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Cardiac Remodeling in Response to 1 Year of Intensive Endurance Training

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Abstract

**Background**—It is unclear if, and to what extent, the striking cardiac morphologic manifestations of endurance athletes are a result of exercise training or a genetically determined characteristic of talented athletes. We hypothesized that prolonged and intensive endurance training in previously sedentary healthy young individuals could induce cardiac remodeling similar to that observed cross-sectionally in elite endurance athletes.

**Methods and Results**—12 previously sedentary subjects (29±6 yr; 7 men and 5 women) trained progressively and intensively for 12 months such that they could compete in a marathon. Magnetic resonance images for assessment of right and left ventricular mass and volumes were obtained at baseline and after 3, 6, 9, and 12 months of training. Maximum oxygen uptake (VO$_2$max) and cardiac output at rest and during exercise (C$_2$H$_2$ rebreathing) were measured at the same time periods. Pulmonary artery catheterization was performed before and after 1 year of training, and pressure/volume and Starling curves were constructed during decreases (lower body negative pressure) and increases (saline infusion) in cardiac volume. Mean VO$_2$max rose from 40.3±1.6 to 48.7±2.5 ml/kg/min after 1 year (p<0.00001), associated with an increase in both maximal cardiac output and stroke volume. Left and right ventricular mass increased progressively with training duration and intensity and reached levels similar to those observed in elite endurance athletes. In contrast, LV volume did not change significantly until six months of training, though RV volume increased progressively from the outset; Starling and pressure/volume curves approached, but did not match those of elite athletes.

**Conclusions**—One year of prolonged and intensive endurance training leads to cardiac morphologic adaptations in previously sedentary young subjects similar to those observed in elite endurance athletes; however it is not sufficient to achieve similar levels of cardiac compliance and performance. Contrary to conventional thinking, the left ventricle responds to exercise with initial concentric not eccentric remodeling during the first 6-9 months after commencement of endurance training depending on the duration and intensity of exercise. Thereafter, the left ventricle dilates and restores the baseline mass to volume ratio. In contrast, the right ventricle responds to endurance training with eccentric remodeling at all levels of training.

**Key words:** exercise training, exercise physiology, hypertrophy/remodeling, athletes heart, endurance training
Introduction

The capacity to generate a high cardiac output is essential to support the very high rates of oxygen uptake required for excellence in endurance sports\textsuperscript{1, 2}. Since the maximal heart rates of athletes compared to sedentary individuals are similar\textsuperscript{3,4,5} virtually all of this increase in cardiac output is achieved by an exceptionally large maximal stroke volume\textsuperscript{5}. This large stroke volume in turn is mediated predominantly by a large left ventricular (LV) end-diastolic volume\textsuperscript{5, 6}, which is the hallmark of “the athlete’s heart”\textsuperscript{7}.

Cross-sectional cardiac magnetic resonance imaging (cMRI) studies have consistently reported increased LV and right ventricular (RV) mass and volumes in endurance trained athletes compared to age and sex-matched sedentary subjects\textsuperscript{8, 9, 10, 11, 12}. The magnitude of the change in ventricular remodeling is dependent on the degree of static and dynamic exercise required for the specific sport; such studies have typically identified “eccentric hypertrophy” in endurance type athletes, with a balanced increase in volume and mass\textsuperscript{13, 14}. This type of eccentric hypertrophy is associated with a marked increase in LV compliance in endurance athletes which facilitates the elaboration of large stroke volumes during exercise via the Frank-Starling mechanism\textsuperscript{15}.

It is controversial however, if this extreme cardiac remodeling, is purely the result of prolonged endurance training or rather in part, a genetically determined characteristic of a talented athlete\textsuperscript{16}. For example, although longitudinal training studies do demonstrate increases in mass and volume with training\textsuperscript{17, 18} the magnitude of this increase and the associated increase in maximal aerobic power (VO\textsubscript{2max}) is well below that typically observed cross-sectionally in endurance athletes. Moreover, when endurance athletes detrain\textsuperscript{19}, even over prolonged periods of time, there is a reduction in both mass and volume, but not to the degree typically seen in...
sedentary individuals. Prior reports about the angiotensin converting enzyme allele polymorphism in athletes have fueled discussions about the genetic disposition to optimized cardiovascular adaptations in response to training.\textsuperscript{20-23} Alternatively, previous longitudinal studies may simply not have been prolonged or intensive enough to induce the same kind of cardiac adaptation in previously sedentary individuals as is typically observed in competitive athletes. The central hypothesis of the present study was that the cardiac adaptation to endurance training is a function of training load, rather than genetic predisposition. To test this hypothesis, we prescribed a progressive training plan, based on a strategy derived from optimal training by competitive athletes, to healthy sedentary volunteers and assessed RV and LV adaptations using cMRI and right heart catheterization in response to a 12-month endurance training program designed to enable each subject to compete in a marathon.

Methods

Subjects

Twelve previously sedentary men (n=7) and women (n=5) with a mean age of 29±6 years completed all the testing and training; one female subject completed all the initial testing but became pregnant in the second quarter of her training and was excluded from further study. None of the participants had engaged previously in any regular endurance training; subjects were excluded if they exercised for >30 min/day more than three times per week regularly using either dynamic or static exercise. Subjects were screened with a careful history and physical examination, as well as with an ECG and echocardiogram. None of the subjects smoked, used recreational drugs, or had significant chronic medical problems. All subjects signed an informed consent form, which was approved by the Institutional Review Boards of the University of Texas.
Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

**Exercise Training**

Endurance training was designed to enable all subjects to compete in a marathon at the end of a 12-month period (Fig 1). To determine specific training zones for optimal training prescription, heart rate at ventilatory and lactate thresholds, and VO$_2$max were determined by analysis of gas exchange and lactate obtained during incremental treadmill tests performed at baseline, and every three months to document exercise performance. “Maximal steady state” was estimated from the ventilatory and lactate thresholds according to standard criteria$^{24}$. Based on this maximal steady state heart rate and peak heart rate, five training zones were determined for individualized training prescription: zone 1 = recovery, zone 2 = base pace, zone 3 = maximal steady state or “threshold”, zone 4 = race pace/critical power, and zone 5 = intervals, as described previously$^{25}$. During the early phases of the training program, the subjects trained 3-4x/week for 30-45 minutes/session at base pace by brisk walking, slow jogging, swimming or cycling. As the subjects became fitter, the duration of the base training sessions was prolonged, including the addition of one long run per week, which was performed at the lower end of the base pace heart rate range. In addition, during the second and third quarters of the training program, sessions of increased intensity (maximal steady state and interval sessions) were added first once, then twice, and occasionally 3x/week. Interval sessions were followed the next day by recovery sessions to maximize performance gains. By the end of the year-long training program, subjects were exercising for 7-9 hours/week, including long runs of up to 3 hours, plus regular interval sessions on the track and races. The purpose of this template was to maximize training efficiency and to provide a periodization of the training program. This strategy of varying the intensity and duration of training sessions within any given week (microcycle),
applying periods of increasing stress followed by recovery from month to month (mesocycle) with an ultimate outcome goal of a specific competition (macrocycle) is routinely used by competitive athletes, and is widely considered the optimal approach to training. Modifications of the training program occurred with some subjects; however, the overall pattern of training was consistent with this template in all. Duration of exercise and training heart rates were carefully monitored and documented using heart rate monitors (Polar, Kempele, Finland).

To quantify the training stimulus we used the method of Banister et al for the calculation of the training impulse (TRIMP). This method multiplies the duration of a training session by the average heart rate achieved during that session, weighted for exercise intensity as a function of the heart rate reserve. Thus, exercise sessions of longer duration and/or higher intensity (higher heart rate, and higher weighting factor), such as interval workouts are assigned relatively higher TRIMP values than sessions of lower intensity. The details of this calculation as used in this study are available elsewhere, but for example, a 30 min workout at a HR of 150, in a young person with a resting HR of 50, and a max HR of 200 would equate to 46 TRIMPs; in contrast, a 60 minute workout at a HR of 140 would provide 73 TRIMPs, and a 28 minute interval workout at a HR of 190 would provide 100 TRIMPs.

Cardiac MRI measurements
cMRI was performed on a 1.5 T Philips NT MRI scanner. Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of 39 ms were obtained to calculate ventricular volumes as previously described. Ventricular mass was computed as the difference between epicardial and endocardial areas multiplied by the density of heart muscle, 1.05 g/ml. Previous studies in our laboratory and others have demonstrated that MRI with Simpson’s rule technique results in highly accurate and reproducible measurements of LV mass.
For LV volume determination, the endocardial border of each slice was identified manually at end-diastole and end-systole and volumes were calculated by summation\textsuperscript{31}. End-diastole was defined as the first frame in each sequence and end-systole the frame with smallest endocardial area. LV volumes were calculated using Simpson’s rule technique as previously described\textsuperscript{31}.

Mean wall thickness (MWT) for the entire LV included the papillary muscle and was calculated as previously described\textsuperscript{32}. For each short-axis slice the epicardial area (LV chamber plus myocardial wall) and endocardial area (chamber area) were determined using software on the imaging device. The “average” radius for each area was calculated by approximating the cross-section as a circle and using the equation for the area of a circle (Area=πr\textsuperscript{2} or r=√\text{Area}/\pi).

**Exercise Testing**

Measurements were made standing quietly on a treadmill, at two submaximal steady state work rates (5 min each) at approximately 33\% and 66\% of peak work rate, and during an incremental test to max. During initial familiarization sessions, two speeds were chosen for each subject: a brisk walking pace (usually 3.0 – 4.0 mph), and a comfortable jogging speed (generally 5-8 mph). These constant speeds were used for each subsequent test. After a brief rest, the incremental portion of the test was performed at the second submaximal speed, with the grade increased by 2\% every 2 minutes until subjective exhaustion, despite vigorous encouragement. Measures of ventilatory gas exchange were made using the Douglas bag technique. Gas fractions were analyzed by mass spectrometry (Marquette MGA1100) and ventilatory volume was measured by a calibrated dry-gas meter (Collins). VO\textsubscript{2max} was defined as the highest VO\textsubscript{2} measured from at least a 40s Douglas bag. In nearly all cases, a plateau in VO\textsubscript{2} was observed with increasing work rate, confirming the identification of VO\textsubscript{2max}\textsuperscript{1}. In addition, heart rate was
monitored continuously via ECG (Polar$^R$), and fingertip capillary blood was obtained during the second minute of each stage for measurement of lactate concentration.

At baseline, and at each quarterly testing session, all subjects underwent measurement of plasma volume using the Evans Blue dye indicator dilution technique. Briefly, after at least 30 min of quiet, supine rest, a known quantity of Evans blue dye was injected through a peripheral intravenous catheter, and venous blood was drawn at 10, 20, and 30 min after injection for the measurement of absorbance at 620 and 740 nm via spectrophotometry (DU 600, Beckman). Hematocrit was measured via microcapillary centrifuge, and blood volume was estimated by dividing plasma volume by 1- hematocrit, using appropriate corrections for trapped plasma and peripheral sampling.$^{33}$

**Cardiac Catheterization and Experimental Protocol**

Catheterization was performed at baseline and after the completion of the training period. All experiments were performed in the morning at least 2 hours after a light breakfast and at least 12 hours after the last caffeinated or alcoholic beverage in a quiet, environmentally controlled laboratory with an ambient temperature of 25° C. A 6 French balloon-tipped fluid filled catheter (Swan-Ganz, Baxter) was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. All intracardiac pressures were referenced to atmospheric pressure with the pressure transducer (Transpac IV, Abbott) zero reading set at 5 cm below the sternal angle. The mean pulmonary capillary wedge pressure (PCWP) was determined visually at end expiration and was used as an estimation of left ventricular end-diastolic pressure (LVEDP).

Cardiac output (Qc) was measured with a modification of the acetylene rebreathing technique using acetylene as the soluble and helium as the insoluble gas.$^{34,35}$ Stroke volume (SV) was calculated from Qc and heart rate measured during rebreathing. Left ventricular end-
diastolic volume (LVEDV) was measured with two-dimensional echocardiography using standard views and formulas as described by the American Society of Echocardiography\textsuperscript{36}. Images were obtained with an annular phased-array transducer using a frequency of 2.5 to 3.5 MHZ (Interspec Apogee CX) and stored on VCR tape for off-line analysis by a skilled technician. Measurements of left ventricular (LV) endocardial areas were made from the parasternal short-axis window at the level of the mitral valve and the papillary muscles and from the apical window in the four-chamber view, with care taken to avoid foreshortening of the major axis. The major-axis distance was measured from the apex to the mitral annulus. For the calculation of LVEDV for each subject, either a modified Simpson’s rule method, the area length method, or the bullet model (cylinder hemiellipsoid) was chosen on the basis of which views provided the most optimal endocardial definition\textsuperscript{37}. The same formula was used for each individual subject throughout the study.

**Testing protocols**

Cardiac filling was decreased by applying lower body negative pressure (LBNP) as previously described\textsuperscript{15, 38, 39}. Briefly, LBNP was achieved by placing the subject in a Plexiglas box sealed at the level of the iliac crest. The suction was provided using a vacuum pump with a variable autotransformer. Measurements of PCWP, Qc (and therefore SV), LVEDV, heart rate, and blood pressure were made after 5 minutes each of -15 mmHg and -30 mmHg LBNP. The LBNP was then released. After repeat baseline measurements to confirm a return to hemodynamic steady state (usually 20-30 min), cardiac filling was increased by rapid (200 ml/min) infusion of warm (37°C), isotonic saline. Measurements were repeated after 15 ml/kg and 30 ml/kg had been infused.
curves. For the purposes of the present study, we characterized and here define explicitly two
different but related mechanical properties of the heart during diastole: a) static stiffness or
overall chamber stiffness (or its inverse compliance) refers to the stiffness constant $S$, of the
logarithmic equation describing the $P/V$ curve (see below); and b) distensibility is used to mean
the absolute left ventricular end-diastolic volume at a given distending pressure, independent of
d$P$/d$V$, or $S$.

To characterize LV PV relations, we modeled the data in the present experiment
according to the logarithmic equation described by Nikolic et al$^{40}$:

$$P = -S \ln \left( \frac{V_m - V}{V_m - V_0} \right)$$

where $P=PCWP$, $V=LVEDV$, $V_0$ is equilibrium volume or the volume at which $P=0$, $V_m$ is the
maximal volume obtained by this chamber, and $S$ is a stiffness constant that describes the shape
of the curve. In addition, PV curves were also calculated using the difference between PCW and
RA pressure (PCW-RA) as an index of transmural filling pressure$^{41}$, in order to assess the
contribution of pericardial constraint.

**Statistical Analysis**

Continuous variables measured over the 12 month study duration were analyzed longitudinally
using linear mixed effects model repeated measures analysis. The repeated measures model had
five repeated measurements (time points at baseline, 3, 6, 9, and 12 months) and the study
participant was modeled as a random effect. The covariance structure was selected based on
Akaike’s Information Criteria and model parsimony. Multiple comparisons were made using the
least squares means contrasts that were derived from the mixed models, and use the Hochberg-
Bonferroni method to adjust for multiple testing. To express the dose-response relationship
between the exercise stimulus, changes in peak oxygen uptake and changes in cardiac
dimensions, the relationship between the quarterly training impulse (Monthly TRIMP) and cardiac adaptations at baseline, 3, 6, 9, and 12 months was estimated with quadratic polynomial regression models. To account for the correlation between repeated observations within the same individuals, random effects linear regression models were used. Similar regression models were used to assess pressure-volume curves with the addition of a fixed effect to test for the difference and response interactions between the baseline and training curves. A two-sided p value <0.05 was considered statistically significant. The analysis was performed using SAS version 9.3, SAS Institute, Cary, NC. Data are presented as mean ± standard deviation unless otherwise specified.

Results

All subjects successfully completed a marathon (n=10), Olympic distance triathlon (n=1), or 100 mile endurance cycling race (n=1) as the ultimate performance goal of the training program. The exercise training prescribed during this study led to significant changes in several resting parameters over the 12-month training period (Table 1). Lean body mass increased while the overall weight of the subjects did not change, indicating a decrease in body fat. Plasma volume increased slightly over the twelve-month period, though because the program had different start and stop dates over the course of the year in Texas, we speculate that the variable timing of heat acclimatization increased the variability of this outcome. Compared with baseline, heart rate significantly decreased (R-R interval significantly increased). Details of the hemodynamic and autonomic response to this training program have been reported previously25.

Training Impulse

An overview of the achieved TRIMP scores over the entire training period is given in Figure 1.
Average TRIMP score increased from 676±215 in the first month to 2528±925 in month 12. For comparison, competitive endurance runners achieve monthly TRIMP scores around 2500-3500\textsuperscript{12,43}.

**Maximal Exercise**

As expected, VO\textsubscript{2}\text{max} increased prominently with this training regimen from 40.3 at baseline to 48.7 ml/kg/min with training (Table 3; p<0.00001). Heart rate decreased at both submaximal and maximal work whereas maximum SV increased with training, which resulted in an overall increase of maximum cardiac output with training.

**Left ventricular adaptations**

All cardiac morphology measurements reported in the tables and figures were derived from cardiac MRI, except for the pressure/volume curves which because of the invasive instrumentation and manipulations of cardiac loading (LBNP and saline infusion) were derived from echocardiography. Results for measurements of LV mass, LVEDV, and mean wall thickness (MWT) are given in Figures 2 and 3. The largest increase in LV mass and MWT occurred in the first 6 months of endurance training. In contrast, LVEDV did not change significantly after three months and it increased only by 8% after six months reaching 39% of its maximum change within the testing period (Figure 3). The largest increase in LVEDV occurred during the last half of the training program, after the addition of interval sessions, and long bouts lasting more than 60 minutes. Similarly, SV showed its largest quarterly increase between 6 and 9 months. Accordingly, the LV mass to volume ratio increased from 1.44 at baseline to 1.58 at 3 month and 6 month ("concentric hypertrophy") and then returned to values close to baseline after 9 and 12 month of training, leading ultimately to the classic "eccentric hypertrophy" of endurance athletes. The average relative LV mass achieved in these subjects approached a level
close to that reported by the same laboratory in elite endurance athletes.\textsuperscript{44,45} When the mean quarterly values for LV mass were compared to the average TRIMP values obtained for each quarter there was a close positive relationship between training impulse and development of LV mass (Figure 4). Ventricular ejection fraction at rest was 69\% at baseline and 71\%, 71\%, 72\%, 71\% after 3, 6, 9, and 12 months respectively (statistically not significant).

**Right ventricular adaptations**

Results for measurements of right ventricular mass, right ventricular end-diastolic volume and stroke volume are given in Table 2. In contrast to the changes in the left ventricle, the mass and volume increased in an eccentric pattern at all levels of training such that the mass to volume ratio (0.46, 0.46, 0.45, 0.44, 0.47) did not change significantly throughout the training (Figure 2,3). The relative increase of mass (RV free wall only) and volume in the right ventricle (30\% and 27\%) was more pronounced than in the left ventricle (22\% and 20\% mean increase respectively).

**Pressure-Volume Curves**

These morphologic adaptations caused a parallel shift of the pressure-volume curve to the right after the 12-month training period (Figure 5a). Thus, for any given filling pressure LV\textsubscript{EDV} was greater after training compared to baseline (P=0.0001 for regression model), consistent with increased ventricular distensibility and/or reduction of pericardial constraint. Both V\textsubscript{max} and V\textsubscript{o} increased with training confirming the larger left ventricular dimensions and consistent with the eccentric remodeling observed by MRI. There was no difference of the S value with endurance training indicating that there was no change in overall chamber compliance; however when the influence of the pericardium was taken into effect by estimating LV transmural pressure (PCW – RA pressure)\textsuperscript{41}, the shift in the PV curve to the right persisted (p=0.05; interaction p=0.08),
particularly at higher filling volumes (5b). Together these curves suggest that a combination of reduced pericardial constraint, and improved myocardial compliance occurred after training.

**Starling Curves**

In accordance with the changes in the pressure-volume relationship there was a significant increase in SV for any given filling pressure after 12 months of training (random effects regression p<0.0001; interaction p=0.6 consistent with a parallel upward shift; **Figure 6**). Maximum SV increased from 100ml at baseline to 119ml after training.

**Discussion**

The primary new findings from this study were: 1) Prolonged and intensive endurance training in previously sedentary individuals resulted in a large increase in LV mass, approaching a level similar to that reported cross-sectionally in elite endurance athletes; 2) Contrary to conventional thinking, the LV responded to the initiation of endurance training with an increase in mass without a change in volume (concentric hypertrophy); an increase in LV end-diastolic volume occurred only after 6-9 months of progressive training restoring the baseline mass to volume ratio (eccentric hypertrophy); 3) In contrast to the LV, the RV responded to endurance training with a balanced increase in mass and volume, thereby maintaining a constant mass to volume ratio (eccentric hypertrophy) at all levels of training; 4) Despite these morphologic adaptations, and although maximal cardiac output and VO2max increased substantially during the training period they did not reach levels typically observed in trained endurance athletes; 5) One year of intensive endurance training led to a modest increase in LV distensibility and compliance, but remained substantially below that observed in elite athletes.

**Time course of the change and pattern of cardiac remodeling with endurance training**
Cross-sectional cMRI studies examining the ‘athletes heart’ have consistently demonstrated that endurance trained athletes have increased LV and RV volumes and mass (eccentric hypertrophy) compared to age and sex-matched healthy controls \(^8,11,46\). Longitudinal cMRI studies confirmed that eccentric ventricular remodeling is inducible in previously sedentary younger individuals with moderate to high-intensity endurance training over relatively brief periods of time\(^18,47,48\).

However, the extent of remodeling varied greatly among these reports and no longitudinal study reported adaptations as seen in elite athletes. We speculated that the reason for the inconsistent and insufficient (compared to athletes) cardiac remodeling previously reported resided in the training methods and duration of training used in these studies. We hypothesized that cardiac remodeling might be induced in previously sedentary young subjects similar to that observed in elite endurance athletes when an “optimized” training schedule is applied and when sufficient time is given for morphological adaptations. In the present study, we employed a training program which is shared with many elite athletes worldwide including careful periodization and allowing sufficient time for structural changes to occur.

A major new finding of our study is that the pattern of ventricular remodeling with prolonged endurance training was closely related to the intensity of exercise performed. During the first six months when lower intensity training was performed the increased LV mass was secondary to the increase in mean wall thickness (concentric hypertrophy). Thereafter when high-intensity interval training and longer duration exercise was performed, the LV dilated and restored the mass to volume ratio close to baseline values (eccentric hypertrophy). In accordance with Laplace’s law \(^49\), our finding that the LV responds to lower-intensity exercise with initial concentric hypertrophy suggests a primary ‘pressure overload’ stimulus, or perhaps
an adaptive response to the increased cardiac work during training as a function of both increased HR as well as arterial pressure. Thus contrary to a wide-held belief in sport cardiology, endurance exercise may not be a primary LV ‘volume overload’ stimulus; rather the pattern of LV remodeling depends on the intensity and duration of the exercise performed (Fig 4).

In contrast to the changes in the LV, the RV mass and volume increased in an eccentric pattern at all levels of training such that the mass to volume ratio did not change significantly throughout the training period. This finding is likely due to the relatively greater wall stress imposed on the RV compared to the LV during incremental to peak endurance exercise. For example, LaGerche et al. reported that the relative change in RV end-systolic wall stress from rest to peak exercise was significantly greater than the change in LV end-systolic wall stress (125% vs. 14%, respectively) in endurance athletes and non-athletes alike. Although RV and LV diastolic wall stress were not measured in these studies, other investigators have shown that the percent change in pulmonary artery systolic pressure is markedly higher than the change in peak systemic pressure during exercise (182% vs. 35%, respectively). Also, RV EDV and RV ESV are 2% and 15% greater than LV EDV and LVESV during peak exercise, which together with the above noted pressures would result in greater change in diastolic wall stress. Accordingly, it appears that RV is subject to both a ‘pressure and volume’ load during acute sub-maximal and maximal endurance exercise, which when repeated over years of training, may explain greater RV (compared to LV) remodeling reported in endurance trained athletes.

**Relationship between training intensity and LV mass**

The increase in cardiac mass was closely related to our training impulse score TRIMP. While there seemed to be a linear relationship between TRIMP and cardiac mass for the first 9 months,
the curve flattened towards the end of the training period. One explanation for the flattening of the curve may be the approximation of limits in cardiac growth, at least over the period of 1 year\textsuperscript{31}. Thus, at least in response to an intermittent stimulus of exercise training more training might lead to only a small further increase in cardiac mass. On the other hand, one of the limitations of the TRIMP score is that it does not distinguish well between the contribution of intensity and duration. For example, a shorter and highly intense training session would yield the same score as a very prolonged but less intense session. It is conceivable though, that these two types of training result in a different stimulus to myocardial growth and chamber remodeling. The most intense training sessions were maximized during the month 7-9 while towards the end of the year the focus of training shifted to longer, less intense sessions in order to prepare for the requirements of the upcoming competition. Therefore, we cannot exclude the possibility, that the change in training intensity near the end of the training year influenced the flattening of the LV mass/TRIMP relationship. Either of these hypotheses could also explain the apparent lack of continued increase, or even a slight decrease in resting cardiac output (Table 1) during the last quarter of the training program, though multiple other factors could be involved in this observation including changes in plasma volume, cardiovascular regulation, and perhaps even a slight degree of over-training in some of these subjects.\textsuperscript{25}

**Improvement in myocardial compliance and VO\textsubscript{2max} with endurance training**

Several investigators have shown that 6 months to 1 year of moderate-intensity endurance training increases VO\textsubscript{2max} in younger men and women (mean change=6 mlO\textsubscript{2}/kg/min)\textsuperscript{18,52,53}. We confirm these findings by showing that 1-year of endurance training increased VO\textsubscript{2max} by 8 ml/kg/min, though the training loads used at the end of our year-long training program were substantially greater than any previous study. Moreover, we extend prior work by demonstrating
the mechanism for the improvement in aerobic power with training. Specifically, the increase in VO2max was primarily due to the increase in maximal cardiac output (Table 3) secondary to the increase in maximal stroke volume, as maximal heart rate was significantly lower after 1-year of training compared to baseline. Given that myocardial contractility improved minimally (pre-load recruitable stroke work at rest was unchanged; data not shown) with training, the increase in stroke volume is likely due to increased LV filling. Figure 5 shows that 1-year of endurance training increased LEDV during cardiac loading, such as might occur during exercise, though we were unable to measure LVEDV accurately during maximal exercise. A consequence of this adaptation is that it will allow for greater utilization of the Starling mechanism and concomitant increase in stroke volume during maximal exercise. Our group has previously shown that endurance trained athletes have greater myocardial compliance compared to controls15. To the best of our knowledge, this is the first invasive hemodynamic study to report an improvement in myocardial compliance in previously sedentary individuals after 1-year of prolonged and intensive endurance exercise training.

Interestingly, while the relative cardiac mass of our subjects reached levels close to that of elite endurance athletes, their VO2max at the end of the training period still was substantially below that of even mediocre endurance athletes. Further, LV chamber compliance after 1-year of endurance training (supplemental Fig 1) was lower than that previously reported by our group for elite male athletes 15. Therefore even after 1-year of training, LV diastolic filling may be limited by pericardial constraint. We speculate (but cannot prove) that to attain the same myocardial and or chamber compliance as elite athletes may take years to occur. It is also possible that only training during growth and development, while the heart itself is growing along with body size, may be required to get the maximal cardiac training response and allow the
full expression and elaboration of the athlete’s heart.

**Limitations**

Because we did not include a control group that did not train, we cannot exclude the possibility that some of the changes observed in this study were a function of time and day-to-day variability, and not just to endurance training. However multiple studies from our group have shown that measures of cardiac compliance, and exercise performance are highly reproducible, and remarkably constant over periods of one year. In addition, our training program was progressive over time with the specific goal to achieve a level of training typically practiced by competitive athletes. However because of the intensive and invasive nature of our measurements, the total number of subjects studied was relatively small, and we did not include multiple groups of subjects that held their training constant at each quarterly “dose”. So we cannot distinguish between the effects of progression of training duration and intensity, from the effects of time alone.

**Conclusions**

One year of prolonged and intensive endurance training leads to cardiac morphologic adaptations in previously sedentary young subjects similar to those observed in elite endurance athletes; however it is not sufficient to achieve similar levels of cardiac compliance and performance. Contrary to conventional thinking, the left ventricle responds to exercise with initial concentric not eccentric remodeling during the first 6-9 months after commencement of endurance training depending on the duration and intensity of exercise. Thereafter, the left ventricle dilates and restores the baseline mass to volume ratio. In contrast, the right ventricle responds to endurance training with eccentric remodeling at all levels of training.
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Conflict of Interest Disclosures: None.

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1. Levine BD. \( \text{Vo}_2\text{max}: \) What do we know, and what do we still need to know? *J Physiol.* 2008;586:25-34.


heart: Right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. *J Am Coll Cardiol.* 2002;40:1856-1863.


1999;87:1313-1316.


Table 1. Resting Hemodynamics and Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>70±10</td>
<td>70±10</td>
<td>69±9</td>
<td>69±10</td>
<td>70±10</td>
<td>0.35</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>55.9±9.6</td>
<td>57.0±10.3</td>
<td>57.9±9.2*</td>
<td>57.7±9.4*</td>
<td>58.7±9.0*</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma Volume (L)</td>
<td>2.87±0.40</td>
<td>2.97±0.57</td>
<td>3.01±0.47</td>
<td>3.08±0.49</td>
<td>3.10±0.61*</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67±6</td>
<td>66±6</td>
<td>68±8</td>
<td>66±9</td>
<td>60±5*</td>
<td>0.004</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>113±6</td>
<td>113±8</td>
<td>107±4*</td>
<td>109±8</td>
<td>116±7*</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>67±6</td>
<td>63±7</td>
<td>61±3*</td>
<td>66±9*</td>
<td>68±6</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.5±1.1</td>
<td>7.1±1.1*</td>
<td>7.6±1.2*</td>
<td>7.5±1.5*</td>
<td>6.7±1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>TPR (dynes-s-cm⁻5)</td>
<td>1033±180</td>
<td>917±167*</td>
<td>820±146*</td>
<td>838±173*</td>
<td>1026±168</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure, TPR: total peripheral resistance.
Results presented as mean and standard deviation.
†p-value from repeated measures analysis time effect from baseline to 12 months.
* indicates statistically significant difference compared to baseline from mixed model repeated measures analysis.

Table 2. Adaptations of left and right ventricular mass, enddiastolic volume, mean wall thickness, and stroke volume in response to endurance training. Values are given as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV MASS (g)</td>
<td>168±38</td>
<td>188±36*</td>
<td>198±42*</td>
<td>199±45*</td>
<td>203±46*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>117±20</td>
<td>119±22</td>
<td>125±23*</td>
<td>136±22*</td>
<td>138±27*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVMWT (cm)</td>
<td>1.00±0.10</td>
<td>1.15±0.10*</td>
<td>1.20±0.11*</td>
<td>1.15±0.13*</td>
<td>1.16±0.10*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV SV (ml)</td>
<td>79±12</td>
<td>85±14*</td>
<td>89±16*</td>
<td>97±14*</td>
<td>98±19*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV Mass (g)</td>
<td>63±9</td>
<td>71±11*</td>
<td>72±14*</td>
<td>75±16*</td>
<td>82±15*</td>
<td>0.0005</td>
</tr>
<tr>
<td>RVEDV (ml)</td>
<td>136±25</td>
<td>156±30*</td>
<td>161±33*</td>
<td>172±27*</td>
<td>173±34*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV SV (ml)</td>
<td>78±12</td>
<td>87±14*</td>
<td>90±17*</td>
<td>97±14*</td>
<td>97±16*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV MASS: left ventricular mass, LVEDV: left ventricular enddiastolic volume, LVMWT: left ventricular mean wall thickness, LV SV: left ventricular stroke volume. RV MASS: right ventricular mass. RVEDV: right ventricular enddiastolic volume. RV SV: right ventricular stroke volume.
Results presented as mean and standard deviation.
†p-value from repeated measures analysis time effect from baseline to 12 months.
* indicates statistically significant difference compared to baseline from mixed model repeated measures analysis.
Table 3. Exercise Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max (ml/kg/min)</td>
<td>40.3±5.5</td>
<td>45.5±5.9*</td>
<td>47.4±6.4*</td>
<td>47.6±7.0*</td>
<td>47.4±7.2*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>197±12</td>
<td>187±8.0*</td>
<td>188±9.2*</td>
<td>185±9*</td>
<td>186±9*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Max stroke volume (ml)</td>
<td>98.1±18.2</td>
<td>108.2±21.6*</td>
<td>113.7±18.9*</td>
<td>115.1±25.3*</td>
<td>113.6±23.2*</td>
<td>0.002</td>
</tr>
<tr>
<td>Max cardiac output (ml/min)</td>
<td>20.1±5.1</td>
<td>22.4±5.7*</td>
<td>20.5±5.2</td>
<td>20.7±5.2</td>
<td>21.9±5.4*</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Results presented as mean and standard deviation.
†p-value from repeated measures analysis time effect from baseline to 12 months
* indicates statistically significant difference compared to baseline from mixed model repeated measures analysis.
Figure Legends:

**Figure 1.** Average training impulse TRIMP scores per month for all subjects over the training year. Group values are given as mean± standard deviation. Examples of training work outs provided in each quarter (vertical dashed line); bottom dotted line represents the average monthly TRIMP that would be accomplished in a typical cardiac rehab program exercising for 45 minutes at 75% of maximum predicted HR, 3x/week; upper bar represents the range of TRIMPs accumulated by typical middle distance runners as quantified by studies performed in the senior author’s laboratory (ref 41 and 42).

**Figure 2.** Changes in left (LV mass, left graph) and right (RV mass, right graph) ventricular mass measured by MRI every 3 months during the 1 year training program. Mean data (bars) ± SD are shown for each time point. Note differences in scale for each graph, with LV mass being ~ 2.5 x the RV free wall mass. Overall P value from the linear mixed effects model repeated measures analysis p<0.001 for each; * represent post-hoc comparisons for p<0.05. Individual data are reported separately in supplemental figure 1.

**Figure 3.** Mean changes ± SD in left (LVEDV, left graph) and right (RVEDV, middle graph) ventricular end-diastolic volume by MRI measured every 3 months during the training program. Note that in contrast to figure 3, the scale for LV and RV EDV is the same. Mean wall thickness is shown on the right graph to facilitate a visual representation of the year-long changes in cardiac morphology. Overall P value from the linear mixed effects model repeated measures analysis p<0.001 for each; * represent post-hoc comparisons for p<0.05. Individual data are reported separately in supplemental figure 2.
Figure 4. Quadratic regression analysis between average quarterly TRIMP values as a measure of training stimulus, and LV mass (top graph), LVEDV (bottom left) and LV mean wall thickness (LVMWT, bottom right). Solid black lines represent the random effect regression that uses all individual data points and models the study participant as a random effect to account for the lack of independence between observations on the same individual; dotted lines represent the 95% confidence limits for this regression. Individual data are reported separately in supplemental figure 3.

Figure 5. a. Pressure-volume curves representing pulmonary capillary wedge pressure (PCW) as an index of LV end diastolic pressure vs LVEDV obtained from 2-D echo, over range of LV filling produced by lower body negative pressure (two lowest values of PCW), quiet baseline (two middle values of PCW), and rapid saline infusion (two highest values of PCW) with modeling of the p/v curves as described in the text. Each data point represents the mean ± SE of all subjects pre (filled symbol) and post (open symbol) 1 year of training. LVEDV: left ventricular end-diastolic volume. S: stiffness constant; V_max: Maximum volume obtained by this chamber; V_0: Equilibrium volume. Asterisk marks statistically significant difference. b. Pressure-volume curves derived as in figure 6a but using the difference between PCW and RA pressure as an index of transmural filling pressure.

Figure 6. Starling curves representing pulmonary capillary wedge pressure (PCW) as an index of LV end diastolic pressure vs stroke volume (SV) over range of LV filling produced by lower body negative pressure (two lowest values of PCW), quiet baseline (two middle values of PCW), and rapid saline infusion (two highest values of PCW) as described in the text (pre vs post
p<0.0001). Each data point represents the mean ± SE of all subjects pre (filled symbol) and post (open symbol) 1 year of training.
Month of Training

Monthly TRIMP

- Typical Cardiac Rehab
  - Brisk walking
  - Slow jogging
  - 30 min
  - 3-5x/wk

- Typical Endurance Athlete
  - Training 7-9 h/wk
  - 45m-1hr base
  - 3 hr long runs
  - Threshold runs
  - Intervals/races

Figure 1
Figure 2
Figure 3
Figure 4

% change LV mass

% change LV EDV

TRIMP
Pulmonary Capillary Wedge Pressure (mmHg) vs. LVEDV (ml)

**PRE Training**
- \( S = 8.00 \)
- \( V_{\text{max}} = 131.30 \)
- \( V_0 = 42.18 \)

**POST Training**
- \( S = 9.01 \)
- \( V_{\text{max}} = 140.67 \)
- \( V_0 = 62.49 \)

* \( p < 0.05 \)
Figure 5B
Figure 6

The graph shows the relationship between PCWP (mmHg) and SV (ml) for both PRE and POST conditions. The graph indicates an increase in SV (ml) as PCWP (mmHg) increases. The PRE condition shows a more gradual increase compared to the POST condition, which has a sharper rise at higher PCWP values.
SUPPLEMENTAL MATERIAL
Supplemental Figure Legends

**Supplemental Figure 1:** Individual changes in left (LV mass, left graph) and right (RV mass, right graph) ventricular mass measured by MRI every 3 months during the 1 year training program. Light gray bars represent the mean values for each time point as depicted in manuscript Figure 2 with statistical analysis reported in the text.

**Supplemental Figure 2:** Individual changes in left (LVEDV, left graph) and right (RVEDV, middle graph) ventricular end-diastolic volume and mean wall thickness measured by MRI every 3 months during the 1 year training program. Light gray bars represent the mean values for each time point as depicted in manuscript Figure 3 with statistical analysis reported in the text.

**Supplemental Figure 3:** Quadratic regression analysis between average quarterly TRIMP values and LV mass (left graph), LVEDV (middle) and LV mean wall thickness (LVMWT, right). Individual curves are shown in the black lines; the solid gray line represents the random effect regression as depicted in manuscript Figure 4 with statistical analysis reported in the text.

**Supplemental Figure 4:** Pressure-volume curves representing pulmonary capillary wedge pressure (PCW) as an index of LV end diastolic pressure vs LVEDV obtained from 2-D echo, over range of LV filling produced by lower body negative pressure (two lowest values of PCW), quiet baseline (two middle values of PCW), and rapid saline infusion (two highest values of PCW) with modeling of the p/v curves as described in the text. The first two curves show the data for the men only from the current study using both pre and post training data. The far right curve shows the p/v curve for elite male endurance athletes modified from reference 15.
Supplemental Fig 1
Supplemental Fig 2
Supplemental Fig 3
Supplemental Fig 4

Elite curve from Levine et al, Circulation 1991;84:1016-23