Cardiovascular response to prescribed detraining among recreational athletes.

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ABSTRACT (246 words)

Exercise-induced cardiac remodeling (EICR) and the attendant myocardial adaptations characteristic of the athlete's heart may regress during periods of exercise reduction or abstinence. The time course and mechanisms underlying this reverse remodeling, specifically the impact of concomitant plasma volume (PV) contraction on cardiac chamber size, remain incompletely understood. We therefore studied recreational runners (n=21, aged 34 ± 7 years; 48% male) who completed an 18-week training program (~7 $h \cdot w^{-1}$) culminating in the 2016 Boston Marathon after which total exercise exposure was confined to <2 $h.w^{-1}$ (no single session >1 hour) for 8 weeks. Cardiac structure and function, exercise capacity, and PV were assessed at peak fitness (10-14 days before) and at 4- and 8-weeks post marathon. Mixed linear modeling adjusting for age, sex, $\dot{V}O_{2peak}$ and marathon finish time was used to compare data across time points. Physiologic detraining was evidenced by serial reductions in treadmill performance. Two distinct phases of myocardial remodeling and hematologic adaptation were observed. After 4 weeks of detraining, there were significant reductions in PV (Δ -6.0%, P<0.01), left ventricular (LV) wall thickness (Δ -8.1%, <0.05), LV mass (Δ -10.3%, P<0.001), and right atrial area (Δ -8.2%, P<0.001). After 8 weeks of detraining, there was a significant reduction in right ventricle chamber size (end-diastolic area Δ = -8.0%, P <0.05) without further concomitant reductions in PV or LV wall thickness. Abrupt reductions in exercise training stimulus result in a structure-specific time course of reverse cardiac remodeling that occurs largely independently of PV contraction.

Key Words: sports cardiology, left ventricle, cardiac morphology, echocardiography, hemoglobin mass

NEW AND NOTEWORTHY (max 75 words)

Significant reverse cardiac remodelling, previously documented among competitive athletes, extends to recreational runners and occurs with a distinct time course. Initial reductions in plasma volume and LV mass, driven by reductions in wall thickness, are followed by contraction of the right ventricle. Consistent with data from competitive athletes, LV chamber volumes appear less responsive to detraining and may be a more permanent adaptation to sport.

Glossary

EICR	Exercise induced cardiac remodeling
LV	Left ventricle or left ventricular
RV	Right ventricle or right ventricular
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_2$peak	Peak oxygen uptake
tHb-mass	Total hemoglobin mass
CO	Carbon monoxide
[Hb]	Hemoglobin concentration
COHb	Carboxyhemoglobin
%COHb	Percent carboxyhemoglobin
PV	Plasma volume
BV	Blood volume

INTRODUCTION

Routine vigorous endurance exercise stimulates numerous changes in cardiovascular structure and function and concomitant increases in blood volume (BV). Specifically, the process of exercise induced cardiac remodeling (EICR) is characterized by mild to moderate biventricular eccentric hypertrophy, preserved or enhanced diastolic function, bi-atrial dilation, and BV expansion. EICR has been thoroughly characterized among elite athletes (2, 11, 18, 19, 21, 33) and has recently been documented among recreational exercisers who typically perform comparatively lower volumes and intensities of exercise training (1, 8, 13, 28, 35). Similarly, the hematologic response to endurance exercise training has been described in novice exercisers where a rapid increase in plasma volume (PV) precedes a slow increase in red blood cell volume (16). A recent meta-analysis concluded that increases in red blood cell volume of 4% can be expected over 15 weeks of endurance training in young and middle aged exercisers (16).

While several studies document reductions in left ventricular (LV) wall thickness and chamber size following periods of exercise abstinence among elite competitive athletes (15, 20, 34), and during periods of bed rest in non-athletes (9), the reversibility of EICR among recreational athletes has not been described. In addition, no prior studies have described the change in blood volume that occur during exercise detraining in this population. Consequently, several key issues pertaining to EICR regression including the time course, the mechanistic role of blood volume contraction, and the response of cardiac chambers other than the left ventricle remain incompletely understood.

We therefore studied cardiac structure, function and blood volume components among recreational marathon runners who participated in an 8-week prescribed exercise detraining program following completion of a marathon race (42.2 km). We hypothesized

that participants would demonstrate significant reverse cardiac remodeling characterized by reductions in chamber volumes and wall thickness and that this reverse remodeling would parallel and perhaps be mechanistically driven by reductions in blood volume.

METHODS

Study Design Overview

We used a prospective, longitudinal, and repeated measures study design to examine the cardiovascular response to prescribed detraining among healthy recreational marathon runners participating in the 2016 Boston Athletic Association's Boston Marathon (42 km foot race). An initial sample of 24 runners (50% men) were recruited and consented to this study. No participants had established cardiovascular disease at the time of enrollment and all were free of inducible myocardial ischemia and arrhythmia during baseline cardiopulmonary exercise testing. Five female participants were routinely taking oral contraceptive pills. Otherwise, no participants started or stopped any prescription or over-the-counter medications during the study period. In preparation for the marathon, participants completed a standardized running training program that has previously been shown to be an adequate exercise dose to stimulate exercise-induced cardiac remodeling (35), and all participants completed the marathon without medical complications. Following the marathon, participants were instructed to restrict their exercise dose to < 2 hours/week of low intensity exercise, with no single exercise session > 1 hour in duration and no interval training of any kind.

Participants underwent study measurements at 3 time points: peak fitness at 1-2 weeks prior to the marathon, 4-weeks post-race, and 8-weeks post-race (**Figure 1**). Assessment at each study time point included measurement of height, weight, fasting

blood sampling, cardiac structure and function using transthoracic echocardiography, maximal exercise capacity using cardiopulmonary exercise testing, and hematologic parameters using carbon monoxide rebreathing as described in detail below. The study was approved by the Partners Healthcare System Human Research Committee, and written informed consent was obtained from each participant at the time of enrollment.

Exercise exposure during the study period

Self-reported exercise participation data were gathered on a weekly basis during the study period using a written questionnaire. Running distance and duration, aerobic cross training, and any other deliberate exercise training sessions were collected. Exercise exposure was categorized into running (total mileage; **figure 2**, panel A) and durations of: 1.) Running, 2.) Cross-training (including outdoor cycling, stationary cycling, elliptical trainer, skiing, zumba, and team sports such as soccer), 3.) Yoga or pilates, and 4.) Weight training.

Echocardiography

Transthoracic echocardiographic data were acquired prior to exercise testing and were completed and analyzed by a single experienced cardiac sonographer (A.D). Images were acquired using commercially available ultrasound system (Vivid-Q, GE Medical Systems, Israel Ltd), with a 1.5-4 MHz phased array transducer, to acquire 2 dimensional grey scale and Doppler images. All cardiac images were electronically archived as raw data and reported values represent the average of 3 consecutive cardiac cycles to account for heart rate and measurement variability. LV volumes, ejection fraction and left atrial volumes were calculated using the modified biplane technique (14). LV mass was

calculated using the area-length method and LV geometry was assessed using relative wall thickness. Right ventricular (RV) end-diastolic area, end-systolic area, basal diastolic diameter, diastolic length and fractional area change were measured from RV optimized apical 4-chamber images. LV myocardial tissue velocities were measured in 4 basal segments (septum, lateral, inferior and anterior) and RV velocities were measured in the RV free wall base using a modified apical 4-chamber view. LV longitudinal strain was analysed using speckle tracking software (Echopac, GE Medical, Horten, Norway, version 112.1.6) of two dimensional grey-scale images taken from the apical four, two and three chamber views. In order to time-align and adjust for inter-individual variability of heart rate, frame-by-frame data were exported to custom-made software that completed cubic spline interpolation to produce 600 data points for both the systolic and diastolic periods as previously described (29, 30). All measurements are presented as raw data and after body surface area indexing via the Mosteller formula (17) where appropriate. Values defining the limits of normal right and left ventricular structure were adopted from the American Society of Echocardiography/European Association of Echocardiography chamber quantification recommendations (14). Intra and inter-observer variability data from our laboratory for the key echocardiographic variables reported in this study have been previously published (3).

Cardiopulmonary exercise testing

Exercise tests were conducted on a treadmill (Pro XL, Woodway Inc. WI) using a graded maximal effort-limited protocol with continuous electrocardiography and breath-by-breath measurement of metabolic gas exchange. The test protocol consisted of a 2-minute period of standing rest to facilitate ventilatory equilibrium after which treadmill

speed and gradient were increased to 5 miles.hr^{-1} (8.0 km.h^{-1}) and 1% respectively for 10 minutes to facilitate musculoskeletal warm up. After the warm up phase, speed was maintained at 5 miles hr^{-1} and gradient increased by 0.5% every 15 s until volitional exhaustion. Gas exchange was measured using a commercially available metabolic cart (Ultima CardiO2; Medgraphics, St.Paul, MN). Oxygen consumption ($\dot{V}O_2$) data were smoothed using a 5 breath rolling mean with the highest and lowest values in each 7 breaths removed and peak oxygen consumption ($\dot{V}O_2$peak) was defined as the highest 5 breath mean value during exercise. The ventilatory threshold was determined by the modified V-slope method (6). Heart rate was continuously recorded during exercise using a wireless 12-lead electrocardiogram system (Mortara X12+ Transmitter; Mortara Instruments, WI). Primary outcome variables of exercise were time to exhaustion and $\dot{V}O_2$ peak.

Carbon Monoxide Rebreathing

Total hemoglobin mass **(**tHb-mass) and BV were quantified using the optimized carbon monoxide (CO) rebreathing method described in detail by Schmidt and Prommer (26). In brief, since CO binds avidly to hemoglobin (Hb), carboxyhemoglobin (COHb) concentration was measured in blood after 2 minutes of rebreathing a known CO volume (1.0 ml·kg^{-1} in males and 0.9 ml·kg^{-1} in females). Each participant was seated for 15 minutes to allow stabilization of plasma volume, after which a mouthpiece containing ~10g 'soda lime' (calcium oxide/sodium hydroxide mixture as a carbon dioxide scrubber) connected them to a custom made spirometer (Spico-CO Respirations-Applikator, Blood Tec, Germany) and a 3 litre anesthetic bag pre-filled with 100% oxygen. The participants were instructed to completely exhale to residual volume and then take a deep breath in

through the spirometer while the CO dose was administered into the rebreathing circuit via a pre-filled 100 ml syringe. To support the diffusion of CO into the blood, participants were instructed to perform a 10 second breath hold after the first inspiration, after which they continued normal breathing from the spirometer for 1 min 50 s. The participants were then disconnected from the CO rebreathing circuit after exhaling to residual volume. The exhaled volume was collected and analyzed to quantify the amount CO not bound to hemoglobin. Finally, participants fully exhaled to residual volume into a CO gas analyzer (Dräger Pac 7000, Drägerwerk AG & Co. KGaA, Germany) before, and at 4 minutes after CO rebreathing to determine the CO volume exhaled after disconnecting the patient from the spirometer.

Fingertip capillary samples (200 μL) were collected before, and at 6- and 8-minutes after the start of CO rebreathing (Na-heparinized 200 μL RAPIDLyte Multicap Capillary tubes, Siemens Healthcare Diagnostics Inc, Deerfield, USA). Each capillary blood sample was analyzed in duplicate within 10 minutes of acquisition for measurement of percent carboxyhemoglobin (%COHb) using a commercially available blood gas analyzer (ABL80 FLEX CO-OX, Radiometer A/S, Copenhagen, Denmark).

Calculation of tHb-mass, Blood, Plasma and Erythrocyte Volume

tHb-mass was calculated using an excel spreadsheet (Microsoft Excel 2011 for Apple Macintosh) based on the formula:

$$\text{tHb-mass} = K \times \text{MCO(mL)} \times 100 \times (\Delta\%\text{COHb} \times 1.39)^{-1}$$

where:

K = barometric pressure x 760^{-1} x [1(0.003661 x temperature)]

$$\text{MCO} = \text{CO}_{\text{adm}} - (\text{CO}_{\text{system + lung (after disconnection)}} + \text{CO}_{\text{exhaled (after disconnection)}})$$

243 CO_{adm} = CO volume administered into the system

244 $CO_{system + lung (after disconnection)}$ = CO concentration in spirometer x (spirometer volume +

245 lung residual volume)

246 $CO_{exhaled (after disconnection)}$ = end-tidal CO concentration x alveolar ventilation rate

247 Δ%COHb = difference between baseline %COHb and %COHb post CO

248 administration (average of 6- and 8-min %COHb values)

249 1.39 = Hüfners number (constant) (ml CO x g Hb^{-1})

250 Alveolar ventilation rate is assumed to be 5 $L.min^{-1}$

251

252 Blood volume, plasma volume and erythrocyte volume were calculated from the

253 hematocrit, hemoglobin concentration ([Hb]) and tHb-mass using the following formulae:

254 BV (ml) = tHb-mass (g)/[Hb] ($g \cdot dL^{-1}$) x 100

255 Erythrocyte volume (ml) = BV (ml) x hematocrit (%)

256 Plasma volume (ml) = BV – erythrocyte volume

257

258 Hematocrit and hemoglobin concentration values were obtained from capillary

259 blood and were corrected to venous conditions using the following formulae (7, 27):

260 [Hb] ($g \cdot dL^{-1}$) = $[Hb_{capillary}]$ x 0.8787 + 1.24

261 Hematocrit (%) = $[hematocrit_{capillary}]$ x 0.8425 + 5.23

262

263 Reproducibility data using identical methodology for tHbmass (standard error =

264 2.1%) and BV (standard error = 2.4%) were assessed in healthy individuals (n=15) in

265 preparation for this study.

266

Statistical analysis

Normality of distribution for all variables was assessed using the Shapiro-Wilk test. Variables are reported as mean ± standard deviation and median and interquartile range as appropriate for data distribution. The significance of changes across time points was assessed using mixed linear modeling with age, $\dot{V}O_2$peak, and gender as fixed effects and subject identification as a random effect. Akaike's information criterion tool was used to select optimal covariance structures for each model. Post hoc pairwise comparisons of variables between study visits were made using least squares means derived from the mixed-effects models performed with Bonferroni correction. Linear regression was used to identify relationships between changes in left and right ventricular chamber volumes, left and right atrial dimensions, and LV mass, with delta blood volume and delta plasma volume. Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 23 (IBM Corp ©). A *P* value of <0.05 was considered significant.

RESULTS

Twenty-one participants (age = 34 ± 7 years, 48% men) completed the 2016 Boston Marathon (4:28 ± 0:27 hours:mins) and then adhered to the 8-week detraining protocol (**Table 1**). Running volume decreased from 31.6 ± 9.6 miles.week^{-1} during the final marathon training phase to 3.4 ± 3.1 miles.week^{-1} during weeks 0 to 4 weeks and 4.8 ± 3.9 miles.week^{-1} during weeks 4-8 weeks post-marathon (*P*<0.001, **Figure 2**). At baseline, LV and RV chamber sizes, as defined using BSA-indexed LV end diastolic volume and RV end diastolic area, exceeded the upper limits of the clinically recommended normal range (14), in 6/21 and 7/21 participants respectively. No runners

exceeded clinical cut points for LV mass. $\dot{V}O_2$peak was stable across study time points but physiologic detraining was evidenced by serial reductions in time to exhaustion during treadmill testing (baseline = 17.8 min. vs. 4-weeks = 17.3 min. vs. 8-weeks = 17.1 mins, $P<0.01$).

4-Weeks Detraining: "Early" Adaptations

Hematologic and cardiac structural and functional data across study time points are detailed in **Table 2** and **Table 3** respectively. After 4-weeks of detraining, BV and plasma volume were both significantly decreased compared to baseline while erythrocyte volume and total hemoglobin mass were unchanged. This was accompanied by significant reductions in LV wall thickness, LV mass, and right atrial size. In contrast, there were no significant changes in LV chamber dimensions or volume, left atrial volume, and LV indices of systolic and diastolic function. The majority of RV indices of size and function were similarly unchanged after 4 weeks of detraining.

No significant correlations were identified between delta PV and delta BV and delta LV mass or any chamber volume or area delta values at 4 weeks (R^2 values from 0.01-0.14; P values from 0.09 – 0.96).

8-Weeks Detraining: "Late" Adaptations

At 8 weeks post-marathon, no further reductions in either blood or plasma volume were observed, and erythrocyte volume and total hemoglobin mass remained stable. Similarly, there were no further reductions in LV wall thickness and LV chamber dimensions remained unchanged. However, there was a significant reduction in RV size as demonstrated by multiple complementary indices including RV length, basal diameter,

end-diastolic area, and outflow tract diameter. Aside from the tricuspid annular plane systolic excursion, which was decreased but remained within normal limits, there were no statistically significant changes in LV or RV function in systole or diastole at 8 weeks compared to both previous study time points.

No significant correlations were identified between delta PV and delta BV, and delta LV mass or any chamber volume or area delta values at the 8-week time point (R^2 values from 0.01-0.13; P values from 0.12-0.95).

DISCUSSION

This longitudinal study, designed to examine the cardiovascular response to exercise detraining among recreational marathon runners, generated the following principal findings. Eight weeks of reduced training volume led to a decline in peak treadmill exercise time, significant reductions in BV, and reverse cardiac remodeling. Specifically, we observed a 3.6% decline in BV, which was driven by reductions in plasma volume with concomitant stability of erythrocyte volume and total hemoglobin mass. This relatively rapid hematologic response occurred early during the study period and was completed within 4 weeks. In contrast, differential cardiac remodeling occurred during the two phases of the study period. Specifically, we observed an early and highly significant reduction in LV mass, driven by reductions in wall thickness, followed by a subsequent decline in right ventricle size. Contrary to our *a priori* hypothesis, hematologic and myocardial changes were not all temporally coupled and associations between Δ PV and echocardiographic measurements were not significant, with the exception of a weak association between Δ PV and Δ EF%. This suggests that reverse cardiac remodeling, specifically reductions in ventricular chamber dimensions, are not mechanistically driven by a simple reduction in BV. In aggregate, these findings provide novel insights into how the cardiovascular system responds to a sudden and marked reduction in exercise exposure.

A large body of prior work has delineated the cardiovascular structural and functional plasticity in response to endurance exercise training (4, 11). Specifically, endurance exercise stimulates eccentric remodeling of the left ventricle, right ventricular dilation, biatrial dilation, and an expansion of BV. These adaptations have been demonstrated among numerous populations including recreational or novice exercisers

(1, 13, 28, 35), highly trained and collegiate athletes (23, 33) young elite athletes (18), and aging masters athletes (10). Comparatively, few studies have examined the reverse cardiac remodeling associated with physical deconditioning. Important prior work documents cardiac atrophy during prolonged bed rest, with 60 days of head down tilt bed rest in healthy females (a similar duration to the present study) and a similar 6-week study of horizontal bed rest in males reporting highly significant reduction in LV chamber size (~20%) and LV mass (~8.0%) (9). Similarly, there are several studies examining elite athletes following termination of training and competition (5, 15, 20), with one report documenting a 7% decrease in LV cavity dimensions and a 15% decrease in LV wall thickness after long term (1-13 years) deconditioning (20). These prior data may represent the upper limits of the reverse remodeling but are not generalizable to the sizable and rapidly growing population of recreationally exercising people. In addition, we are unaware of any prior data defining the temporal sequence, right heart involvement, and role of vascular volume contraction on reverse cardiac remodeling during detraining. Findings from this study address each of these key areas of uncertainty and thereby enhance our understanding of exercise-related cardiac plasticity in several ways. Our findings suggest that 4 weeks of detraining causes a reduction in left ventricular wall thickness and that 8 weeks of detraining are sufficient to observe reductions in right ventricular chamber size. It is noteworthy and perhaps surprising that we did not observe a reduction in left ventricular chamber dimensions. It is possible that our study duration was insufficient to capture left ventricular regression, the preceding training stimulus was not sufficient to cause a significant dilation prior to our detraining study period, or alternatively, that LV chamber dimensions may be less responsive to removal of exercise as has been previously suggested. (20).

Blood volume, particularly the plasma component, expands acutely in response to endurance training (16, 24, 31) or during acclimatization to environmental stimuli (22). To date, few studies have examined changes in BV during exercise detraining and we are unaware of any work designed to examine the relationship between physiologic BV fluctuation and myocardial structure and function in this context. While biochemical mediators and cellular adaptations underlying exercise-induced cardiac remodeling have been well described (32), the potential role of BV as a physical determinant of cardiac structure and function in this setting has not been rigorously explored. Based on the Frank-Starling mechanism, we hypothesized that a significant percentage of the expected decline in cardiac chamber size would be caused by simple BV or PV contraction. Our data refute this hypothesis and suggest that acute reductions in BV or PV during exercise cessation contribute minimally to reverse cardiac remodeling. While speculative, it is possible that acute contraction of BV during exercise detraining is coupled with a decline in peripheral venous capacitance, which facilitates maintenance of central BV. This speculation is supported by the fact we observed no statistically significant changes across numerous highly preload dependent indices of myocardial function including trans-mitral Doppler velocities. Further research designed to explore this potentially adaptive coupling of the peripheral vasculature with the myocardium represents an important area of future work. Finally, it is noteworthy that the erythrocyte compartment of the blood volume: tHbmass, was not significantly different across study timepoints. The stability of tHbmass parallels our peak $\dot{V}O_2$ data which also did not significantly decline with detraining as these parameters are well known to be tightly coupled (25). Given that red cells have a lifespan of approximately 110 days (12), beyond the length of our study, a longer detraining phase may be required to stimulate a reduction in tHbmass.

Several limitations of the present study must be acknowledged. First, although our sample size was adequately powered to detect clinically and statistically significant changes in cardiac morphology during exercise detraining, we lack sufficient numbers to investigate fully the impact of gender on our observations. While our mixed model analyses adjusted for gender we cannot exclude the notion that men and women may respond differently to prescribed detraining. Second, our study period was confined to 8 weeks and included only 2 detraining study time points. Thus we are unable to comment with any more accuracy than "early" and "late" response regarding the temporal sequence of our observation. More frequent observations over a more extended time period may have yielded a more detailed characterization of the detraining response and should be considered in future similar studies. Third, we employed a detraining protocol involving marked reductions in exercise exposure but not complete abstinence. This choice was a deliberate step to maximize subject recruitment and to make our results generalizable among individuals who do not stop exercising completely, however, this may have resulted in Type 2 error. Fourth, as we previously described exercise-induced cardiac remodeling during marathon training in a similar cohort, we elected not to study our current participants during marathon preparation. We are therefore unable to comment on the completeness of the reverse remodeling we observe during detraining. Finally, our cohort was comprised of recreational marathon runners rather than elite or sub-elite athletes and we are thus unable to comment on how our findings apply to these specialized populations.

In conclusion, a sudden and sustained decrease in exercise volume over 8 weeks results in the regression of exercise-induced cardiac remodeling and a reduced plasma volume in recreational marathon runners. This regression follows distinct structure-

specific ‘early’ and ‘late’ time courses characterized by early reductions in LV wall thickness and mass followed by later reductions in RV chamber size. Contrary to our a priori hypothesis, contraction of blood volume does not appear to represent a causal mechanism in the reverse cardiac remodeling during exercise detraining.

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Figure 1. Study design schematic demonstrating periodized marathon training pre- and in-study exercise exposure and timing of the 3 study visits.

Figure 2: Weekly training volume during each phase of the study period. Panel A represents mean weekly running distance. Error bars represent one standard deviation. Panel B represents running, cross training (includes stationary bike and elliptical trainer), yoga and pilates, and weight training duration.

Figure 3: Schematic diagram of the alterations in blood volume and cardiac morphology prior to the Marathon and following 4 and 8 weeks of prescribed detraining. Percentage changes are detailed only where statistically significant. Downward arrow represents reduction. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; RVOT = right ventricular outflow tract; BV = blood volume; PV = plasma volume; EV = erythrocyte volume; LVPW = left ventricle posterior wall; RWT = relative wall thickness; RVAd = right ventricle area (diastole); RVPLAX = parasternal long axis view of the right ventricle.

562 **Table 1:** Baseline participant characteristics

	All (n=21)	Male (n=10)	Female (n=11)
Age (years)	32.2 (26.4,38.5)	35.3 (28.7,44.1)	27.6 (26.3,36.9)
Height (cms)	168 (161,174)	175 (172,178)	161 (160,167)
Weight (kgs)	69.7 (57.7,73.3)	73.6 (72.3,79.6)	57.7 (57.1,62.6)
BMI ($kg.m^{-2}$)	23.1 (21.9,25.8)	24.6 (23.3,26.4)	22.2 (20.9,23.0)
Marathon completion time (hh:mm)	4:21 (4:08,4:51)	4:17 (4:07,4:49)	4:22 (4:10,4:50)
Baseline $\dot{V}O_2$peak ($ml.kg^{-1}.min^{-1}$)	48.9 (42.2,54.0)	53.6 (46.4,57.1)	47.9 (40.4,49.8)

563 Values are presented as median (interquartile range); BMI = Body Mass Index;

564 $\dot{V}O_2$peak = Peak oxygen uptake.

565

Table 2: Effects of marathon detraining on body mass, blood volume and exercise physiology; values presented as median (interquartile range):

Characteristic	Pre-marathon	+ 4 Weeks	+ 8 Weeks	P
Body mass (kg) mean ± sd	69.4 ± 12.2	69.5 ± 12.8	69.8 ± 12.9	0.294
Blood volume				
Blood Vol., L	5.0(4.5,6.0)	4.7(4.4,5.9)†	4.8(4.3,6.1)	**0.024**
Blood Vol., ml.kg^{-1}	77.9(73.2,81.9)	76.3(69.4,80.2)†	76.3(70.1-79.2)	**0.018**
Plasma Vol., L	3.2(3.0,3.6)	3.0(2.8,3.3)†	3.0(2.7-3.6)	**0.004**
Plasma Vol., ml.kg^{-1}	47.7(44.9,51.5)	46.1(41.7,48.0)†	45.9(42.8,50.1)	**0.003**
Erythrocyte Vol., L	1.7(1.6,2.4)	1.8(1.6,2.5)	1.8(1.6,2.5)	0.745
Erythrocyte Vol., ml.kg^{-1}	28.5(27.4,31.3)	29.0(27.8,32.4)	28.9(27.3,31.9)	0.903
tHbmass, ml	563(536,797)	582(531,831)	575(522,833)	0.901
tHbmass, ml.kg^{-1}	9.5(8.9,10.3)	9.5(9.0,10.7)	9.4(8.9,10.5)	0.977
Cardiopulmonary Exercise Testing				
$T_{Lim,}$ minutes:seconds	17:47(17:10,18:53)	17:23(16:19,18:48)	17:04(16:03,18:18)	0.007
$\dot{V}O_2$ peak, L.min^{-1}	3.0(2.8,4.2)	3.3(2.8,4.2)	3.3(2.8,4.2)	0.12
$\dot{V}O_2$ peak, ml.kg^{-1}.min^{-1}	48.9(42.2,48.9)	50.2(48.9,54.6)	49.5(47.1,54.4)	0.08
$\dot{V}E$ peak, L.min^{-1}	111(93.7,153)	109.5(82.2,145.6)	109.5(88.8,150.3)	0.36
T_{VT}, minutes:seconds	13:14(12:53,14:25)	13:52(12:57,14:37)	13:11(12:43,14:34)	0.42
$\dot{V}O_{2\ VT}$, L.min^{-1}	2.45(2.34,3.31)	2.62(2.34,3.25)	2.64(2.38,3.27)	0.16

P values represent a significant slope across all three measurements. † denotes a highly significant difference from pre-marathon (P<0.01); Vol. = volume; tHbmass = total hemoglobin mass; T_{Lim} = Time to exhaustion; $\dot{V}O_2$ peak = maximal aerobic capacity; $\dot{V}E$ peak = maximal ventilation; T_{VT} = time to reach ventilatory threshold; $\dot{V}O_{2\ VT}$ = oxygen uptake at the ventilatory threshold.

Table 3a: Left heart structure and function; values presented as median (interquartile range):

Characteristic	Pre-marathon	+ 4 Weeks	+ 8 Weeks	P
Left Heart Structure				
LVIDd, cm	5.0(4.8,5.2)	5.0(4.8,5.2)	5.0(4.7,5.3)	0.777
LV wall thickness, mm	8(7,8)	7(6,8)†	7(7,8)*****	**0.02**
LV length, cm	8.5(8.2,9.0)	8.8(8.1,9.0)	8.8(8.4,9.0)	0.26
RWT, cm	0.30(0.26,0.33)	0.26(0.24,0.32)†	0.29(0.26,0.32)‡	**0.009**
LVEDV, mL	108(96,128)	117(95,121)	110(95,120)	0.843
LVEDV / BSA, mL/m^2	62.1(53.1,69.1)	61.5(55.5,71.7)	61.2(57.3,68.1)	0.859
LV mass, g	134(109,148)	116(107,134)†	118(106,131)†	**0.002**
LV mass / BSA, g/m^2	71.8(65.2,80.8)	66.8(60.2,73.0)†	67.2(60.2,71.5)†	**<0.001**
LA Vol., mL	30(24,39)	29(25,39)	30(27,35)	0.981
Left Ventricular Function				
Systolic Function				
Ejection fraction, %	65.2(62.2,67.0)	65.2(63.8,68.8)	64.9(60.9,68.9)	0.182
Basal S', $cm.s^{-1}$	11(10,13)	11(10,12)	11(10,12)	0.876
Longitudinal Strain, %	-21.6(-22.8,-20.3)	-20.7(-23.4,-20.2)	-20.3(-20.2,-18.3)	0.350
Diastolic Function				
LV Basal E', $cm.s^{-1}$	17(15,18)	16(15,17)	17(15,18)	0.623
LV Basal A', $cm.s^{-1}$	9(8,10)	9(8,11)	9(8,11)	0.13
Trans-mitral E-wave, $cm.s^{-1}$	0.78(0.72,0.95)	0.80(0.71,0.88)	0.79(0.71,0.93)	0.44
Trans-mitral A-wave, $cm.s^{-1}$	0.39(0.35,0.47)	0.42(0.31,0.49)	0.39(0.30-0.47)	0.854
E/A Ratio	1.9(1.6,2.3)	1.8(1.6,2.2)	2.0(1.7,2.6)	0.406

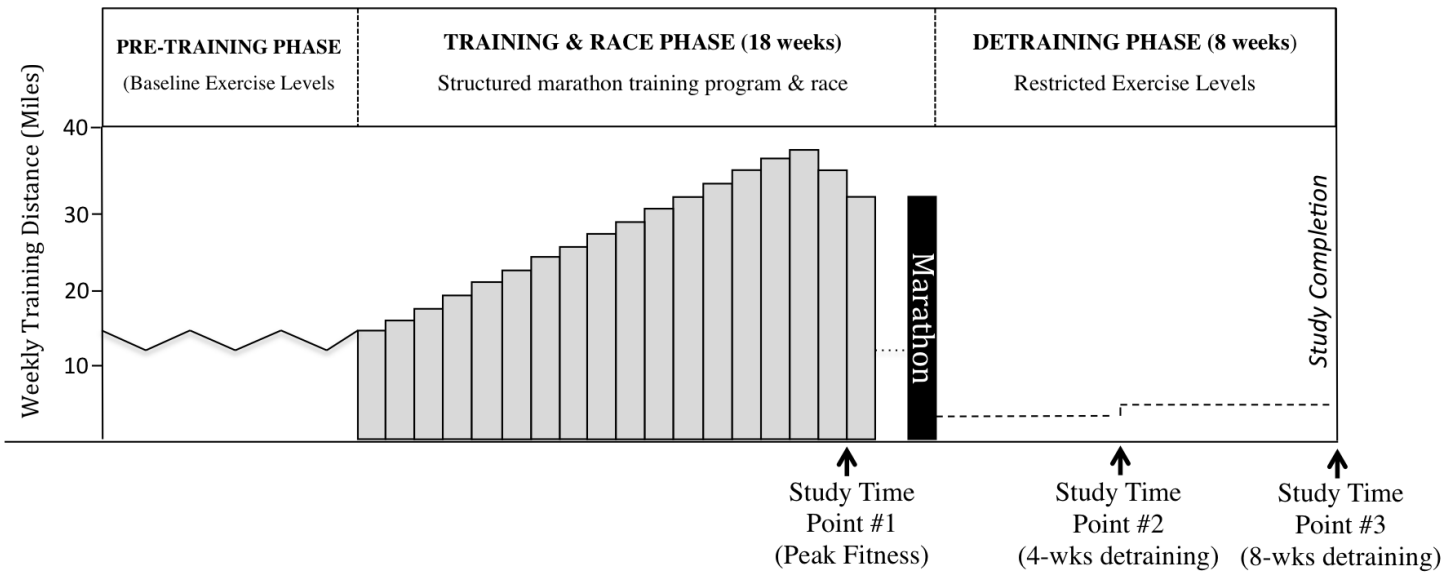
P values represent a significant slope across all three measurements. *denotes a significant difference from pre-marathon ($P<0.05$); † denotes a significant difference from pre-marathon ($P<0.01$); ‡ denotes a significant difference from 4 weeks post marathon ($P<0.05$). LVIDd = left ventricular internal dimension (diastole); LV = left ventricular; RWT = relative wall thickness; LVEDV = left ventricular end-diastolic volume; LA = left atrial; S' = peak systolic tissue velocity ; E' = early diastolic peak tissue velocity; A' = late diastolic peak tissue velocity; E-wave = early mitral inflow filling velocity; A-wave = late mitral inflow filling velocity; E/A ratio = ratio of early to late ventricular filling velocities.

Table 3b: Right heart structure and function; values presented as median (interquartile range):

Characteristic	Pre-marathon	+ 4 Weeks	+ 8 Weeks	P
Right Heart Structure				
RV Length, cm	8.4(7.9,8.9)	8.3(7.9,8.8)	8.0(7.6,8.7)†	**0.002**
RV Basal diameter, cm	3.5(3.2,3.9)	3.5(3.3,3.8)	3.4(3.2,3.7)*****	**0.03**
RVAd, mm^2	18.9(15.1,21.0)	18.6(16.4,21.9)	17.5(16.0,21.8)*****	**0.01**
RVAd / BSA, mm^2/m^2	10.7(9.5,11.9)	10.9(9.7,11.8)	10.4(9.2,11.4)***‡**	**0.02**
RVOT1, cm	3.1(2.7,3.3)	3.0(2.8,3.3)	2.9(2.5,3.0)†‡	**0.015**
RVOT2, cm	2.3(2.0,2.5)	1.9(1.8,2.1)†	1.8(1.7,2.1)†	**<0.001**
RVPLAX, cm	3.1(2.7,3.4)	3.1(2.6,3.4)	3(2.8,3.2)*	**0.014**
RV Strain, %	0.16(0.15,0.17)	0.15(0.14,0.17)	0.15(0.13,0.17	0.615
RA Area, cm^2	11.2(9.9,12.8)	10.8(8.8,12)†	10.5(9.4,12.2)*	**<0.001**
Right Ventricular Function				
Systole – Right Ventricle				
RVFAC, %	48.1(45.3,54.7)	49.4(45.7,53.5)	52.1(46.6,55.2)	0.412
Basal S', $cm.s^{-1}$	0.16(0.15,0.17)	0.15(0.14,0.17)	0.15(0.13,0.17)	0.54
TAPSE, mm	2.9(2.6,3.1)	2.8(2.3,3.1)	2.6(2.3,2.9)†	**0.012**

P values represent a significant slope across all three measurements. *significant difference from pre-marathon (P<0.05); † denotes a significant difference from pre-marathon (P<0.01); ‡ denotes a significant difference from 4 weeks post marathon (P<0.05). RV = right ventricular; RVAd = right ventricular area in diastole; RVOT1 = proximal right ventricle outflow tract; RVOT2 = distal right ventricle outflow tract; RVPLAX = parasternal long axis view of the right ventricle; RA = right atrium; RVFAC = right ventricular fractional area change; S' = peak systolic tissue velocity; TAPSE = tricuspid annular plane systolic excursion.

Figure 1


PRE-TRAINING PHASE
(Baseline Exercise Levels
TRAINING & RACE PHASE (18 weeks)
Structured marathon training program & race
DETRAINING PHASE (8 weeks)
Restricted Exercise Levels
Weekly Training Distance (Miles)
40
30
20
10
Marathon
Study Completion
Study Time Point #1 (Peak Fitness)
Study Time Point #2 (4-wks detraining)
Study Time Point #3 (8-wks detraining)

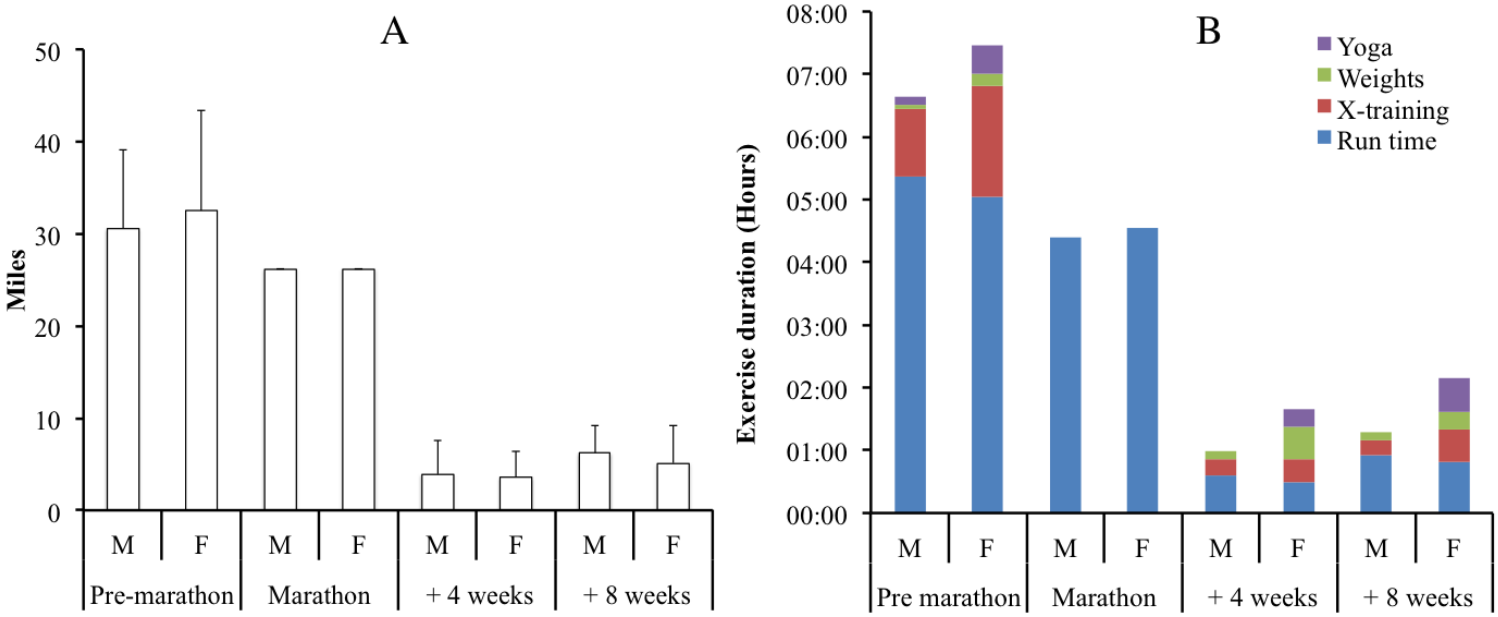
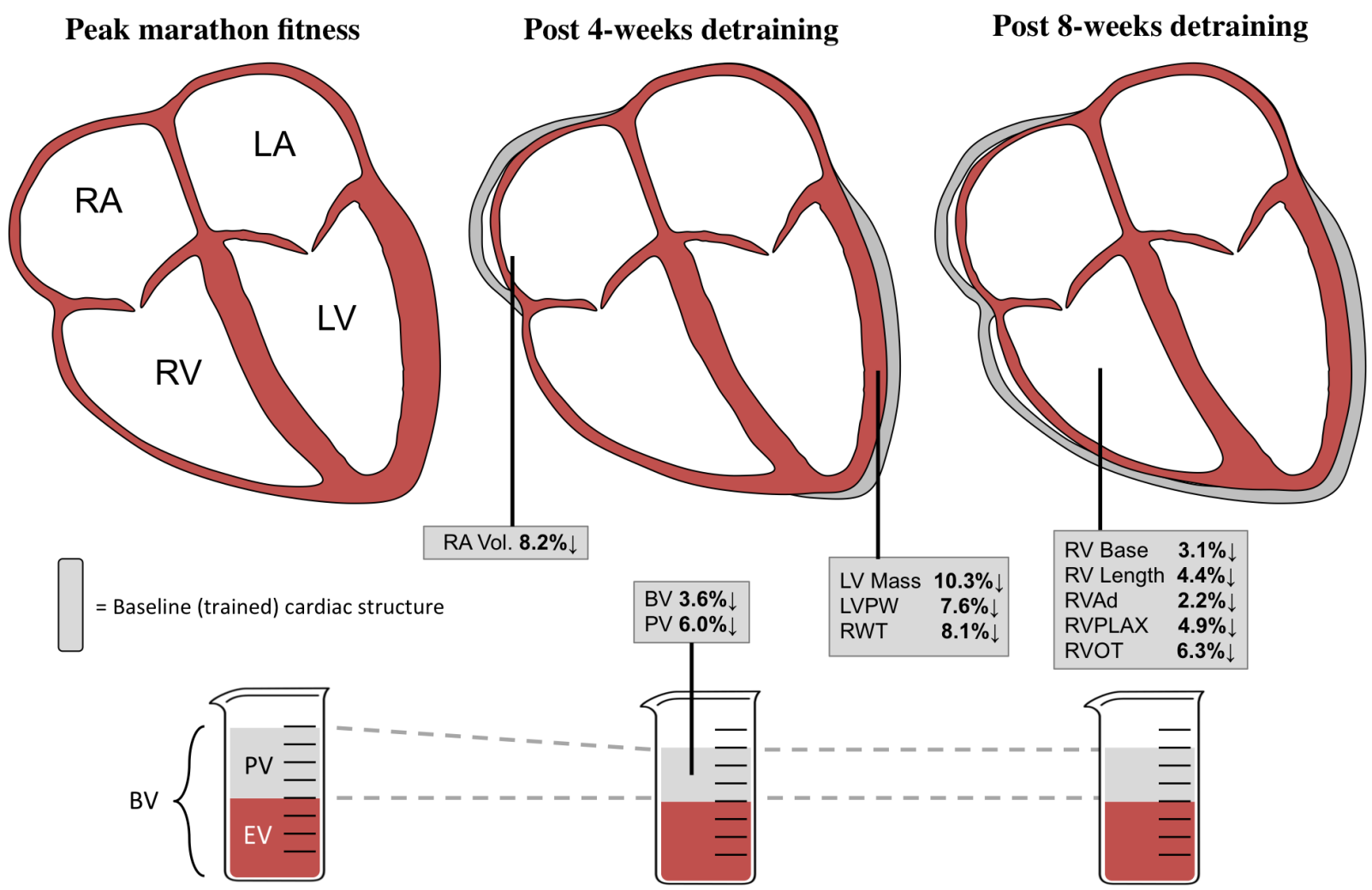

A
Miles
50
40
30
20
10
0
M
F
Pre-marathon
Marathon
+ 4 weeks
+ 8 weeks
B
Exercise duration (Hours)
08:00
07:00
06:00
05:00
04:00
03:00
02:00
01:00
00:00
Yoga
Weights
X-training
Run time
Pre marathon

Figure 3


Peak marathon fitness
Post 4-weeks detraining
Post 8-weeks detraining
LA
RA
LV
RV
RA Vol. 8.2%↓
LV Mass 10.3%↓
LVPW 7.6%↓
RWT 8.1%↓
RV Base 3.1%↓
RV Length 4.4%↓
RVAd 2.2%↓
RVPLAX 4.9%↓
RVOT 6.3%↓
= Baseline (trained) cardiac structure
BV 3.6%↓
PV 6.0%↓
BV
PV
EV