Exercise Induced Left Ventricular Remodeling

Among Competitive Athletes: A Phasic Phenomenon

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ABSTRACT

Background: Contemporary understanding of exercise-induced cardiac remodeling (EICR) is based on cross-sectional data and relatively short duration longitudinal studies. Temporal progression of EICR remains incompletely understood.

Methods and Results: A longitudinal repeated measures study design using 2-dimensional and speckle-tracking echocardiography was used to examine "acute augmentation" phase (AAP; 90 days) and more extended "chronic maintenance" phase (CMP; 39 months) left ventricular (LV) structural and functional adaptations to endurance exercise training among competitive male rowers (n=12, age 18.6±0.5 years). LV mass was within normal limits at baseline (93±9 g/m^2), increased after AAP (105±7 g/m^2; p=0.001), and further increased after CMP (113±10 g/m^2, p<0.001 for comparison to post-AAP). AAP LV hypertrophy was driven by LV dilation (ΔLVEDV = 9±3 mL/m^2, p=0.004) with stable LV wall thickness (Δwall thickness = 0.3±0.1 mm, p=0.63). In contrast, CMP LV hypertrophy was attributable to LV wall thickening (Δ wall thickness = 1.1±0.4 mm, p=0.004) with stable LV chamber volumes (ΔLVEDV = 1±1 mL/m^2, p=0.48). Early diastolic peak tissue velocity increased during AAP (-11.7±1.9 vs. -13.6±1.3 cm/s, p<0.001) and remained similarly increased after CMP.

Conclusions: In a small sample of competitive endurance athletes, EICR follows a phasic response with increases in LV chamber size, early diastolic function, and systolic twist in an acute augmentation phase of exercise training. This is followed by a chronic phase of adaptation characterized by increasing wall thickness and regression in LV twist. Training duration is a determinant of EICR and has implications for the assessment of myocardial structure and function in athletes.

INTRODUCTION

Exercise-induced cardiac remodeling (EICR) refers to changes in cardiac structure and function that occur in response to exercise training. Numerous structural aspects of EICR (i.e. athlete's heart) including ventricular chamber enlargement[1] and/or hypertrophy[2] have been described and several key determinants of the EICR process including age,[3] gender,[4] ethnicity,[5] and sporting discipline[6,7] have been established. However, contemporary understanding of EICR is based largely on cross-sectional data derived from competitive athletes and instructive but relatively short duration longitudinal studies of recreational exercisers.[8,9] Therefore, the temporal progression of EICR among competitive athletes remains incompletely understood.

The myocardial response to hemodynamic perturbation occurs in discrete phases in numerous settings. Specifically, physiological remodeling after 12 months of exercise training in previously sedentary people[9] and cardiac adaptations during pregnancy[10] occurs in different stages. Additionally, numerous cardiac disease states are defined by phasic adaptations in myocardial structural and function.[11,12] Whether the EICR that occurs among competitive athletes develops in a phasic sequence remains unknown due to the lack of long-term longitudinal data. Determining the time course for EICR represents a critical step in further defining the myocardial response to exercise training. Defining the characteristics and magnitude of physiological remodeling as a function of the duration of exercise exposure may ultimately help distinguish between physiology and pathology when athletic patients with equivocal imaging studies are encountered in clinical practice.

We hypothesized that the changes in LV structure and function observed early during a period of high intensity / high volume endurance exercise training would differ from those observed after more sustained exposure to this remodeling stimulus. To address this hypothesis, we utilized a repeated measures longitudinal study design to examine the time of course exercise-induced myocardial adaptations among a cohort of competitive athletes participating in structured team-based training.

METHODS

Study design. This was a prospective, longitudinal study of competitive university rowers that was designed to examine both short-term ("acute augmentation") and more extended-term ("chronic maintenance") cardiac adaptations to endurance exercise training. This 39-month study included 3 measurement time points. Time point #1 represents study enrollment and occurred at the time of university matriculation. Time point #2 occurred after an initial 90-day period of team-based exercise training, a time period during which we have previously documented numerous aspects of EICR in this population.[7,13-16] Thus, the time period between time points #1 and #2 is defined the "acute augmentation phase (AAP)" of training. Time point #3 occurred 36 months after time point #2 and thus the time period between time points #2 and #3 is defined as the "chronic maintenance phase (CMP)" of training. Anthropometric data (height, weight, and resting vital signs) and echocardiographic measurements as detailed below were obtained at all 3 study time points.

Study population. The study was conducted in the context of the Harvard Athlete Initiative (HAI), a collaborative between Massachusetts General Hospital and the

Harvard University Department of Athletics to evaluate myocardial structure and function in competitive athletes. Students participating in the men's competitive rowing program affiliated with the Harvard University Department of Athletics participated in this study. Individuals were considered eligible if they were first-year university student athletes, ≥18 years old, and recruited members of the men's varsity rowing program. This population was chosen for the present study because these athletes: 1) have completed pubertal development thus eliminating this as a confounding factor; 2) have ample baseline exercise experience accrued during participation in high school athletic participation to handle high volume / high intensity training with minimal risk of serious musculoskeletal injury; 3) experience a marked intensification of exercise training at the time of college matriculation (i.e. sufficient stimulus for "acute augmentation" adaptation); 4) experience sustained high volume / high intensity exercise training over several years (i.e. sufficient stimulus for "chronic maintenance" adaptation); and 5) train in a controlled team-based environment that permits accurate data capture of exercise exposure. Written informed consent was obtained from all participants. The Harvard University and Partners Healthcare institutional review boards approved the protocol before study initiation.

Exercise Training. During both the AAP and CMP study periods, all subjects participated in supervised team-based training sessions that were structured around outdoor rowing and indoor rowing ergometer training ≥5 days/week. Daily data were recorded on the duration and the type of training activities performed during the study periods. Training exposure was quantified as total number of hours/week and as hours/week dedicated to either endurance or strength activities. Endurance activity was

defined as running, cycling, swimming, rowing, or aerobic machine use at an effort sustainable for ≥20 min. Strength activity was defined as weight lifting, plyometric exercise, and sprint running drills. To establish a reference baseline, similar data quantifying training exposure during the 8-week pre-study period that preceded enrollment was obtained. All participants were questioned confidentially about anabolic steroid use and were excluded if a history of use was elicited. Additionally, all study participants were subject to standard National Collegiate Athletic Association (NCAA) drug testing policies, including urine and laboratory analyses for substances on a list of banned-drug classes. Subjects were excluded from the final data analysis if they undertook any breaks in training of ≥3 days during the AAP of the study period and ≥14 days during the CMP of the study period.

Cardiac structure and function. Transthoracic echocardiography was performed at all study time points using a commercially available system (Vivid-I, GE Healthcare, Milwaukee, Wisconsin) with a 1.9- to 3.8-mHz phased-array transducer. Echocardiography was performed by a single sonographer credentialed in cardiac ultrasound. Participants were imaged at rest ≥12 h after the most recent training session. Two-dimensional (2D), pulsed-Doppler, and color tissue Doppler imaging were performed from standard parasternal and apical transducer positions with 2D frame rates of 60 to 100 frames/s and tissue Doppler frame rates >100 frames/s. For each participant, apical and basal 2D short-axis images were obtained at the same frame rate to facilitate subsequent LV twist analysis. All data were stored digitally, and offline data analysis was performed (EchoPac, Version 7, GE Healthcare) by 2 cardiologists (RBW, ALB) at the conclusion of the study, blinded to the study time point.

Cardiac structural measurements were made in accord with current guidelines.[17] The LV ejection fraction was calculated using the modified Simpson's biplane technique. The LV length was measured in the apical 4-chamber view and was defined as the end-diastolic length from the mitral valve hinge point plane to the most distal endocardium at the LV apex. Resting heart rates were obtained from the final loop of each study. Stroke volume was calculated as: LV end-diastolic volume – LV end-systolic volume. Cardiac output was calculated as the product of stroke volume and heart rate. To facilitate application of clinical normality cut-points,[17] LV mass and LV end-diastolic volume were indexed using body surface area as calculated at each study time point. Longitudinal tissue velocities were measured offline from 2D color-coded tissue Doppler images and are reported as the average of 3 consecutive cardiac cycles. Diastolic tissue velocities are an average of medial and lateral values.

For the purpose of LV rotation and twist assessment, short-axis imaging standardization within and across subjects was maximized using previously published criteria.[15,18] Speckle tracking analysis was used to measure LV rotation, LV twist, and diastolic untwisting rate (UTR). LV rotation at the basal and apical short-axis planes was determined as the average angular displacement of 6 myocardial segments. Curves of basal and apical LV rotation, LV twist, and UTR were automatically generated by the EchoPac software. Peak systolic LV twist was calculated as the maximum instantaneous difference between peak systolic apical and basal rotation. Peak early diastolic UTR was defined as the peak untwisting velocity occurring in early diastole. LV rotation, LV twist, and UTR are reported as absolute and LV length corrected values using the LV length values measured at each time point. Intraobserver (IAV) and interobserver (IEV)

variability in our laboratory as assessed by linear regression have been previously published, [15,18] and are as follows: peak systolic LV twist (IAV, R^2=0.948; IEV, R^2=0.936) and peak early diastolic UTR (IAV, = R^2=0.942; IEV, R^2=0.921).

Statistical analysis. Measurements are presented as mean ± SD. Normality of distribution for all variables was assessed using the Shapiro-Wilk test. Linear mixed effects models with autocorrelated covariance structure in which study participant was included as a random effect were used to compare variables across study time points. Akaike's information criterion tool was used to select optimal covariance structures for each model. Post-hoc pairwise comparisons of variables (i.e. Time Point #1 vs. Time Point #2) were made using least squares means derived from the mixed effects models performed with Bonferroni correction. A p value of <0.05 was considered significant. Statistical analyses were performed with SPSS (Version 22, IBM Corp ©).

RESULTS

Clinical characteristics. Among initially enrolled athletes (men, n=22), 12 (age 18.6±0.5 years) completed the 39-month training period without interruption and were included in the final analysis. The 10 athletes who did not complete the study had interruptions in training either due to injury or withdrew from crew participation due to competing interests (i.e. academic pursuits). No participants were excluded because of anabolic steroid or other performance enhancing drug use. Clinical characteristics at the 3 study time points are reported in **Table 1.** Weight increased during the study period. Resting heart rate decreased and there was no change in systolic and diastolic blood pressure.

Training regimens. During the 8 weeks prior to enrollment, subjects performed 8.5±6.2

hours/week of training, which comprised 6.3±5.3 hours/week of endurance training and

2.2±1.7 hours/week of strength training. During the AAP of the study period, subjects

engaged in 13.6±0.9 hours/week of organized team training that was nearly exclusively

dedicated to endurance activity (endurance = 12.6±0.7 hours/week; and strength =

1.0±0.9 hours/week). During the CMP of the study period, similar and consistent levels

of endurance and strength exercise training (13.3±1.2 total hours/week; 12.2±1.1

hours/week of endurance training and 1.1±0.9 hours/week of strength training) were

maintained without interruption aside from scheduled tapers and brief training hiatuses

for the purposes of race preparation and recovery respectively.

Left ventricular structure. Changes in LV structural parameters are highlighted in

Figure 1. LV hypertrophy, defined by an LV mass index of ≥103 g/m^2, developed over

the course of the study period. Specifically, LV mass was within normal limits at baseline

(93±9 g/m^2), increased after the AAP (105±7 g/m^2; p=0.001), and further increased after

the CMP (113±10 g/m^2, p<0.001 for comparison to post-AAP). During the AAP,

increased LV mass was driven by an increase in LV end-diastolic volume (LVEDV)

(baseline 81.0±8.7 vs. post-AAP 89.7±9.9 mL/m^2, p=0.004) as there was no statistically

significant change in LV wall thickness (baseline 10.0±1.1 vs. post-AAP 10.2±1.1 mm,

p=0.63). In contrast, continued LV mass increase during the CMP was attributable to

increased LV wall thickness (post-AAP = 10.2±1.2 vs. post-CMP = 11.4±1.2 mm,

p=0.004) with stably elevated LVEDV (post-AAP = 89.7±9.9 vs. post-CMP = 91.0±6.9

mL/m^2, p=0.48). LV length, 9.0±0.5 cm at baseline, was unchanged after the AAP

(9.0±0.5 cm, p = 0.83) but was significantly increased following the CMP (9.5±0.4 cm, p=0.008 for comparison to post-AAP). There was progressive left atrial dilation (anterior-posterior dimension at baseline = 35.6±3.2 mm) after both the AAP (37.0±3.2 mm; p=0.03) and CMP (40.5±2.9 mm, p=0.007 for comparison to post-AAP) of training.

Application of Clinical Cut Points. In addition to depicting the changes in cardiac structure observed over the study period, **Figure 1** examines these findings in the context of established normal values as defined by the American Society of Echocardiography.[17] LV mass index was normal in all athletes at baseline, exceeded the upper limit of normal in 6/12 (50%) after AAP, and exceeded the upper limit of normal in 10/12 (83%) after CMP. Similarly, LV wall thickness was below the normal limit at baseline in all athletes, exceeded the upper limit of normal in only 3/12 (25%) after AAP, but exceeded the upper limit of normal in the majority of athletes (8/12; 66%) after CMP. In contrast, nearly all athletes (11/12; 92%) had indexed LVEDV exceeding the upper limit of normal at baseline and all athletes exceeded the upper limit of normal after both AAP and CMP. Finally, left atrial major dimension was normal in all athletes at baseline and after AAP, but exceeded the upper limit of normal in 7/12 (58%) after CMP.

Measures of left ventricular function. Measures of LV systolic function are detailed in **Table 2**. Compared to baseline, resting stroke volume was increased following AAP but did not increase further after CMP. Cardiac output did not increase significantly over the study period (due to the concomitant decrease in resting heart rate). There were small but statistically significant increases in several complementary parameters of LV systolic function including peak systolic tissue velocity and longitudinal strain that were most prominent after CMP. Measures of LV diastolic function are detailed in **Table 3**.

Diastolic function, measured by early peak tissue velocity (E_m), increased during AAP and remained stably elevated following CMP. In contrast, late diastolic tissue velocity (A_m) did not change during AAP but was significantly increased after CMP.

Left ventricular twist mechanics. Changes in LV rotation and twist parameters are highlighted in **Figure 2.** LV apical rotation and LV twist increased during AAP and then decreased over CMP, with post-CMP values similar to baseline values. Specifically, LV apical rotation was 8.4±3.3° at baseline, increased after AAP (12.6±3.6°, p=0.02) and then decreased after CMP (8.5±2.8°, p=0.03 compared to the post-AAP value, p=0.79 compared to the baseline value). In contrast, peak early diastolic UTR increased during AAP and remained stable during CMP (baseline = -102±38 °/s vs. post-AAP = -145±35 °/s, p=0.04; post-CMP = -139±29 °/s, p=0.79 compared to post-AAP). The pattern of change in UTR (increase in AAP and no further change in CMP) was similar to that observed with E_m, a complimentary measure of early diastolic function (**Table 3**).

Comparison of athletes completing the study protocol and athletes not completing the protocol. Comparison of baseline cardiac structural and functional measurements between the 12 athletes who completed the study and the 10 who dropped out revealed no statistically significant differences between the two groups. Specifically, comparison of LVEDV index (81.0±8.7 vs. 78.2±8.9 mL/m^2, p=0.47), LV wall thickness (10.0±1.1 vs. 9.4±1.3 mm, p=0.27), LV mass index (92.5±9.1 vs. 100.2±14.7 g/m^2, p=0.15), LA dimension (35.6±3.2 vs. 33.4±3.9 mm, p=0.44), LVEF (60.3±3.0 vs. 57.6±5.3 %, p=0.15), E_m (-11.7±1.9 vs. -10.9±0.8 cm/s, p=0.36), LV twist (13.3±3.8 vs. 15.9±6.4 °, p=0.30), untwisting rate (-102.4±37.6 vs. -138.2±57.8 °/sec, p=0.13), and longitudinal strain (-18.2±2.0 vs. -16.8±2.2 %, p = 0.21) showed no differences between the two

groups.

DISCUSSION

To our knowledge, this is the longest prospective repeated-measures study of detailed echocardiographic characterization of exercise-induced cardiac remodeling (EICR) to date. Data from this study suggest that EICR among young athletes follows a phasic pattern (**Figure 3**). In this 39 month longitudinal assessment of competitive rowers, we observed an "acute augmentation" phase of adaption characterized by ventricular dilation, enhanced early diastolic relaxation, and enhanced left ventricular systolic twist mechanics. In contrast, subsequent "chronic maintenance" adaptations included thickening of ventricular walls, augmentation in late diastolic function, and regression in resting left ventricular apical rotation and peak LV systolic twist. In aggregate, these data begin to define the time course of EICR among competitive athletes and support the notion that this process follows a step-wise remodeling response similar to that seen in less experienced exercisers and among patients with common forms of cardiovascular disease.

Prior cross-sectional, brief duration longitudinal studies, and one longer term evaluation of Italian Olympic athletes have provided precise quantification of cardiac structure in athletes[1,2,19] and some initial insights into the corollary functional myocardial mechanics of EICR.[13,15,20,21] EICR is a highly variable process with well-established determinants of this variability including factors such as age,[3] gender,[4] ethnicity[5] and sporting discipline.[6,7] The current study was designed to examine the temporal nature or

"time course" of EICR, which we hypothesized, would be an additional contributing factor to EICR variability. Data from this effort confirm this hypothesis and thereby support the notion that training duration represents an important determinant of both the magnitude and geometry of EICR.

Prior to this report, an important and recently published prospective study of EICR examined adaptations to a 12-month training program.[9] Arbab-Zadeh et al. utilized a progressive exercise protocol to prepare 12 sedentary subjects (men, n=7; age = 29±6 years) to complete a marathon (42 km) run. Specifically, participants advanced through an incremental training protocol that began with light aerobic work characteristic of a clinical cardiac rehab program (1.5-3 hours/week) and progressed to a more intense, recreational endurance athlete regimen (7-9 hours/week). In this setting, participants experienced a biphasic increase in LV mass with initial hypertrophy caused by LV wall thickening (0-6 months) and subsequent hypertrophy attributable to LV dilation (6-12 months). Our current study complements this important recent paper in several ways. First, our study examined the impact of consistent, relatively fixed, high intensity / high volume endurance exercise rather than an incremental load protocol and showed that this form of training also stimulates a phasic remodeling response. These distinctly different forms of exercise are both scientifically and clinically relevant as the former is common among those initiating exercise and the latter typical of competitive athletes who typically train over months to years without cessation. Second, while both papers characterize structural cardiac adaptations, corollary functional variables differ in a complementary fashion between the two studies. Specifically, Arbab-Zadeh et al. utilized invasive hemodynamic assessment to elegantly examine pre- and post-training pressure-volume

relationships while our study focused on adaptive changes in myocardial mechanics (i.e. tissue velocities, strain, and twist). Finally, and most importantly, we examined competitive athletes with substantial baseline exercise exposure (~ 8 hours/week) while Arbab-Zadeh et al. studied exercise naïve subjects who reached this exercise training "dose" in the final phase of study. Integration of the findings from these 2 studies suggests that exercise-induced LV remodeling is more complex than suggested by either study in isolation. Furthermore, a subsequent gender-specific analysis[22] of the data from the Arbab-Zadeh study facilitates additional comparison with the current study. Specifically, LV mass in our subjects was higher at both study initiation and study conclusion than that reported in the Arbab-Zadeh cohort which is consistent with the fact that our subjects entered the study with a background of exercise training and subsequently reached elite levels of training in the chronic maintenance phase. Comparison of these two distinct but complementary datasets highlights the notion that exercise-induced cardiac remodeling occurs over a continuum and therefore the phase of training should be considered when clinically evaluating an athletic patient."

Although the mechanisms underlying the differential adaptations observed in the acute augmentation phase (AAP) and chronic maintenance phase (CMP) in our study remain speculative, several possible explanatory factors deserve mention. We suspect that the principal underlying mechanism for the observed AAP LV dilation and enhanced early diastolic function was the plasma volume expansion that accompanies initiation or significant intensification of endurance exercise training.[23] A mechanistic role for plasma volume expansion is supported by the directionally consistent changes in many of the pre-load sensitive indices of myocardial structure (LVEDV and left atrial size) and

function (early diastolic relaxation velocity, apical rotation, twist) that we studied. In contrast, it is likely that the subsequent LV wall thickening that we observed with more extended training was driven by adaptive cellular hypertrophy. Adaptive myocyte hypertrophy, a process controlled by several recently proposed distinct cellular signal transduction pathways,[24] may require a more extended exposure to exercise than the 90-days that we utilized to examine AAP adaptations. It is noteworthy that the eccentric hypertrophy that developed during CMP was coupled with preservation of supra-normal diastolic function thereby emphasizing the uniquely adaptive nature of EICR in endurance athletes. Future work including the direct measurement of plasma volume and the use of recently developed imaging techniques capable of resolving cellular architecture[25] will be required to confirm these putative mechanisms.

Highlighting the novelty of the current investigation with respect to myocardial function, LV twist mechanics data from our study begins to reconcile one of the most intriguing inconsistencies in this field of cardiac mechanics. Several elegant cross-sectional studies have reported reduced resting LV apical rotation and LV twist in predominantly endurance trained athlete cohorts including professional soccer players[26] and elite cyclists.[20] In contrast, short duration longitudinal studies have shown that endurance training is associated with increases in LV apical rotation and LV twist.[15,27] Results from this current, more extended duration, longitudinal study help to resolve this apparent paradox. Specifically, our data show that LV apical rotation and LV twist increase after a short duration of endurance training then regress toward baseline values with continuation of training. Therefore, the apparent paradox in the literature regarding LV twist in endurance athletes is best explained by accounting for the athletes' "stage of

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training" with previous cross-sectional studies likely having captured more "seasoned" athletes at advanced levels of training (i.e. chronic adaptation) and prior short-term longitudinal studies having focused exclusively on an acute phase of adaptation. Future studies examining the relationship between physiologic perturbations such as exercise training and LV twist mechanics should be designed to address this important concept.

There are several distinct implications from our findings. From a scientific perspective, the observation that EICR follows a phasic trajectory is novel and advances our overall understanding of how the cardiovascular system responds to sustained high-intensity exercise in athletes. Additional longitudinal studies will be required to more precisely define the temporal nature of EICR, its reversibility with prescribed or elective deconditioning, and to determine whether the adaptive aspects of EICR may progress into a maladaptive phenotype after more extended periods of high intensity / high volume training. In the interim, any cross sectional work examining cardiac adaptation to exercise should be designed to account for prior cumulative exercise exposure, which our data suggest is an important confounding variable. In the clinical setting, our findings suggest that duration of exercise training should be considered during the diagnostic differentiation of physiologic adaptation (i.e. "athlete's heart") from occult cardiomyopathy. Specifically, LV dilation in the absence of substantial myocardial wall hypertrophy appears to represent a physiologic response to acute augmentation of endurance exercise. Physiological wall thickening in endurance athletes that exceeds 11 mm appears to require more extended endurance training time and represent a chronic adaptation. It is noteworthy that early diastolic function, as reflected by E_m velocity, was supranormal at both phases of adaptation thereby substantiating its use as a robust marker

of physiologic cardiac remodeling in endurance athletes regardless of prior training exposure.

Several limitations of this study warrant mention. In an attempt to reduce confounding factors, we deliberately studied a cohort of young, healthy, post-pubertal, Caucasian men. As such, our results may have limited generalizability and future similarly designed studies in alternative athlete populations are warranted, with comparison to a matched, sedentary control group. In addition, we acknowledge the relatively small sample size of our study population. However, a multi-year longitudinal study of competitive athletes poses numerous methodological challenges including subject attrition due to interruption in training due to injury and other factors and it is possible that this high rate of drop out introduced a component of selection bias. Despite the fact that comparison of baseline cardiac structural and functional parameters between the athletes who completed the study and those who dropped out revealed no statistically significant differences, it is possible that dropout bias may have played a role in the findings. Additionally, we were able to measure the volume (i.e. hours per week) of exercise in this study but have no data defining exercise intensity. While competitive rowing training inherently consists of both high volumes and high intensity of exercise, we are unable to comment on the relative importance of these fundamental training properties on our observations. Although our study design accurately captures the impact of real world competitive rowing participation and thereby maximizes the likelihood for direct applicability in the clinical setting, further work will be required to parse out the individual contributions of volume and intensity on cardiac remodeling. Finally, our study involved competitive rowers and therefore the pattern of remodeling

that we observed may be specific to this unique form of exercise training. Specifically, the repetitive surges in systemic arterial pressure that occurs during rowing, a sport characterized by high-dynamic and high static physiology,[28] may in part account for our observations including the increase in wall thickening that was observed following CMP.

In conclusion, we conducted a long-term, prospective longitudinal study in competitive athletes to determine the features and time course of exercise-induced cardiac remodeling in response to extended duration endurance exercise training. We observed that the acute augmentation phase of EICR is characterized by increases in LV chamber size, early diastolic function, and systolic apical rotation / twist while more chronic maintenance phase exposure is associated with increased wall thickness, augmentation in late diastolic function, and regression in LV apical rotation and twist. These findings indicate that EICR is a complex process that is determined in part by the stage and duration of exercise training. Further examination of prolonged exposures to exercise training will be necessary to determine normative values across the age and training spectrums of athletic patients. This information will be required to definitively distinguish the boundaries between physiology and pathology in athletic patients.

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Table 1. Comparison of baseline, post-"acute augmentation" phase, and post-"chronic maintenance" phase clinical characteristics

Clinical Parameter	Baseline	Acute Augmentation	Chronic Maintenance	P-value
Age, years	18.6±0.5	18.9±0.5*	21.9±0.5*·†	<0.001
Height, cm	188±8	188±8	188±8	1.0
Weight, kg	86.2±8.5	86.8±8.4	89.3±8.2*	<0.001
Body surface area, m^2	2.26±0.1	2.27±0.1	2.30±0.1*	0.002
Heart rate, beats/min	61±7	54±5*	51±5*	0.003
SBP, mmHg	126±10	124±8	125±9	0.87
DBP, mmHg	69±11	69±7	69±8	0.98

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

Values are mean±SD

Overall P-values were derived using linear mixed effects models. Pairwise comparisons were assessed using the Bonferroni method.

*P < 0.05 for comparison with baseline measurement
†P < 0.05 for comparison with acute augmentation measurement

Table 2. Comparison of baseline, post-"acute augmentation" phase, and post-"chronic maintenance" phase indices of LV systolic function

LV Systolic Function Parameter	Baseline	Acute Augmentation	Chronic Maintenance	P-value
Stroke volume, mL	110.3±11.3	134.2±21.3*	138.1±20.4*	<0.001
Cardiac output, L/min	6.7±1.1	7.2±1.1	7.0±1.1	0.52
LV ejection fraction, %	60.3±3.0	63.1±3.7	63.3±2.9	0.23
LV peak S_m, cm/s	7.1±0.9	8.0±0.9*	8.9±1.3*·†	<0.001
LV longitudinal strain, %	-18.2±2.0	-19.2±2.5	-19.9±2.5*	0.04

LV indicates left ventricular; S_m, systolic peak tissue velocity.

Values are mean±SD

Overall P-values were derived using linear mixed effects models. Pairwise comparisons were assessed using the Bonferroni method.

*P < 0.05 for comparison with baseline measurement
†P < 0.05 for comparison with acute augmentation measurement

Table 3. Comparison of baseline, post-"acute augmentation" phase, and post-"chronic maintenance" phase indices of LV diastolic function

LV Diastolic Function Parameter	Baseline	Acute Augmentation	Chronic Maintenance	P-value
Transmitral E-wave, cm/s	94±20	100±25	97±18	0.72
Transmitral A-wave, cm/s	38±7	35±8	44±9†	0.02
E/A ratio	2.6±0.7	3.1±1.1	2.3±0.9†	0.03
E_m, cm/s	-11.7±1.9	-13.6±1.3*	-13.3±1.5*	<0.001
A_m, cm/s	-3.4±1.0	-3.2±1.1	-4.9±1.1*,†	<0.001

A_m indicates late diastolic peak tissue velocity; E_m, early diastolic peak tissue velocity.

Values are mean±SD

Overall P-values were derived using linear mixed effects models. Pairwise comparisons were assessed using the Bonferroni method.

*P < 0.05 for comparison with baseline measurement
†P < 0.05 for comparison with acute augmentation measurement

FIGURE LEGENDS

Figure 1. Baseline, post-acute augmentation phase (AAP), and post-chronic maintenance phase (CMP) echocardiographic structural measurements. **A,** Left ventricular end-diastolic volume (LVEDV) index increased after AAP (90-days) of endurance exercise training while there was no further increase during the CMP of training (3-years). **B,** LV wall thickness did not change during AAP but was increased after CMP. **C,** LV mass and **D,** left atrial dimension increased during the both the AAP and CMP. All four structural parameters (A-D) are applied to established clinical cut points (red dashed horizontal lines represent the established clinical cut points). Overall *P values were derived from linear mixed effects models. P values denoted by brackets reflect pairwise comparison derived using the Bonferroni method.
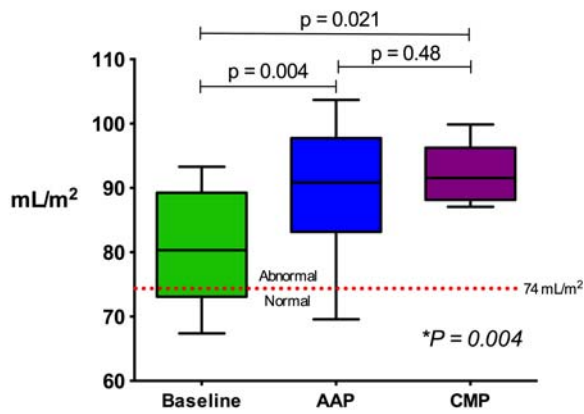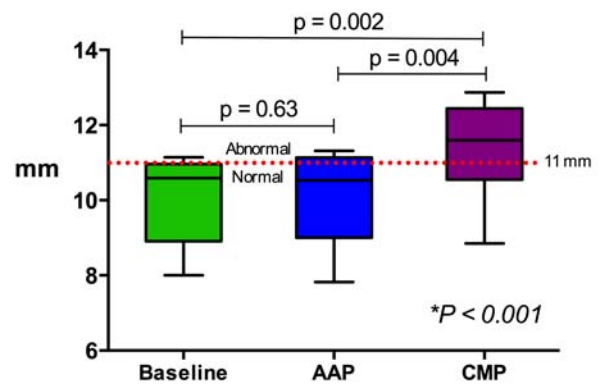
Horizontal lines indicate median values; whiskers, interquartile ranges.

Figure 2. Baseline, post-acute augmentation phase (AAP), and post-chronic maintenance phase (CMP) measurements of left ventricular (LV) twist mechanics. **A,** LV apical rotation and **C,** peak LV systolic twist were increased after AAP (90-days) and then reduced back to baseline values following CMP (3-years). **B,** LV basal rotation was stable over the study period. **D,** Peak early diastolic untwisting rate increased during AAP (a more negative value) and remained increased after CMP. Overall *P values were derived from linear mixed effects models. P values denoted by brackets reflect pairwise comparison derived using the Bonferroni method.

Horizontal lines indicate median values; whiskers, interquartile ranges.

Figure 3. Structural and functional left ventricular remodeling in response to 39 months of endurance exercise training among competitive athletes highlighting phasic adaptations.
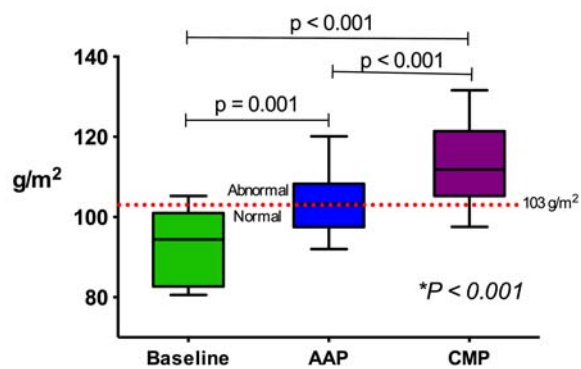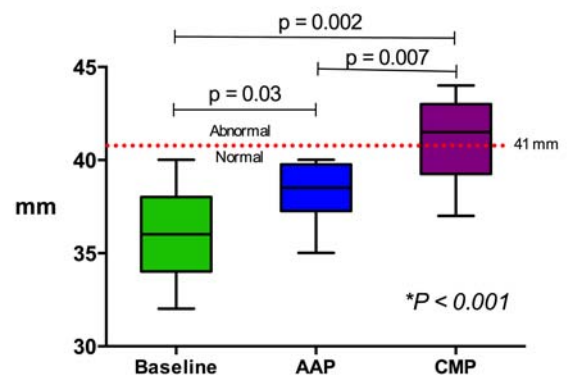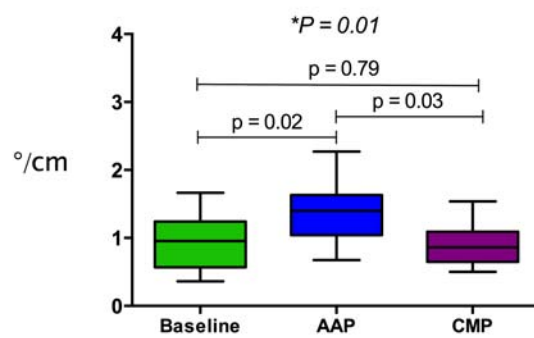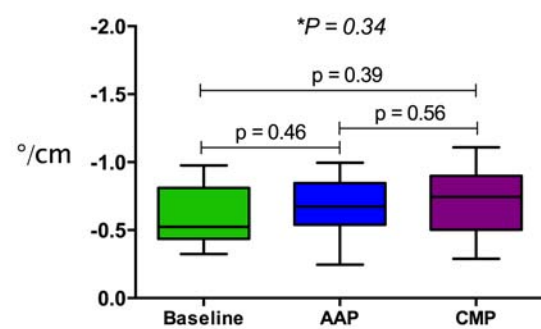
A. LV End-Diastolic Volume Index

p = 0.021
p = 0.004
p = 0.48

mL/m²

110
100
90
80
70
60

Abnormal
Normal
74 mL/m²

*P = 0.004

Baseline   AAP   CMP

B. LV Wall Thickness

p = 0.002
p = 0.004
p = 0.63

mm

14
12
10
8
6

Abnormal
Normal
11 mm

*P < 0.001

Baseline   AAP   CMP

C. LV Mass Index

p < 0.001
p < 0.001
p = 0.001

g/m²

140
120
100
80

Abnormal
Normal
103 g/m²

*P < 0.001

Baseline   AAP   CMP

D. Left Atrial Major Dimension

p = 0.002
p = 0.007
p = 0.03

mm

45
40
35
30

Abnormal
Normal
41 mm

*P < 0.001

Baseline   AAP   CMP

A.

Normalized LV Apical Rotation

P = 0.01

p = 0.79

p = 0.02   p = 0.03

°/cm

Baseline   AAP   CMP

B.

Normalized LV Basal Rotation

P = 0.34

p = 0.39

p = 0.46   p = 0.56

°/cm

Baseline   AAP   CMP

C.

Normalized Peak LV Systolic Twist

P = 0.005

p = 0.45

p = 0.004   p = 0.03

°/cm

Baseline   AAP   CMP
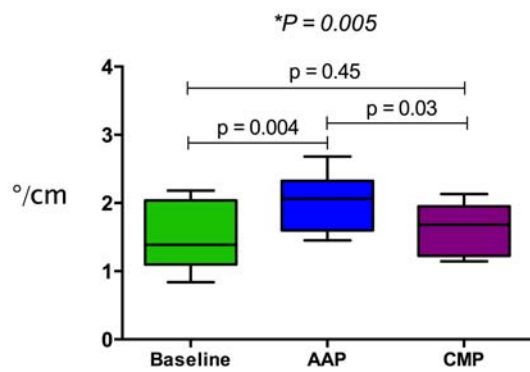
D.

Normalized Peak LV Diastolic Untwisting Rate

P = 0.02

p = 0.03

p = 0.04   p = 0.79

°/cm*s^{-1}

Baseline   AAP   CMP

Baseline LV Morphology

Wall Thickness = 10 mm
LV Mass = 92.5 g/m²
LV Length = 89 mm
LVEDV = 183 mL
LA = 35 mm
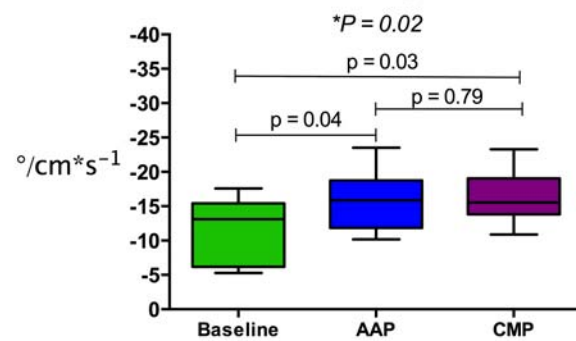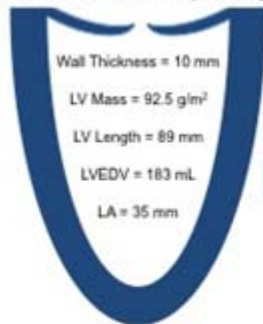
"Acute" Exercise
Exposure Phase

3 mos.

Eccentric LV Remodeling

Δ Wall Thickness = +2%
Δ LV Mass = +14%
Δ LV Length = -0%
Δ LVEDV = +11%
LA = +5%
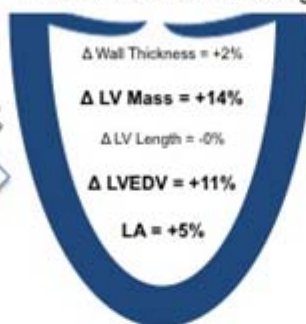
"Chronic" Exercise
Exposure Phase

36 mos.

Eccentric LV Hypertrophy

Δ Wall Thickness = +11%
Δ LV Mass = +9 %
Δ LV Length = +5.8%
Δ LVEDV = 2.0%
LA = +7%
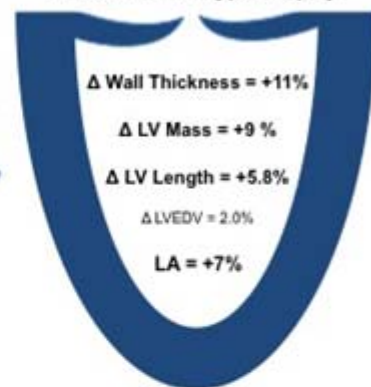
Bold font indicates p<0.05 for Δ from previous stage

Functional Parameter	Baseline Value	Acute Phase Δ	Chronic Phase Δ
LV Early Diastolic Relaxation Velocity (E_m)	11.7 cm/s	↑ 18%	No Change
LV Late Diastolic Relaxation Velocity (A_m)	3.4 cm/s	No Change	↑ 64%
LV Peak Systolic Twist Normalized for LV Length	1.5° / cm	↑ 44%	↓ 24%
LV Diastolic Untwisting Rate Normalized for LV Length	11.5°/cm*s⁻¹	↑ 58%	No Change