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Version: Accepted Version

Article:
Swoboda, P.P., Garg, P., Levelt, E. et al. (2019) Regression of left ventricular mass in athletes undergoing complete detraining is mediated by decrease in intracellular but not extracellular compartments. Circulation: Cardiovascular Imaging, 12 (9). ISSN: 1941-9651

https://doi.org/10.1161/circimaging.119.009417

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Regression of left ventricular mass in athletes undergoing complete detraining is mediated by decrease in intracellular but not extracellular compartments

Swoboda, Regression of myocardial compartments on detraining

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Total word count: 5967

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Abstract

Objectives

To establish if athletic cardiac remodelling assessed by cardiovascular magnetic resonance (CMR) is mediated by changes in intracellular or extracellular compartments, and whether this occurs by one or three months of detraining.

Background

Athletic cardiac remodelling can occasionally be difficult to differentiate from pathological hypertrophy. Detraining is a commonly used diagnostic test to identify physiological hypertrophy which can be diagnosed if hypertrophy regresses.

Methods

Twenty-eight athletes about to embark on a period of forced detraining due to incidental limb bone fracture underwent clinical assessment, electrocardiogram and contrast enhanced CMR within a week of their injury, and then one month and three months later.

Results

After one month of detraining there was reduction in left ventricle (LV) mass (130±28g to 121±25g, $P<0.0001$), increase in native T1 (1225±30ms to 1239±30ms, $P=0.02$) and extracellular volume fraction (ECV, 24.5±2.3% to 26.0±2.6%, $P=0.0007$) with no further changes by three months. The decrease in LV mass was mediated by a decrease in intracellular compartment volume (94±22ml to 85±19ml, $P<0.0001$) with no significant change in the extracellular compartment volume.

High LV mass index, low native T1 and low ECV at baseline were all predictive of regression in LV mass in the first month.

Conclusions

Regression of athletic LV hypertrophy can be detected after just one month of complete detraining and is mediated by a decrease in the intracellular myocardial compartment with no change in the extracellular compartment. Further studies are needed in athletes with overt and pathological hypertrophy to establish if native T1 and ECV may complement electrocardiography, echocardiography, cardiopulmonary exercise testing and genetic testing in predicting the outcome of detraining.

Key words

Cardiovascular magnetic resonance, athlete's heart, T1 mapping, extracellular volume fraction

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Commentary

Regular athletic training leads to physiological cardiac adaptation, namely biventricular dilatation and left ventricle hypertrophy, sometimes termed “athlete’s heart”. Cross-sectional studies using cardiovascular magnetic resonance T1 mapping imply that athletic left ventricle hypertrophy is mediated by an increase in the intracellular compartment (predominantly myocytes), with a relatively constant extracellular compartment (extracellular matrix and capillary vasculature).

We studied athletes who were about to embark on a period of forced detraining due to incidental limb bone fracture within a week of their injury, and then one month and three months later. On complete detraining athletic left ventricle hypertrophy regressed within a month, which was mediated by decrease in the size of the cellular compartment with no change in the extracellular compartment.

T1 mapping is a powerful tool to investigate mechanisms and reversibility of hypertrophy in athletes and may have a role in predicting the outcome of detraining. However, it remains to be validated in athletes with abnormal ECG and suspected cardiomyopathy.

Introduction

The regular training that is required to participate in competitive sport leads to physiological cardiac adaptation, namely biventricular dilatation and left ventricle (LV) hypertrophy, sometimes termed "athlete's heart". [1] LV hypertrophy that overlaps into the pathological range is relatively rare although does occur more commonly in participants of certain sports such as rowing and cycling, and in male and black athletes. [2]

Cardiovascular magnetic resonance (CMR) is commonly used in the assessment of athletes with LV hypertrophy as it allows both visualisation of the LV in multiple imaging planes and detection of focal scar by late gadolinium enhancement imaging (LGE). T1 mapping by CMR has been proposed to investigate cardiac tissue characteristics in athletes. Athletes have lower cardiac extracellular volume fraction (ECV) than sedentary controls and the fittest athletes have the lowest ECV. [3, 4] These cross-sectional findings imply that athletic LV hypertrophy is mediated by an increase in the intracellular compartment (predominantly myocytes), with a relatively constant extracellular compartment (extracellular matrix and capillary vasculature). Conversely, areas of hypertrophy in hypertrophic cardiomyopathy have increased ECV and initial data suggests that this divergent pattern might be useful to differentiate it from athlete's heart. [5]

Neither native T1 or ECV has been validated histologically in athletic hypertrophy. However preclinical models of athlete's heart have shown that increase in LV mass in exercise trained rats is not associated with increase in collagen fraction, therefore implying it is mediated by increase in myocyte mass. [6, 7]

Detraining is a commonly used test to diagnose athletic remodelling, although data supporting its use are limited. After long term cessation of training regression of hypertrophy and dilatation occurs in 80% of athletes with cardiac dimensions outside the normal range. [8] A minimum of

three months detraining is typically required to demonstrate regression of LV hypertrophy albeit with reduction in training rather than complete cessation. [9, 10] Compliance with detraining is often poor and it is unpopular with athletes of all level. There is therefore a need to improve the identification of athlete's heart by non-invasive imaging and predict the outcome of detraining.

We hypothesised that in athletes who completely stop all forms of training, regression of LV hypertrophy occurs in one month and is mediated by a decrease in intracellular compartment volume. We aimed to investigate whether T1 mapping findings at baseline are predictive of the cardiac consequences of detraining.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. We prospectively recruited athletes presenting to the emergency department in Leeds Teaching Hospitals NHS Trust with a limb bone fracture for which they were advised to stop training for a minimum of six weeks. Only athletes age 18-45 were included and had to be training for >4 hours a week for >2 years to participate. Exclusion criteria were any significant past medical history, any regular medication or self-reported use of anabolic steroids. Some athletes were able to recommence light training (fewer hours and lower intensity than pre-injury levels) prior to their three month appointment and this was not prohibited by the research team. The study was approved by the National Research Ethics Service (16/EM/0399) and all participants gave written informed consent.

Appointments occurred within a week of the injury, one month and three months later. At each appointment athletes underwent clinical assessment, contrast enhanced CMR and 12 lead electrocardiogram (ECG). 12 lead ECG (MAC500, GE Medical Systems, Milwaukee, WI, USA) was analysed by 2 physicians blinded to clinical details according to international

guidelines for ECG interpretation in athletes. [11] LV mass was estimated from ECG by the Sokolow-Lyon product, the voltage sum of the greatest S wave in V1/2 and R wave in V5/6. [12] A full blood count, for measurement of haematocrit, was taken at the time of intravenous cannulation prior to each CMR study.

Cardiovascular Magnetic Resonance Acquisition

Participants underwent CMR on a dedicated cardiovascular 3 Tesla Philips Achieva system equipped with a 32 channel coil and MultiTransmit® technology. Data were acquired during breath-holding at end expiration. Balanced steady state free precession (SSFP) cine images covering the entire heart in the LV short axis were acquired prior to contrast administration (repetition time (TR) 2.7ms, echo time (TE) 1.3ms, matrix 320 x 320, slice thickness 10mm with no gap, 30 cardiac phases).

T1 maps were acquired in a three short axis slices. Native T1 mapping used a breath-held Modified Look-Locker Inversion recovery (MOLLI) acquisition (ECG triggered 5s(3s)3s, single-shot, SENSE factor 2, prepulse delay 350ms, trigger delay set for end-diastole (adaptive), flip angle 20°, matrix 400 x 400, slice thickness 10mm, giving a reconstructed voxel size of 1.17 x 1.17mm).

0.15 mmol/kg of gadobutrol was administered through an intravenous cannula with a 10ml saline flush (Gadovist®, Bayer Pharma, Berlin, Germany).

Tissue tagging by spatial modulation of magnetization (SPAMM) (spatial resolution 1.51 × 1.57 × 10 mm3, tag separation 7 mm, ≥18 phases, TR 5.8ms, TE 3.5ms, flip angle 10°, typical temporal resolution 55 ms) was acquired in the three short axis slices. [13]

Late gadolinium enhancement (LGE) in matching LV short axis planes were carried out more than 6 minutes after contrast administration. Typical parameters were TR 3.7ms, TE 2.0ms, flip angle 25^{o}, matrix 512 x 512, slice thickness 8mm with 2mm gap.

Post contrast T1 mapping was carried out exactly 15 minutes following last contrast injection using 4s(3s)3s(3s)2s MOLLI acquisition with identical positioning and planning to the native T1 map.

Cardiovascular Magnetic Resonance Analysis

CMR data were assessed quantitatively using commercially available software blinded to detraining status (CVI42, Circle Cardiovascular Imaging Inc. Calgary, Canada). Epicardial and endocardial borders were traced offline on the short axis cine stack at end-diastole and end-systole to calculate LV and right ventricle (RV) end-diastolic volume (EDV), end- systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and LV mass. Papillary muscles were excluded from all measurements. Indexed cardiac parameters were divided by body surface area calculated by the Mosteller equation at baseline. [14] LGE imaging was analysed visually to assess for the presence of scarring.

Pre and post contrast myocardial T1 values with a 3-parameter exponential fit with Look-Locker correction were measured from short axis slices in the septum.Average measurements from the basal and mid ventricular slices were used. Data from the apical slice was not used because it was vulnerable to partial volume effects due to decreased wall thickness. ECV was calculated from native and post contrast T1 times of myocardium and blood pool and haematocrit as previously reported. [15]

Intracellular compartment volume was calculated by multiplying (1-ECV) x (LV mass/1.05). Extracellular compartment volume was calculated by multiplying ECV x (LV mass/1.05). [16]

Tagging analysis was conducted using inTag (v1.0 CREATIS lab, Lyon, France). Endocardial and epicardial contours were drawn on the short axis SPAMM sequences using a semi-automated process as reported previously. [13] Peak LV circumferential strain was measured for the three slices.

Statistical analysis and power calculation

Statistical analysis was performed using IBM SPSS® Statistics 22.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean ± SD or median (interquartile range) depending upon normality. Categorical variables were expressed as N (%). Paired data at baseline one and one month were compared by paired t test. When comparing three paired groups, analysis of variance (ANOVA) with repeated measures was used. $P<0.05$ was considered statistically significant.

Receiver operating characteristic analysis was used to determine the diagnostic accuracy baseline imaging parameters to predict regression of left ventricular hypertrophy (>10g) or cavity dilatation (>10ml). The diagnostic accuracy is expressed as area under the curve (AUC) and 95% confidence interval. Optimal sensitivity and specificity were calculated using Youden index. Variables were combined by binary logistic regression. AUCs were compared by using validated methods described by DeLong et al [17].

The study was powered to detect a 7.5% decrease in indexed intracellular compartment volume after one month of detraining. Assuming that baseline indexed intracellular compartment volume would be comparable to low performance athletes in our previous study, which was $47\pm6ml/m^2$ a minimum sample size of 25 athletes would be required (power=0.8, $\alpha=0.05$). [3]

Results

Thirty-five athletes agreed to take part in the study between November 2016 and March 2018. One athlete was unable to complete the study because of claustrophobia, one withdrew because of possible pregnancy and five withdrew consent after the first scan but before the second scan. The final cohort of 28, included 23 male and 5 female athletes with a median age of 24 (IQR: 21 - 30) years. Twenty-three athletes completed the whole protocol, with five athletes withdrawing after their one month scan because they had resumed full training. Baseline characteristics and their progression throughout the study are shown in **Table 1**. There were 31 ± 5 days between the baseline and one month scan, and 94 ± 10 days between the baseline and three month scans. Athletes trained in a wide range of sports including soccer 9, rugby 5, running 4, mixed sports 4, cycling 3, hockey 1, netball 1 and triathlon 1. Prior to their injury athletes trained median 7 hours per week (IQR 5-9).

Changes in Surface Electrocardiogram

On one month detraining there was a significant decrease in the voltage of the R wave in chest lead V_5 and the Sokolow-Lyon product, both electrical markers of left ventricular mass, **Table 2**. There were no significant changes in heart rate, PR interval or QTc.

Changes in Ventricular Morphology

After one month of complete detraining there was a 9.3g (7%, P<0.0001) reduction in LV mass with no further reduction between one and three months, **Figure 1 and Table 3**. This remained significant when indexed to baseline body surface area. In the first month there were significant increases in native T1 and ECV, **Figure 2**. There was a decrease in intracellular compartment volume (8.4ml, 9%, P<0.0001) with no significant change in the extracellular compartment mass, **Figure 3**.

After one month of complete detraining there were significant comparable decreases in the end diastolic volumes of both ventricles (ΔLV -8.2ml, -4.3%, P=0.003; ΔRV -7.8ml, -4.1%, P=0.03). By three months of detraining there was no further decrease in end diastolic volume of either ventricle, **Table 3**. There was no difference in these temporal changes when they were indexed to baseline body surface area. There was no significant change in LV EF throughout detraining, but there was a reduction in RV EF after one month due to decreased RV EDV.

No athlete had scarring detected on LGE imaging on any scan.

After one month of detraining there were non-significant absolute increases in peak circumferential strain all three levels (Δapex 0.4%, P=0.61; Δmid LV 1.1%, P=0.30; Δbase 1.4% P=0.06). There were no further changes at three months.

Comparison of those who had and who had not resumed training.

Between the one month and three month scan 11/23 athletes were able to restart light training, but were still not able to resume full training. When athletes were split according to those who had resumed light training (N=11) and those who had not (N=12) there was no difference in any LV or RV volumetric parameter, native T1 or ECV, **Supplementary Table 1**.

Baseline parameters to predict cardiac regression

High LV mass index, low native T1 and low ECV at baseline were all predictive of an absolute LV mass regression in one month of detraining of more than 10g (P=0.0006, 0.04 and 0.03 respectively) **Supplementary Table 2**. The difference in diagnostic accuracy between LV mass index and native T1 (P=0.58) or ECV (P=0.71) was not significant. When LV mass index was combined with either native T1 or ECV by a binary logistic model there was an improvement in diagnostic accuracy, **Supplementary Table 2**. None of LV EDV index, native T1 or ECV were predictive of absolute LV EDV regression in one month of detraining of more

than 10ml. Only RV EDV index, but not native T1 or ECV, were predictive of absolute RV EDV regression in one month of detraining of more than 10ml.

Discussion

We have shown that in athletes after just one month of complete detraining there is regression of LV mass, LV EDV and RV EDV. There was no further regression of any measure by three months of detraining. The regression of LV mass is mediated by a decrease in intracellular compartment volume (predominantly cardiac myocytes) with no change in extracellular compartment volume. High baseline LV mass is the strongest predictor of regression of LV hypertrophy after one month of detraining. Low native T1/ECV were also predictive of LV mass regression at one month and may have a role in the diagnosis of athlete's heart.

Insights into the mechanisms of athletic ventricular remodelling

We have demonstrated that regression in LV mass is mediated by a decrease in the intracellular myocardial compartment with no change in the size of extracellular compartment. Previous studies have demonstrated that athletes have lower ECV than sedentary controls and that the fittest athletes have the lowest ECV. [3,4] These studies were cross-sectional and therefore cannot be used to attribute causality. Our present study is the first to show a longitudinal relationship between LV mass, ECV and training, confirming the hypothesis that athletic hypertrophy is mediated by an increase in the cellular compartment.

When T1 mapping data and LV mass are combined it is possible to dichotomise the myocardium into cellular and extracellular compartments. This pattern is particularly relevant in hypertrophic phenotypes and has been validated most comprehensively in aortic stenosis where the derived extracellular compartment volume has a strong correlation with diffuse fibrosis on biopsy [18] and there is regression of both the cellular and extracellular compartments after aortic valve replacement. [16]

The most important differential diagnosis in the young athlete with LV hypertrophy is hypertrophic cardiomyopathy. CMR tissue characterisation has been histologically validated in hypertrophic cardiomyopathy and can be used to detect both diffuse fibrosis (increased ECV) and replacement fibrosis (focal LGE). [19, 20] High level athletes with hypertrophic cardiomyopathy are reported to have an altered phenotype with more prominent cavity dilatation but replacement fibrosis is still identified in 33%. [21] In hypertrophic cardiomyopathy focal fibrosis is progressive and the extent of LGE increases progressively over the course of the disease. [22] Saberi et al performed a study of 113 patients with hypertrophic cardiomyopathy who were randomised to a 16 week programme of moderate intensity exercise or standard care. [23] They reported that exercise training led to increased exercise capacity, but did not change ventricular volumes or the extent of focal fibrosis on LGE.

It would be appealing to conduct a study of detraining in high level athletes with HCM to investigate reversibility of changes in cellular and extracellular compartments. However, in practice such a study would be almost impossible given the small number of patients with hypertrophic cardiomyopathy who participate in competitive sport and their low willingness to voluntarily detrain.

T1 mapping in athlete's heart has not been validated histologically. However there are preclinical rat models of exercise induced cardiac hypertrophy, which suggest physiological hypertrophy is not mediated by increase in myocardial collagen. [6, 7] Benito et al trained rats to run on a treadmill for an hour a day. [24] After 8 weeks of training there was an 11% increase in LV mass, but no alteration in the hydoxyproline (a modified amino-acid found specifically in collagen) content of the whole left ventricle. These results are in keeping with our finding that athletic hypertrophy is mediated by preferential expansion of the intracellular compartment.

Effects of detraining on cardiac morphology

Previous studies have demonstrated that the heart is highly adaptable to physical training and cross sectional studies have clearly demonstrated a dose response relationship between degree of fitness (measured quantitatively by cardiopulmonary exercise test) and extent of LV and RV remodelling.[25] Arbab-Zadeh *et al* demonstrated in a longitudinal study of 12 previously sedentary subjects when trained for endurance sport development of cardiac athletic remodelling, albeit to a lesser extent than that seen in elite athletes. [26] They reported that in the first three months of training there were significant increases in RV EDV and LV mass with increase in LV EDV by 6 months. Most of the subjects were training for the marathon and it is not known whether these longitudinal patterns of remodelling apply to other sports or training regimes. Cardiac hypertrophy regression with detraining in our study was quicker, taking only one month, compared to remodelling on commencement of training which took at least 3 months in the previous study. [26] Although it should be noted the previous study did not conduct imaging at one month and participants in both studies conducted different sports with different baseline fitness.

The evidence of regression of athletic ventricular remodelling with detraining largely predates CMR and studies were conducted by echocardiography. Maron et al reported that LV mass measured by echocardiography in 6 Olympic rowers/canoeists decreased by 75g (24%) in a voluntary period (mean 13 weeks) of detraining following the 1988 Seoul Olympic Games. [9] Weiner et al reported a significant regression in LV mass of 4 college American Football players with LV hypertrophy after 3 months of voluntary detraining that returned to pre-training level by 6 months. [10] In a cohort of 40 Olympians Pellicia et al reported a 28% reduction in LV mass after long term detraining (1-13 years). [8] These studies included athletes with LV hypertrophy at baseline (>12mm interventricular septum) and included athletes at the pinnacle of fitness. The LV hypertrophy was more pronounced in these studies than ours,

reflecting the fitness of the athletes studied. The extent of LV mass regression was therefore greater (24-28% vs 7%). These studies defined detraining as reduction in exercise intensity rather than complete cessation perhaps explaining why regression of LV mass not reported until three months compared to one month in our study.

Pedlar et al performed echocardiography in 21 amateur runners after an 18 week training programme and then after 4 and 8 weeks when participants were limited to <2 hours of training a week. [27] Similarly to our findings they reported a 10.4% reduction in LV mass after 4 weeks with no change in LV EDV even 8 weeks post-race.

The finding of early regression of LV mass is not unique to athletes, and has been reported in by CMR in healthy individuals (N=5) after 6 weeks complete voluntary bed rest [28] and by echocardiography in astronauts (N=38) immediately after a 9-16 day spaceflight. [29]

The mean LV mass in the present study (130 ± 28g) was comparable to low performance male athletes in our previous study (129 ± 17g) who had a mean VO_{2max} of 60 ± 8mls/kg/min. If we had been able to recruit higher performance athletes with higher LV mass at baseline we may have been able to detect a further decrease in LV mass between one and three months. An alternative explanation is that the pattern of regression reflects the nature of detraining. Athletes were most incapacitated immediately after their fracture leading to most regression in this period. Throughout the subsequent recovery the levels of physical activity gradually increased affecting the regression response.

Using the same CMR tagging methodology we have previously shown that athletes have lower peak circumferential strain than sedentary controls. [13] In the current study, we found that in all three levels there was a no significant increase in strain on detraining, despite significant decreases in LV mass and intracellular compartment in the same period.

Limitations

In this study we relied upon self-reported abstinence from training and it is therefore possible that athletes carried out training that was not reported to the research team. We have not conducted an objective assessment of fitness using cardiopulmonary exercise test but this was not possible due to the nature of the participants' injuries. Athletes in this study participated in a range of sports which giving different patterns of athletic remodelling at baseline. We did not collect data on non-steroidal anti-inflammatory use which may have caused fluid retention and altered the myocardial extracellular compartment. We have not studied athletes with an abnormal ECG, overt LV hypertrophy (12-15mm) or cardiomyopathy and patterns of regression in these groups remains to be established.

T1 mapping has only been validated histologically in disease and is difficult to validate in athlete's heart. Native T1 (and less so ECV) vary by field strength, manufacturer and pulse sequence. At present it is recommended that normal values specific to the scanner and acquisition protocol are used to determine ECV in the athlete with unexplained LV hypertrophy [30].

Conclusions

Regression of athletic LV hypertrophy can be detected after just one month of complete detraining and is mediated by a decrease in the intracellular myocardial compartment with no change in the extracellular compartment. Further studies are needed in athletes with overt and pathological hypertrophy to establish if native T1 and ECV may complement electrocardiography, echocardiography, cardiopulmonary exercise testing and genetic testing in predicting the outcome of detraining.

Acknowledgements: We thank for their assistance Gavin Bainbridge, Caroline Richmond, Lisa Lewis and Margaret Saysell (CMR radiographers), Fiona Richards, Hannah Newman and Petra Bijsterveld (CMR clinical research nurses).

Funding: This work is supported by an Academy of Medical Sciences Starter Grant awarded to PS and the National Institute Health Research (NIHR) Leeds Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health. EDA is a British Heart Foundation Intermediate Clinical Research Fellow.

Disclosures: The authors have no relevant relationships with industry

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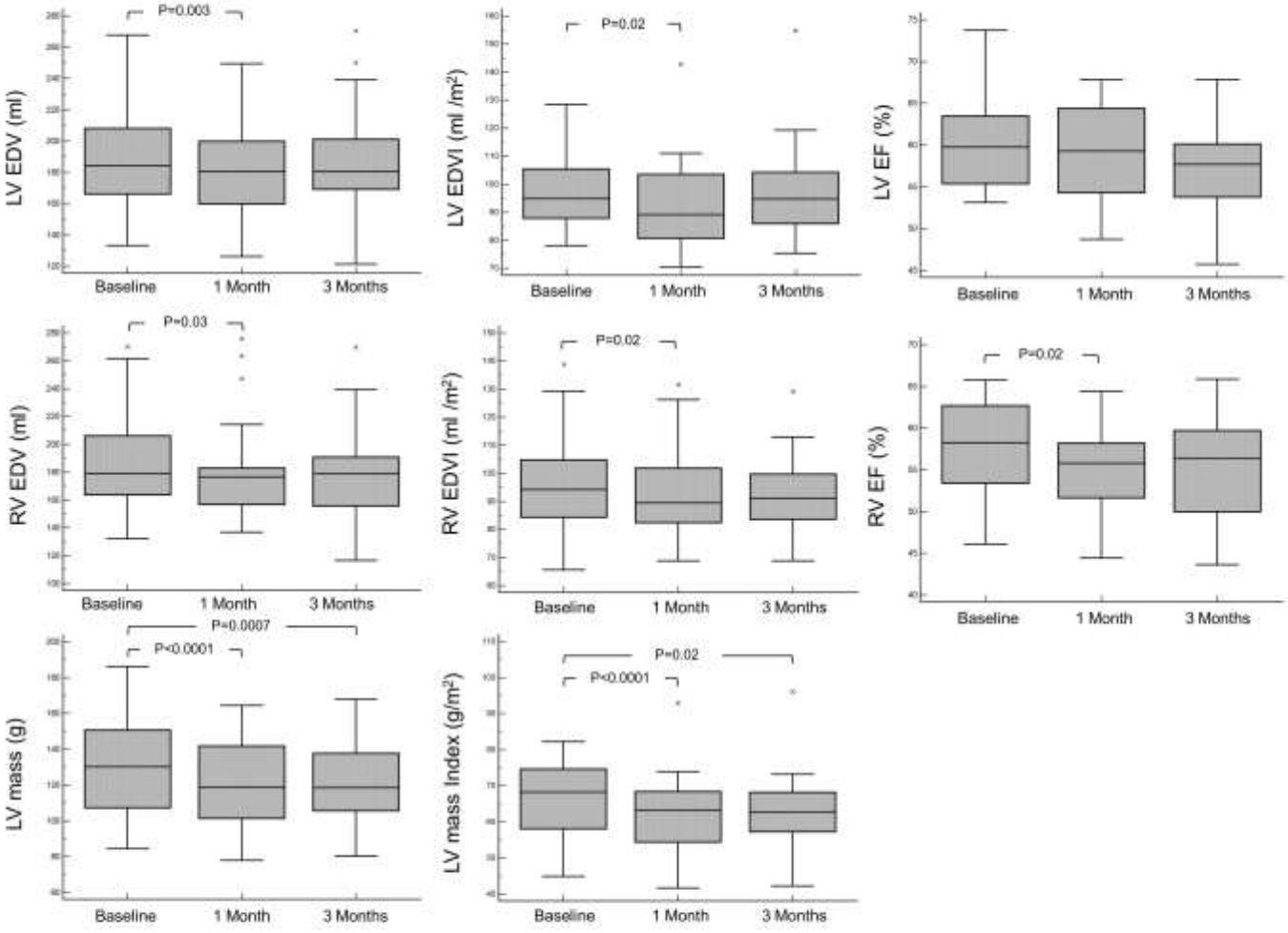

Figure 1. Change in cardiac morphology on detraining. Change in left and right ventricular end diastolic volume (EDV), ejection fraction (EF) and mass after one and three months detraining.

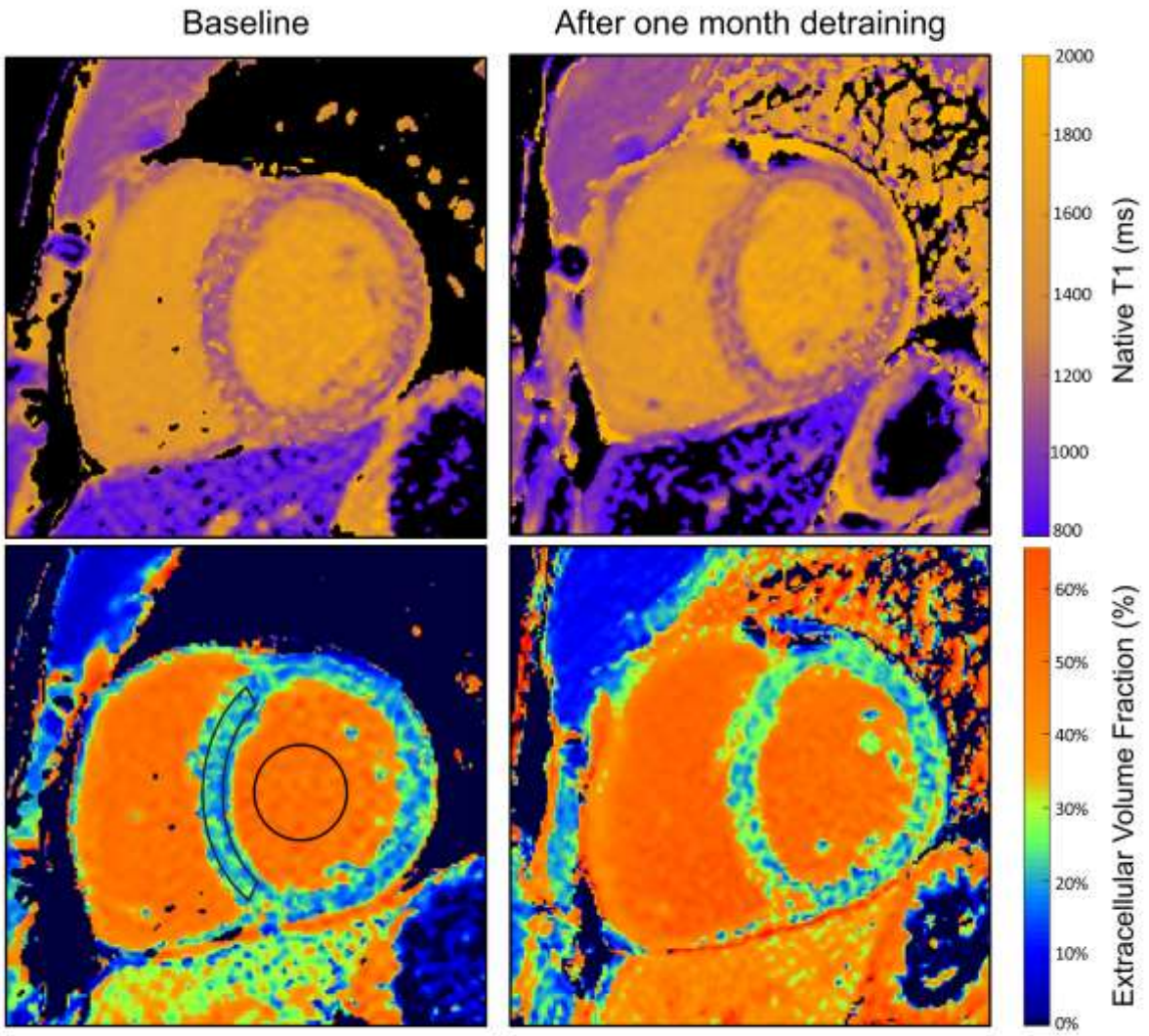

Figure 2. Native T1 and ECV (extracellular volume fraction) maps before and after one month of detraining. Native T1 (above) and ECV (below) maps from a rugby player before and after one month of detraining. Over this period native T1 increased from 1160ms to 1213ms, ECV increased from 19.5% to 23.3% and LV mass decreased from 186g to 164g. Typical myocardial and blood pool contours are shown in the lower left panel.

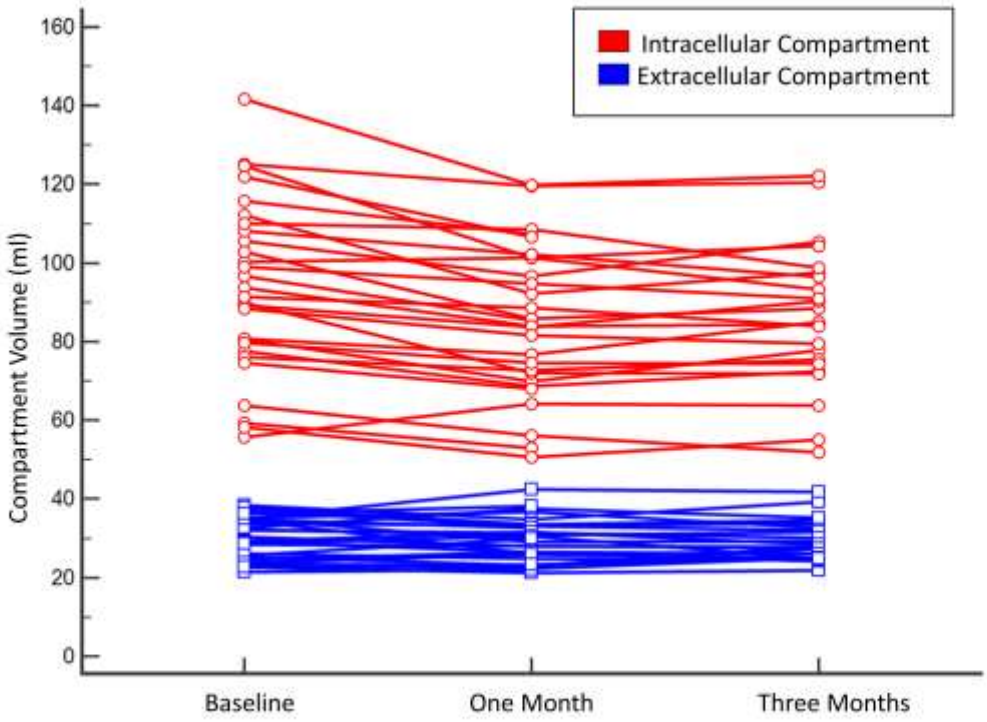

Figure 3. Change in cardiac compartment volumes on complete detraining. Individual participant data showing volumes of intracellular (red) and extracellular (blue) compartments at baseline and then after one and three months of detraining.

Table 1: Clinical characteristics subjects presented as mean ± standard deviation or median (interquartile range)

	Baseline	**One month detraining**	***P value vs baseline***	**Three months detraining**	***P value vs baseline***	***P value vs 1 month***
N	28	28		23		
Age	24 (21 - 30)					
Male Sex (%)	23 (82)	23 (82)		20 (87)		
Height (cm)	177 ± 8					
Weight (kg)	78 ± 14	77 ± 12	*0.21*	76 ± 12	*1.0*	*1.0*
Hours per week spent training	7 (5 - 9)	0 (0 - 0)	*<0.0001*	0.5 (0 - 6)	*<0.0001*	*0.0001*
Heart Rate	65 ± 10	68 ± 11	*0.20*	62 ± 9	*0.19*	*0.05*
Systolic Blood Pressure (mmHg)	121 (118 - 131)	122 (114 - 130)	*0.39*	119 (113 - 124)	*0.01*	*0.17*
Diastolic Blood Pressure (mmHg)	64 (60 - 75)	65 (57 - 72)	*0.64*	63 (54 - 68)	*0.16*	*0.18*

Table 2: Electrocardiogram findings

	Baseline	**One month detraining**	***P value vs baseline***	**Three months detraining**	***P value vs baseline***	***P value vs 1 month***
Heart Rate (bpm)	67 ± 11	70 ± 9	*0.17*	64 ± 8	*0.06*	*0.05*
PR interval (s)	145 ± 21	148 ± 22	*0.13*	147 ± 19	*0.64*	*1.0*
QTc inverval (s)	410 ± 19	416 ± 22	*0.08*	409 ± 21	*1.0*	*0.45*
SV_2, mV	14 ± 6	14 ± 6	*0.36*	14 ± 5	*0.52*	*1.0*
RV_5, mV	16 ± 5	14 ± 4	*0.006*	16 ± 6	*1.0*	*1.0*
Sokolow-Lyon Product, mV	31 ± 8	29 ± 8	*0.01*	30 ± 7	*0.82*	*0.52*
Incomplete RBBB, n (%)	5 (18)	4 (14)		4 (17)		
T wave inversion, n (%)	1 (4)	1 (4)		0 (0)		

Table 3: Cardiovascular magnetic resonance findings

	Baseline	**One month detraining**	***P value vs baseline***	**Three months detraining**	***P value vs baseline***	***P value vs 1 month***
LV EDV (ml)	190 ± 32	182 ± 30	*0.003*	188 ± 35	*1.0*	*0.38*
LV EDV index (ml/m^2)	98 ± 13	94 ± 15	*0.007*	98 ± 17	*1.0*	*0.34*
LV ESV (ml)	76 ± 17	75 ± 17	*0.72*	81 ± 21	*0.18*	*0.37*
LV EF (%)	60 ± 5	59 ± 5	*0.27*	57 ± 5	*0.07*	*0.69*
LV mass (g)	130 ± 28	121 ± 25	*<0.0001*	121 ± 23	*0.0007*	*1.0*
LV mass index (g/m^2)	66 ± 10	62 ± 11	*0.0005*	63 ± 11	*0.02*	*1.0*
RV EDV (ml)	188 ± 39	181 ± 35	*0.03*	180 ± 35	*0.59*	*1.0*
RV EDV index (ml/m^2)	97 ± 17	93 ± 15	*0.02*	93 ± 13	*0.53*	*1.0*
RV ESV (ml)	80 ± 18	81 ± 15	*0.76*	81 ± 19	*1.0*	*1.0*
RV EF (%)	57 ± 6	55 ± 5	*0.02*	55 ± 7	*0.51*	*1.0*
Native T1 (ms)	1225 ± 30	1239 ±30	*0.02*	1228 ± 47	*1.0*	*0.79*
ECV (%)	24.5 ± 2.3	26.0 ± 2.6	*0.0007*	25.6 ± 2.8	*0.04*	*1.0*
Extracellular compartment volume (ml)	30 ± 5	30 ± 5	*0.49*	29 ± 5	*1.0*	*1.0*
Intracellular Compartment volume (ml)	94 ± 22	85 ± 19	*<0.0001*	86 ± 18	*0.0002*	*1.0*
Circumferential strain Apex (%)	12.8 ± 4.5	13.2 ± 3.1	*0.61*	14.0 ± 3.2	*0.57*	*0.32*
Circumferential strain Mid LV (%)	13.4 ± 4.5	14.5 ± 2.7	*0.30*	14.1 ± 2.3	*1.0*	*1.0*
Circumferential strain Base (%)	13.0 ± 4.1	14.4 ± 2.6	*0.06*	14.1 ± 2.9	*0.45*	*1.0*