.05 respectively). Resting heart rate was unchanged at follow-up.

**Allometry**

After training, weight fell by 900g (p=0.001) and body fat by 1% (p=0.006) driven by O35 (on average -2%, p<0.001). Height decreased by 6mm in both groups. See Table2.

**Cardiac remodeling**
After training, biventricular volumes increased by an average of 2ml/m² (EDVi) and 1ml/m² (ESVi) (p<0.05 for both). At post hoc analysis, the chambers size increase was observed only in the U35 (LVEDVi: +3%, LVESVi: +8%, RVEDVi: +4%, RVESVi: +5%, p<0.001 for all), while no change was observed in O35. A similar 4% (~3g/m²) increase in LV mass was observed in both groups (p<0.001) representing mild concentric remodeling (LV mass/volume ratio increase of 0.2), driven by O35, in whom LV mass/volume ratio went from 0.73±0.1 to 0.76±0.1 (p=0.001).

Synthetic ECV and native myocardial T1 mapping were unchanged after training. No changes were observed in the myocardial partition coefficient, post-contrast T1 myocardial, full blood count or kidney function in either group.

See Table 2 and Table 1S.

Systemic hemodynamics and vascular remodeling.

There was a mean 4% decrease in SVR after training (p=0.04), driven by O35 (baseline vs follow-up in U35: p=0.31; O35: p=0.060), associated with a 7% reduction in SAC (p=0.020), similar in U35 and O35 (baseline vs follow-up p=0.002 for both), and a mild reduction in the PWV of the whole aorta (p=0.040), without differences between age groups. Training reduced BP, with the largest falls observed in O35. Brachial SBP/DBP dropped by 3/1mmHg in U35 (p=0.030 for SBP, p=0.08 for DBP) and by 6/3mmHg in O35 (p<0.001 for both SBP and DBP); central SBP/DBP dropped by 3/2mmHg in U35 (p=0.05 for SBP, p=0.004 for DBP) and dropped by 6/4mmHg in O35 (p<0.001 for both SBP and DBP).

See Table 2 and Table S1.
Discussion
This study explored the cardiac and vascular remodeling occurring in healthy sedentary adults of different age groups undergoing medium-term, unsupervised physical training of mild intensity. Our main findings were a more pronounced cardiac remodeling observed in younger subjects and more vascular changes, associated with early cardiac remodeling features, in older subjects (Figure 2). Specifically, the U35 showed an increase in ventricular LV size consistent with 6-months of endurance training in a similar age-group,[30] associated with an increase in LV mass consistent with a light training schedule and a very mild reduction in BP. On the other hand, in the O35s only early cardiac remodeling was noted (i.e. a LV mass increase similar to O35 but no measurable cavity dilatation), associated with a more marked reduction in BP and SVR, corresponding to the effect of a low-dose BP lowering drug on BP and to an overall reduction in vascular age of approximately four years. [20],[21], [31]
Ageing is associated with impaired cardiovascular elasticity [32],[7] and reduced cardiac responsivity to sympathetic stimulation.[33] Histologically, these features correspond to 1) quantitative and qualitative changes in collagen, 2) a reduction in cardiomyocyte number with compensatory hypertrophy of the remaining cells [1] and 3) changes in cardiac innervation.[6], [12] Functionally, this translates into cardiac diastolic dysfunction and dromotropic/inotropic impairment, associated with increased afterload and leading to increased ventricular filling pressure and impaired exercise tolerance. Combined, cardiac and vascular ageing is critical in determining exercise tolerance: in fact, the impairment in cardiac response during strenuous exercise observed in aged people [34] is entirely reversible by reducing the loading conditions. [35]
On the other hand, endurance training is known to increase stroke volume, improve endothelial function and coronary perfusion, decrease peripheral resistance, lower blood pressure and induce cardiac and skeletal muscle cell remodeling. [15], [32], [36]
Here, in the O35 group, we observed an improvement in vascular function, and peripheral resistance, consistent with previous observations. [37] We hypothesize that mild-intensity training may unload the myocardium and improve ventriculo-arterial coupling, thereby increasing cardiovascular efficiency meaning that stimulated cardiac growth was counteracted – an overall beneficial set of linked changes.[38]
For the U35s, possessing a greater number of smaller myocytes, an effective response to sympathetic stimulation and loading conditions already well coupled to vascular function, a mild increase in LV volumes along the lines expected for “athlete’s heart” was seen.[39], [40]

Finally, no changes in ECV were observed in different study conditions, arguably because any changes were proportionate with equal changes in intracellular and extracellular compartments or because the amount of exercise undertaken was insufficient to induce a measurable change in the cellular/extracellular tissue component ratio.[41]

We acknowledge a number of limitations, including the lack of a non-running control group, a potential selection bias related to the availability to take part in a research study and the lack of ethnic diversity. Here, the U35s and O35s were all first-time marathon runners, but they differ by more than just age. Although it is not possible to fully unravel the contribution of differences (birth cohort bias with different nutrition, gestational conditions and lifestyle, as suggested by ex-smoker rates different between cohorts; baseline fitness; training schedule; commitment; age-related whole-organism responsivity to training) and the net amount of physical exercise against age in determining cardiovascular remodeling, baseline age adjusted peak oxygen consumption and marathon completion and injury rates were not age dependent, suggesting that baseline fitness, training schedules and commitment were not the primary cause of the remodeling differences. Actual physical activity during the training period is unknown due to excessive number of missing data, but average completion times exceed those reported in age-matched wide cohorts (including professionals athletes) by ~40 minutes in U35 and by ~70 minutes in O35,[18] suggesting that training intensity was mild.

Exercise-induced cardiovascular remodeling is dose-dependent, with mass increase observed earlier than volume increase. [30] The mild amount of cardiovascular remodeling observed is proportional to the entity of training undertaken, and more marked changes would have been unexpected. We believe that the potential significance of our results is also related to their epidemiological impact: this kind and entity of exercise is generalizable to the real-world population and is feasible outside a structured training program.

Finally, the study had a high drop-out rate (42%), mostly due to musculoskeletal injury (71% of total drop-out). We did not find any differences between study completers and non-completers at baseline examination.
(Table 3S), thus excluding a selection bias were study completers could be a selection of the cohort with better cardiovascular adaptation to exercise.

With the aforementioned limitations, this study may contribute to cardiac rehabilitation research, where vascular function and peripheral resistance changes could be tested as an efficacy endpoint. There may also be relevance to HFpEF, where a component of reversible vascular dysfunction may explain the benefits observed after physical training despite unchanged cardiac function – the idea that at least some HFpEF has a significant and reversible vascular dysfunction component is not widely considered.[42], [43] Additional points that need clarification are the mechanisms underlying these observations and the impact of sex on cardiovascular ageing and its interaction with physical exercise. [37], [44]

In conclusion, these data show how different age groups shift on the training-induced cardiovascular remodeling spectrum, with more relevant cardiac changes observed in the youth, resembling an early athlete’s heart phenotype, and more vascular changes, tending to improved efficiency through optimization of cardiac load and corresponding to a decrease in vascular age, in the elderly.
Aknowledgements

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Conflict of interest:

The authors report no relationships that could be construed as a conflict of interest.

Authors’ contribution:

AD, ANB, ADH, GL, CHM, SS, JCM contributed to the conception or design of the work. CT, AD, JAA, ANB, KDK, AF, GB, SJ, JVZ, PS, IL contributed to the acquisition, analysis, or interpretation of data. CT
drafted the manuscript. AD, ANB, GP, ADH, GL, CHM, SS, JC critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

References


Figure Legends:

**Figure 1:** Consort flow diagram illustrating subject recruitment and follow up. LQTS, long QT syndrome. U35: Under 35, <35 years old. O35: Over 35, ≥ 35 years old.

**Figure 2:** Effects of ageing and physical training on the continuum of cardiovascular system remodeling. Panel 1: cardiac and vascular assessment by cardiac magnetic resonance (A: extracellular volume. B: function and mass; C, D, E: vascular function acquisitions to derive pulse wave velocity and arterial compliance by obtaining distance and high temporal resolution [G] flow and using least squares estimate of systolic upslopes [F]. Graphical schematics of systemic vascular resistance [H]). Panel 2: healthy ageing is characterized by a reduction in myocytes number, compensatory hypertrophy, and collagen alterations with vascular changes of arterial stiffening, increased pulse wave velocity, reduced arterial compliance and increased systemic vascular resistance. Physical training here induced cardiac plasticity (increase in left ventricular mass and chambers volume) in individuals <35 years (U35), with minimal blood pressure changes (panel 1 to 3). In individuals aged ≥35 years (O35), more vascular plasticity (systemic vascular resistance drop, systemic blood pressure drops) along with mild left ventricular mass increase (panel 2 to 4) are observed.
Figure 1

Enrollment

London Virgin Money Marathon places (won 2005 + 2007)  
~10,000

Targeted populations invited to take part  
~2,000

Contacted study team  
620

Recruited  
237

Excluded  
313
- Not meeting inclusion criteria  
48
- Declined to participate  
45
- Unavailable on study date/locations  
210

Allocation

Under 35 (n=123)  
Over 35 (n=114)

Excluded on discovery of:  
- DIabetes (n=1)
- Arterial hypertension (n=5)

Training

180 ± 20 days of unsupervised training - Marathon -  
42.195km

Discontinued training (n=20)  
- Musculoskeletal injury (n=29)  
- Unknown reasons (n=10)  
- Completed the marathon but were lost to follow-up (n=15)

Follow-up

Analysis

Under 35 (n=76)  
Over 35 (n=67)
<table>
<thead>
<tr>
<th></th>
<th>Whole cohort (n=138)</th>
<th>U35 (≤34 years) (n=71)</th>
<th>O35 (≥35 years) (n=68)</th>
<th>p condition</th>
<th>p age</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSA (m²)</strong></td>
<td>Baseline 1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td></td>
<td>Follow-up 1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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<td><strong>CMR</strong></td>
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<tr>
<td><strong>LV EDV (ml)</strong></td>
<td>Baseline 162 ± 5</td>
<td>169 ± 8</td>
<td>154 ± 5</td>
<td>§ 0.159</td>
<td>0.001</td>
<td>0.008</td>
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<td></td>
<td>Follow-up 164 ± 6</td>
<td>174 ± 9</td>
<td>152 ± 5</td>
<td>§</td>
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<tr>
<td><strong>LV ESV (ml)</strong></td>
<td>Baseline 57 ± 1</td>
<td>61 ± 8</td>
<td>52 ± 1</td>
<td>0.068</td>
<td>0.001</td>
<td>0.009</td>
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<td>Follow-up 58 ± 6</td>
<td>65 ± 8</td>
<td>52 ± 1</td>
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<tr>
<td><strong>LV SV (ml)</strong></td>
<td>Baseline 105 ± 4</td>
<td>108 ± 5</td>
<td>101 ± 2</td>
<td>0.83</td>
<td>0.047</td>
<td>0.341</td>
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<td>Follow-up 105 ± 3</td>
<td>110 ± 5</td>
<td>101 ± 2</td>
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<tr>
<td><strong>RV EDV (ml)</strong></td>
<td>Baseline 164 ± 4</td>
<td>173 ± 4</td>
<td>155 ± 3</td>
<td>0.017</td>
<td>0.001</td>
<td>0.316</td>
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<td></td>
<td>Follow-up 168 ± 1</td>
<td>179 ± 4</td>
<td>157 ± 3</td>
<td>§</td>
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<tr>
<td><strong>RV ESV (ml)</strong></td>
<td>Baseline 65 ± 8</td>
<td>74 ± 0</td>
<td>55 ± 1</td>
<td>0.61</td>
<td>0.688</td>
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<td>Follow-up 67 ± 0</td>
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<td>0.678</td>
<td>0.258</td>
<td>0.514</td>
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<tr>
<td><strong>RV SV (ml)</strong></td>
<td>Baseline 99 ± 2</td>
<td>99 ± 2</td>
<td>100 ± 2</td>
<td>0.678</td>
<td>0.258</td>
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<td>Follow-up 101 ± 2</td>
<td>101 ± 2</td>
<td>100 ± 2</td>
<td>0.678</td>
<td>0.258</td>
<td>0.514</td>
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<tr>
<td><strong>LV mass (g)</strong></td>
<td>Baseline 117 ± 2</td>
<td>121 ± 2</td>
<td>112 ± 2</td>
<td>&lt;.0001</td>
<td>0.061</td>
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<td>Follow-up 121 ± 2</td>
<td>127 ± 2</td>
<td>116 ± 2</td>
<td>§</td>
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<tr>
<td><strong>Septal wall thickness (mm)</strong></td>
<td>Baseline 6.8 ± 1.6</td>
<td>6.8 ± 1.7</td>
<td>6.8 ± 1.8</td>
<td>0.61</td>
<td>0.688</td>
<td>0.975</td>
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<tr>
<td></td>
<td>Follow-up 6.9 ± 1.7</td>
<td>6.9 ± 1.7</td>
<td>6.9 ± 1.8</td>
<td>0.678</td>
<td>0.258</td>
<td>0.514</td>
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<tr>
<td><strong>Lateral wall thickness (mm)</strong></td>
<td>Baseline 6.4 ± 2.6</td>
<td>6.7 ± 2.2</td>
<td>6.2 ± 1.8</td>
<td>0.61</td>
<td>0.688</td>
<td>0.975</td>
</tr>
<tr>
<td></td>
<td>Follow-up 6.3 ± 1.8</td>
<td>6.4 ± 1.8</td>
<td>6.2 ± 1.8</td>
<td>0.678</td>
<td>0.258</td>
<td>0.514</td>
</tr>
<tr>
<td><strong>Native blood T1 (msec)</strong></td>
<td>Baseline 1606 ± 6.9</td>
<td>160 ± 6.7</td>
<td>161 ± 7.1</td>
<td>0.176</td>
<td>0.543</td>
<td>0.212</td>
</tr>
<tr>
<td></td>
<td>Follow-up 1600 ± 8.8</td>
<td>160 ± 6.8</td>
<td>159 ± 6.8</td>
<td>0.176</td>
<td>0.543</td>
<td>0.212</td>
</tr>
<tr>
<td><strong>Myocardial T1 post-Gd (msec)</strong></td>
<td>Baseline 620 ± 6.5</td>
<td>632 ± 7.3</td>
<td>607 ± 5.5</td>
<td>0.8334</td>
<td>&lt;.0001</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Follow-up 621 ± 6.5</td>
<td>635 ± 7.5</td>
<td>606 ± 4.4</td>
<td>0.8334</td>
<td>&lt;.0001</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Blood T1 post-Gd (msec)</strong></td>
<td>Baseline 503 ± 5.1</td>
<td>514 ± 5.5</td>
<td>491 ± 6.8</td>
<td>0.431</td>
<td>0.001</td>
<td>0.291</td>
</tr>
<tr>
<td></td>
<td>Follow-up 508 ± 5.8</td>
<td>514 ± 4.9</td>
<td>490 ± 6.6</td>
<td>0.431</td>
<td>0.001</td>
<td>0.291</td>
</tr>
<tr>
<td>Partition coefficient (Lambda)</td>
<td>Baseline</td>
<td>46 ± 3</td>
<td>45 ± 3</td>
<td>46 ± 4 §</td>
<td>0.444</td>
<td>0.045</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td>46 ± 3</td>
<td>45 ± 3</td>
<td>46 ± 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECV</td>
<td>Baseline</td>
<td>27.1 ± 2</td>
<td>26.9 ± 2</td>
<td>27.4 ± 2</td>
<td>0.006</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>26.2 ± 2</td>
<td>25.5 ± 5</td>
<td>27.3 ± 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA volume (ml)</td>
<td>Baseline</td>
<td>69 ± 2</td>
<td>67 ± 2</td>
<td>70 ± 1</td>
<td>0.788</td>
<td>0.615</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>69 ± 2</td>
<td>70 ± 2</td>
<td>68 ± 1</td>
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</table>

**CPET**

<table>
<thead>
<tr>
<th>% of predicted VO2 max (%)</th>
<th>Baseline</th>
<th>108 ± 1</th>
<th>106 ± 1</th>
<th>113 ± 1</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up</td>
<td>112 ± 1</td>
<td>110 ± 1</td>
<td>116 ± 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>Baseline</td>
<td>164 ± 5</td>
<td>168 ± 4</td>
<td>159 ± 1</td>
<td>0.354</td>
<td>&lt;.0001</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>165 ± 5</td>
<td>172 ± 1</td>
<td>158 ± 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE max</td>
<td>Baseline</td>
<td>95 ± 9</td>
<td>97 ± 3</td>
<td>92 ± 2</td>
<td>0.001</td>
<td>0.21</td>
<td>0.922</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>88 ± 9</td>
<td>91 ± 2</td>
<td>85 ± 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak O2 pulse</td>
<td>Baseline</td>
<td>15.4 ± 4</td>
<td>16 ± 4</td>
<td>14.8 ± 4</td>
<td>0.167</td>
<td>0.019</td>
<td>0.629</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>15.5 ± 4</td>
<td>16.4 ± 4</td>
<td>14.8 ± 4</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Biochemistry**

<table>
<thead>
<tr>
<th>Hb (g/dl)</th>
<th>Baseline</th>
<th>14 ± 1</th>
<th>14 ± 1</th>
<th>14 ± 1</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct (%)</td>
<td>Baseline</td>
<td>42 ± 4</td>
<td>42 ± 3</td>
<td>42 ± 4</td>
<td>0.002</td>
<td>0.174</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>43 ± 4</td>
<td>43 ± 3</td>
<td>42 ± 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>Baseline</td>
<td>0.74 ± 1</td>
<td>0.74 ± 1</td>
<td>0.75 ± 1</td>
<td>0.002</td>
<td>0.166</td>
<td>0.386</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0.7 ± 1</td>
<td>0.70 ± 1</td>
<td>0.72 ± 1</td>
<td></td>
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</tbody>
</table>

Table 15: Baseline and post-marathon tests results for the patients who completed the study, whole sample, U35 and O35. Data are expressed as mean ±SD.

* = p pre vs post <0.05; ** = p pre vs post <0.01; *** = p pre vs post <.0001; § = p U35 vs O35 <.05; §§ = p U35 vs O35 <.01; §§§ = p U35 vs O35 <.0001.

<table>
<thead>
<tr>
<th>Allometry</th>
<th>Timepoint</th>
<th>Whole cohort (n=138)</th>
<th>U35 (≤34 years) (n=71)</th>
<th>O35 (≥35 years) (n=67)</th>
<th>P condition</th>
<th>P age</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>Follow-up</td>
<td>172 ± 9</td>
<td>174 ± 3</td>
<td>171 ± 6</td>
<td>9.5</td>
<td>9.5</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>172 ± 4</td>
<td>173 ± 7</td>
<td>171 ± 0</td>
<td>9.5</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Follow-up</td>
<td>73.2 ± 13</td>
<td>71.8 ± 12</td>
<td>74.5 ± 15</td>
<td>0.001</td>
<td>0.09</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>Follow-up</td>
<td>24.4 ± 0.3</td>
<td>23.6 ± 0.3</td>
<td>25.1 ± 0.4</td>
<td>0.000</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>Follow-up</td>
<td>25 ± 8</td>
<td>23 ± 8</td>
<td>27 ± 8</td>
<td>0.006</td>
<td>1.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Central MAP (mmHg)</td>
<td>Follow-up</td>
<td>108 ± 10</td>
<td>106 ± 10</td>
<td>109 ± 15</td>
<td>0.000</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Central DBP (mmHg)</td>
<td>Follow-up</td>
<td>75 ± 7</td>
<td>73 ± 5</td>
<td>76 ± 8</td>
<td>0.000</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Brachial MAP (mmHg)</td>
<td>Follow-up</td>
<td>85 ± 10</td>
<td>84 ± 7</td>
<td>86 ± 10</td>
<td>0.000</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>PWV Arch (m/s)</td>
<td>Follow-up</td>
<td>4.7 ± 1.4</td>
<td>3.9 ± 0.6</td>
<td>5.6 ± 1.6</td>
<td>0.000</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>PWV Descending aorta (m/s)</td>
<td>Follow-up</td>
<td>8.3 ± 2.5</td>
<td>8.2 ± 2.6</td>
<td>8.5 ± 2.3</td>
<td>0.000</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>PWV Whole aorta (m/s)</td>
<td>Follow-up</td>
<td>6.0 ± 1.5</td>
<td>5.3 ± 1</td>
<td>6.7 ± 1.7</td>
<td>0.000</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>SAC (ml/m²)</td>
<td>Follow-up</td>
<td>3.0 ± 0.8</td>
<td>3.2 ± 0.7</td>
<td>2.9 ± 0.9</td>
<td>0.000</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>SVR (dyn-s/cm²)</td>
<td>Follow-up</td>
<td>1135 ± 262</td>
<td>1052 ± 239</td>
<td>1225 ± 275</td>
<td>0.000</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>LV EDV i (ml/m²)</td>
<td>Follow-up</td>
<td>86 ± 14</td>
<td>90 ± 14</td>
<td>82 ± 13</td>
<td>0.014</td>
<td>0.01</td>
<td>0.027</td>
</tr>
<tr>
<td>LV ESV i (ml/m²)</td>
<td>Follow-up</td>
<td>30 ± 7</td>
<td>33 ± 8</td>
<td>28 ± 6</td>
<td>0.019</td>
<td>0.01</td>
<td>0.023</td>
</tr>
<tr>
<td>SV i (ml/m²)</td>
<td>Follow-up</td>
<td>56 ± 10</td>
<td>58 ± 10</td>
<td>54 ± 9</td>
<td>0.000</td>
<td>0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**P** significance levels: *p < 0.05, **p < 0.01, ***p < 0.001.
LV EF (%) | Baseline 0.65 ± 0.05 | 0.64 ± 0.05 | 0.66 ± 0.05 | 0.00 | 0.254 |
| Follow-up 0.64 ± 0.05 | 0.63 ± 0.05 | 0.66 ± 0.05 | 0.00 |

CO (l/min) | Baseline 6.7 ± 1.6 | 7.1 ± 1.7 | 6.3 ± 1.5 | § | 0.2 | 3 | 0.8 |
| Follow-up 6.6 ± 1.7 | 7 ± 1.8 | 6.1 ± 1.5 |

LV mass (g/m²) | Baseline 62 ± 12 | 65 ± 12 | 59 ± 12 | <.00 | 1 | 0.8 |
| Follow-up 65 ± 13 | 68 ± 12 | 62 ± 13 | * |

LV mass/volume ratio | Baseline 0.72 ± 0.1 | 0.71 ± 0.1 | 0.73 ± 0.1 | 0.00 | 9 | 0.06 |
| Follow-up 0.74 ± 0.1 | 0.73 ± 0.1 | 0.76 ± 0.1 | ** |

Synthetic ECV (%) | Baseline 21 ± 4 | 20 ± 4 | 19 ± 4 | ** |
| Follow-up 21 ± 4 | 20 ± 4 | 19 ± 4 | ** |

RV EDV (ml/m²) | Baseline 88 ± 15 | 92 ± 15 | 82 ± 13 | <.00 |
| Follow-up 90 ± 16 | 96 ± 17 | 85 ± 14 |

RV ESV (ml/m²) | Baseline 35 ± 10 | 39 ± 9 | 29 ± 8 | <.00 |
| Follow-up 36 ± 11 | 41 ± 10 | 31 ± 9 |

RV SV (ml/m²) | Baseline 53 ± 9 | 53 ± 10 | 53 ± 9 | 0.08 | 0.9 | 0.6 |
| Follow-up 54 ± 9 | 55 ± 9 | 54 ± 9 |

RV EF (%) | Baseline 0.61 ± 0.06 | 0.58 ± 0.07 | 0.65 ± 0.07 | §§ |
| Follow-up 0.61 ± 0.06 | 0.57 ± 0.07 | 0.64 ± 0.07 | §§ |

LA volume (ml/m²) | Baseline 51 ± 29 | 51 ± 28 | 50 ± 31 | 0.9 | 0.8 | 0.09 |
| Follow-up 50 ± 29 | 48 ± 26 | 52 ± 31 |

Native myocardial T1 (msec) | Baseline 1009 ± 29 | 1009 ± 28 | 1009 ± 28 | 0.3 | 0.4 | 0.8 |
| Follow-up 1006 ± 33 | 1006 ± 33 | 1006 ± 33 |

Synthetic ECV (%) | Baseline 26.3 ± 3 | 25.8 ± 3 | 26.7 ± 3 | 0.8 | 0.1 | 0.2 |
| Follow-up 26.3 ± 3 | 26 ± 3 | 26.6 ± 3 |

** Table 2: Baseline and post-marathon tests results for the patients who completed the study, whole sample, U35 and O35. Data are expressed as mean ±SD.**

* = p pre vs post <.05; ** = p pre vs post <.01; *** = p pre vs post <.001; § = p U35 vs O35 <.05; §§ = p U35 vs O35 <.01; §§§ = p U35 vs O35 <.001.