PERICARDIAL-MEDIATED DIASTOLIC VENTRICULAR INTERACTIONS IN ENDURANCE-TRAINED ATHLETES DURING ORTHOSTATIC STRESS

by

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Abstract

Purpose: To assess diastolic ventricular interaction (DVI) and its consequences in endurance athletes and normally active individuals during lower body positive (LBPP) and negative pressure (LBNP).

Methods: Eight male endurance athletes (VO_2 max 65.4 ± 5.7 mL·kg^{-1}·min^{-1}) and eight normally active individuals (VO_2 max 45.1 ± 6.0 mL·kg^{-1}·min^{-1}) underwent three experimental days: 1) assessment of VO_2 max 2) a negative orthostatic tolerance test, and 3) LBPP (0 to 60 mmHg) and LBNP (0 to -80 mmHg) during which time ventricular volumes were examined via echocardiography.

Results: All normally active individuals completed the tolerance test on experimental day two, but seven out of eight athletes did not complete this test due to signs of presyncope. There were no statistically significant differences between groups in resting left ventricular end-diastolic volume (LVEDV), stroke volume, or cardiac output. In response to LBNP on experimental day three there was a similar decrease in right ventricular (RV) end-diastolic area in both groups. However, there was a differential group response to LBNP (a greater decrease in the endurance athletes) during day three with respect to LVEDV ($p<0.05$). The endurance athletes also had significantly greater decreases in stroke volume and cardiac output during LBNP compared to the normally active group ($p<0.05$). During LBPP on day three, the endurance athletes showed greater increases in LVEDV and stroke volume, despite similar responses in RV end diastolic area ($p<0.05$).

Conclusion: Endurance athletes likely had a relatively slack pericardium causing minimized DVI during conditions of orthostatic stress, whereas the normally active

individuals appear to have more marked DVI during orthostatic stress which allows for a

paradoxically greater maintenance of LV filling in response to LBNP.

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Introduction and Literature Review

The Pericardium and Diastolic Ventricular Interaction

The four chambers of the heart are haemodynamically connected by blood flow, physically connected by the structures they share, and interdependent due to the common encasing of the pericardium [1-3]. The pericardium is comprised of an inner serous membrane (visceral pericardium), and a tough, fibrous outer layer (parietal pericardium) consisting primarily of collagen [4]. The visceral layer is responsible for lubricating the heart within the thoracic cavity, allowing it to beat in an almost frictionless bath [5]. The parietal pericardium serves to protect the heart from the spread of infection [4, 6], position the heart within the chest [4], and prevent extreme distension of the myocardium [6, 7].

Although the pericardium may prevent myocardial distension, this characteristic may also constrain diastolic filling. The role of the pericardium as a limiting factor to cardiac filling has been investigated since 1898 [7]. Barnard discovered that an intact cat heart could hold approximately 12 mL of blood. However, upon removal of the pericardium, the myocardium held an additional 11 mL, nearly doubling the initial total [7]. Barnard also demonstrated that an intact pericardium allowed the heart to sustain an additional 200 mmHg before rupturing [7]. Initially, it was proposed that by limiting diastolic filling, the pericardium reduces stress on the myocardium preventing cardiac hypertrophy, dysfunction, or rupturing [7, 8] .

It has since been established that the pericardium exhibits a J-shaped (refer to figure 1, page 34) pressure-volume relationship, whereby small initial increases in pericardial volume are met with small increases in pressure, but further increases in

cardiac volume are met with large increases in pressure [4, 9-12]. In fact, the pericardium may be partially responsible for the diastolic limits of the heart (in conjunction with myocardial stiffness and relaxation). Research has shown that the internal pressure-volume relationship of the four-chambered heart mirrors the J-shaped pressure-volume relationship of the pericardium [4]. When the pericardium is removed from the heart, this relationship shifts to the right, allowing for enhanced myocardial filling at lower pressures [4] (refer to figure 2, page 35).

The pericardium limits the total volume within the heart; however, the volume within each of the four cardiac chambers may vary while total cardiac volume remains unaltered [13]. Diastolic ventricular interaction (i.e. the influences the ventricles exert on one another during diastole) is of vital importance when examining cardiac function. When cardiac volumes become increased (such as in patients with heart failure or in healthy individuals during exercise), pericardial pressures rise and the diastolic filling capacities of the ventricles may be limited [14-19]. Further attempts at increasing preload result in several detrimental characteristics: increased right atrial pressure (an established surrogate of pericardial pressure [20]), a leftward shift in the interventricular septum [21-23], and a decreased left ventricular end-diastolic volume (LVEDV). Collectively, these characteristics are known as pericardial constraint, and are characterized by a taut, unyielding pericardium encompassing the myocardium [24]. Reductions in LVEDV as a result of pericardial constraint can directly limit stroke volume (SV) (via the Frank-Starling mechanism), cardiac output (Q), oxygen consumption (VO$_2$) , and ultimately functional and/or exercise capacity [8, 11, 17, 25, 26].

Endurance Athletes and Diastolic Filling

Endurance-trained athletes have an enhanced ability to increase LVEDV and stroke volume during exercise compared to sedentary or normally active individuals [27-35]. This advantage in diastolic function culminates in larger cardiac outputs, higher VO_2 max values, and an increased capacity for exercise.

There are dramatic differences in the diastolic pressure-volume relationships over a range of end-diastolic pressures between endurance-trained and normally active individuals [30, 31]. The diastolic pressure-volume relationship of endurance athletes is shifted to the right when compared to normally active individuals (refer to figure 3, page 36). This implies greater ventricular compliance and an enhanced capacity for diastolic filling in endurance athletes [30, 31]. These diastolic pressure-volume curves of normally active individuals and endurance athletes correspond with the pressure-volume relationships of the intact canine heart and the canine heart following pericardiectomy [4, 30, 31] (refer to figures 2 and 3 for comparison). The comparison of these curves suggests that due to long-term increases in preload, there may be alterations in the pericardium of endurance athletes. A remodeled pericardium may be partially responsible for allowing the myocardium to be more compliant in endurance-trained individuals. The increased exercise capacity and cardiac performance of endurance-trained athletes may be primarily due to their heightened ventricular compliance [30-38].

Several research groups have demonstrated that endurance-trained athletes have the ability to increase SV throughout incremental exercise to VO_2 max, whereas the SV of untrained individuals plateaus at a heart rate of approximately 120 beats per

minute [28, 32]. Gledhill et al. [32] non-invasively measured SV and diastolic filling

time during incremental exercise to maximum. They found that the ability of

endurance athletes to increase SV throughout exercise was largely due to an increase

in diastolic filling capacity [32]. Remarkably, these gains in filling capacity seen in

endurance athletes occurred during a decreased ventricular filling time compared to

untrained individuals [32]. This investigation and others indicate that when compared

to normally active or sedentary individuals, endurance athletes have improved

diastolic function. Our research group has recently postulated that enhanced

ventricular filling may be related, in part, to pericardial remodeling as a result of

exercise-induced hypervolemia and years of exercise training at high LVEDV [27-

35].

The Pericardium and Endurance Performance: Pericardial Remodeling

Previous research from dog models has suggested that a chronic increase in

ventricular filling stimulates pericardial growth [36, 37]. Following nine weeks of an

elevated right atrial preload (as a result of grafting a blood vessel between the aorta

and inferior vena cava) the pericardium increased in both size and mass, but retained

its stress-strain relationship [36]. Both an increase in pericardial mass and the

maintenance of compliance indicate that pericardial growth (rather than stretch)

occurred.

Chronically endurance-trained athletes may provide a human case in which

pericardial growth occurs. As a result of exercise-induced hypervolemia and years of

exercising at high LVEDV, the necessary stimulus may be present in endurance

athletes to provoke pericardial remodeling [24, 36]. A remodeled, enlarged

pericardium would result in a rightward shift in its pressure-volume curve producing an enhanced capacity for filling. The pressure-volume relationship of the heart is directly modulated by the pericardium [4], therefore, a rightward shift in the pericardial pressure-volume curve would allow for a rightward shift in the ventricular pressure-volume curve. Ultimately, an enlarged pericardium in endurance-trained individuals would allow for an increased diastolic filling capacity and SV under conditions of high venous return [28, 38].

The potential increase in exercise performance with the removal of pericardial pressure was demonstrated eloquently by Hammond et al [8]. Their research group exercised untrained pigs to exhaustion on a treadmill before and after pericardiectomy to examine exercise capacity and VO_2 max [8]. Following removal of the pericardium, the pigs exhibited an increase in VO_2 max of 30%. This 30% increase in VO_2 max was attributed directly to a 30% increase in LVEDV, SV, and ultimately Q. Maximal work rate was also significantly increased following pericardiectomy. The work of Hammond and co-workers [8], as well as others [17, 18, 25, 26], indicates that the pericardium acts as a stiff barrier to ventricular expansion ultimately limiting both physiological and functional performance.

Endurance Athletes and Orthostatic Stress

Endurance athletes exhibit a decreased tolerance to orthostatic stress, such as the stress which occurs upon standing from a seated or supine position [39-43]. Orthostatic stress (simulated by lower body negative pressure (LBNP)) can result in a decreased venous return and ventricular preload as well as pooling of blood in the capacitance vessels [44-47]. Normally, the body attempts to combat this

physiological stress by increasing heart rate (to maintain Q), and enhancing venous return by vasoconstriction [45-48]. However, it has been demonstrated clearly that endurance athletes have decreased tolerance to orthostasis, potentially due to over compliant vasculature, abnormal baroreceptor function, end-organ desensitization, and/or decreased sympathetic activity during orthostatic stress [42].

Despite a plethora of research examining the responses of endurance athletes to orthostatic stress, the majority of investigations examine their cardiovascular responses in the minutes following the onset of the gravitational challenge (approximately 5-10 minutes) rather than the immediate cardiovascular responsiveness to orthostasis (5-10 heart beats). It is the belief of our laboratory and others [24], that the ventricular compliance (partially caused by pericardial remodeling) which is beneficial to endurance athletes during exercise may be detrimental to the heart's immediate response following an orthostatic challenge.

Orthostatic Intolerance and Diastolic Interactions: The Role of the Pericardium

Levine et al. [30] directly measured end-diastolic pressure (pulmonary-capillary wedge pressure (PCWP), via a Swan-Ganz catheter) and SV (acetylene re-breathe, echocardiography) over a range of end-diastolic pressures in endurance-trained athletes and sedentary males. End-diastolic pressures were manipulated with LBNP (reduction), and rapid infusions of saline (increase). The results indicated a divergent SV response at a given PCWP between the athletes and sedentary individuals. The athletes' PCWP-SV curve was steeper than that of the sedentary individuals and was shifted up and to the left (refer to figure 4, page 37). At a given end-diastolic pressure the SV of endurance athletes was significantly higher [33]. As well, for a

given change in pressure, endurance athletes exhibited a greater change in SV, indicating a more compliant ventricle. They argued that changes in ventricular (myocardial) compliance were the sole determinant of this finding. However, this may also partially be the result of pericardial remodeling. The cardiovascular response of endurance athletes would be beneficial during exercise where end-diastolic pressures and SV would be increasing; however, this relationship would result in greater declines in SV for a given decrease in end-diastolic pressure, such as occurs during orthostatic stress. This response would be most evident during the seconds immediately following an orthostatic challenge before the baroreceptors are able to respond. Therefore, the increased ventricular compliance and/or pericardial remodeling found in endurance athletes may, in part, account for the decreased orthostatic tolerance exhibited by this population.

Recent research has been conducted to identify the potential role of the pericardium in regulating the pressure-volume relationships of the ventricles, as well as ventricular interdependence [24]. Gibbons-Kroeker and co-workers examined open-chested dogs to ascertain the intracardiac consequences of rapidly changing blood volumes in the atria [24]. These investigators were particularly interested in immediate (within 5 heart beats) diastolic ventricular interaction following an increase or reduction of volume from one of the atria [24]. The experiment was first performed with the pericardium intact. Diastolic ventricular interactions were also examined following pericardiectomy to give a direct indication of the role of the pericardium in mediating these interactions. The results revealed that in an intact heart and pericardium, a volume infusion into one side of the heart resulted in an

immediate (within 5 beats) reduction in the contralateral ventricle. Conversely, the withdrawal of volume from one side of the heart resulted in an increased ventricular volume on the contralateral side of the heart [24]. The contralateral changes in volume were almost identical to the amount of volume infused or withdrawn. Importantly, this ventricular interaction was lost with the removal of the pericardium (or when pericardial pressures became too low). These findings indicate that direct ventricular interactions occur immediately following changes in cardiac volume, and that this interaction is mediated by the pericardium.

A related investigation in human participants produced similar findings to that of Gibbons-Kroeker et al. [24]. Guazzi et al. [48] examined diastolic ventricular interactions in sedentary individuals during orthostatic stress using head-up tilt. Using 2-dimensional echocardiography in the apical 4-chamber view they were able to view the effects of reduced preload on both ventricles simultaneously. As expected they found a reduction in right ventricular (RV) volume, but they found LVEDV to be maintained at mild to moderate levels of orthostatic stress [48]. The investigators hypothesized that the maintenance of LVEDV in the face of a reduction in right atrial preload was due to an enhanced compliance of the left ventricle (as a result of reduced pericardial constraint) [48]. It should be noted that the results of Gauzzi et al. [48] were supportive of the research of Gibbons-Kroeker et al. [24], but not identical. The reasons for this discrepancy likely have to do to differing methodologies (time of measurement post preload reduction, length of volume reduction) and that one study was conducted in humans and one in canines.

Statement of the Problem

To date, there has been very little research examining diastolic ventricular interaction and the pericardium in endurance-trained athletes. However, animal and human clinical research indicates that endurance athletes may exhibit a unique case of diastolic ventricular interaction due to the potential remodeling of their pericardium.

The effective ventricular filling pressure of the left ventricle (i.e. left ventricular diastolic transmural pressure) is the difference between PCWP and right atrial pressure. When SV increases throughout exercise PCWP increases two to three times more than right atrial pressure [18]. However, when the pericardium becomes taut, right atrial pressure rises and reduces left ventricular (LV) filling pressure. This appears to be the case in untrained humans, resulting in a plateau in stroke volume and limited exercise tolerance. Conversely, during an orthostatic challenge, the pericardium of sedentary individuals may maintain LVEDV to a greater degree in response to a reduced right atrial preload via diastolic ventricular interaction.

We believe that chronically endurance-trained athletes, who may have an enlarged pericardium (resulting in low pericardial pressures), may be able to maintain the two to three fold increases in PCWP without rises in right atrial pressure and pericardial pressure. This would partially account for increases in LVEDV and stroke volume throughout (or to a greater degree) exercise found in endurance athletes. Pericardial remodeling and the greater capacity for filling during exercise may result in a relatively slack pericardium at rest (i.e. a smaller heart to pericardium ratio) in endurance athletes compared to sedentary individuals [24]. This would result in a reduced resting pericardial pressure and would not allow for the protective

pericardial-mediated diastolic interactions necessary to compensate immediately for sudden reductions in right atrial preload.

There is a clear lack of evidence examining the consequences of a gravitational challenge on both sides of the heart simultaneously. As well, the literature on orthostatic intolerance and athletes appears to ignore the immediate, beat-by-beat compensations occurring within the heart which are more likely to be responsible for the immediate lightheadedness and dizziness encountered upon standing [24]. Instead, the current research has focused on the steady-state responses (5-10 minutes into the gravitational challenge) which provide insight into the "fainting of the guards" syndrome following prolonged periods of standing.

Therefore, the purpose of this investigation was to examine diastolic ventricular interaction in endurance-trained individuals immediately following increases and reductions in venous return. This investigation was the first of its kind in endurance-trained humans, and provided insights into cardiac function during conditions of physiological stress in endurance-trained athletes.

Hypotheses

1) Endurance-trained athletes will exhibit symptoms of presyncope earlier, and at lower (closer to 0) negative pressures than the normally active individuals.

2) During positive pressure, endurance-trained athletes will experience significantly greater changes in left ventricular volumes than normally active individuals. These differences will be particularly evident during higher positive pressures. Furthermore, the changes in right and left

ventricular volume will parallel each other in the endurance-trained

athletes, but not the normally active individuals (owing to marked

diastolic ventricular interaction).

3) In response to a reduction in right ventricular volume during LBNP,

normally active individuals will show less marked changes in their left

ventricle compared to the endurance-trained group.

4) At low negative pressures the normally active individuals will display a

paradoxical increase in left ventricular volume despite a decrease in right

ventricular volume.

5) During LBNP, endurance athletes will exhibit similar decreases in both

right and left ventricular dimension (reflecting reduced diastolic

ventricular interaction).

<u>Methods</u>

Participants

We recruited eight healthy, normally active males that were not participating in a

regimented exercise program (VO_2 max<50 mL·kg^{-1}·min^{-1}) and eight endurance-

trained males that trained in excess of 10 hours per week and were competitively

active for at least the past three years (VO_2 max>60 mL·kg^{-1}·min^{-1}). Each individual

underwent three days of testing with at least two days between data collection

sessions.

This investigation was approved by the clinical ethics review board of the

University of British Columbia, Canada, and informed consent was provided by all

participants prior to the testing.

Experimental Day One: Familiarization and Maximal Aerobic Power Assessment

Day one involved the completion of a medical screening questionnaire and a physical activity questionnaire (to provide information regarding their training status). On the same day participants also underwent a VO_2 max test, and familiarization with future testing protocols.

Following measurements of height and weight, each participant underwent an incremental, staged exercise test on an electronically-braked cycle ergometer to assess their VO_2 max. Participants were allowed to warm-up as they wanted before commencing the exercise test at 100 W. The workload was increased every 2 minutes by increments of 30 W until volitional fatigue. Expired gases were collected and analyzed with a metabolic cart (Physiodyne, MAX-1 Mark B, Quogue, New York). Heart rate (Polar S810), and arterial oxygen saturation (pulse oximetry, Ohmeda Biox 3740) were monitored and recorded during each minute of the exercise test. Following the exercise test, participants were given the opportunity to become familiar with the lower body pressure chamber which was used on days two and three of the investigation.

Experimental Day Two: Assessment of Orthostatic Tolerance

Day two began with 15 minutes of supine rest prior to commencing the orthostatic challenge in a lower body pressure chamber. Participants remained supine throughout the pressure challenge, and were sealed in the lower body pressure chamber at the level of the iliac crest. The participants were supported by a bicycle-like seat (so as not to be drawn into the chamber), and were asked to refrain from

contracting their leg muscles throughout the test. The orthostatic challenge began at 0 mmHg (barometric pressure) and progressed toward presyncope by increments of -20 mmHg up to a maximum of -80 mmHg. Each pressure stage lasted five minutes. Presyncope was determined by a sudden drop in heart rate (15 beats per minute) or blood pressure in the face of increasing pressure, or a sustained decrease in systolic blood pressure below 90 mmHg, as well as qualitative symptoms of nausea, dizziness, profuse sweating, and lightheadedness. Cardiac output was measured using the single breath-hold technique (using acetylene as the soluble gas, Medisoft Ergocard, Dinant, Belgium) in the final minute of each stage [49]. Heart rate (ECG), and blood pressure (automated sphygmomanometer) were also continuously monitored during the LBNP challenge.

Experimental Day Three: Lower Body Positive and Negative Pressure with Echocardiography

<u>Pressure Challenges</u>

The third day of testing involved 15 minutes of supine rest followed by both a lower body negative and positive pressure challenge (randomly assigned). The negative pressure challenge began at 0 mmHg and decreased to -20 mmHg for three minutes. The participant was then brought back to normobaric pressure for three minutes or until heart rate and blood pressure had returned to resting values (which ever was longer). The pressure was then decreased to -40 mmHg for three minutes. This protocol was repeated down to -80 mmHg. The same protocol was used during the positive pressure challenge with pressures ranging from 20 to 60 mmHg above atmospheric pressure. Ten minutes of supine rest were granted between the lower body positive and negative challenges.

Echocardiography Acquisition

The participant lay in the pressure chamber in a slight left lateral decubitus position. Each participant was scanned for congenital heart abnormalities prior to the onset of pressure. A Hewlet-Packard Sonos 5500 was used to acquire two-dimensional and doppler echocardiography recordings at rest and at each stage of lower body pressure. All echocardiographic imaging was conducted by a single, experienced clinical sonographer, and were completed in accordance with the American Society of Echocardiography guidelines. Prior to the pressure challenges, baseline recordings of doppler peak flow velocities (mitral, tricuspid, and pulmonary venous flow), as well as long-axis, short-axis and apical 2-chamber views were acquired for four cardiac cycles. Left-ventricular mass [50] and total cardiac volume [51] were calculated at rest. The apical 4-chamber view was obtained immediately prior to each pressure challenge (for at least four heart beats) and immediately following the onset of lower body pressure (for 10 heart beats) to provide simultaneous indices of right and left ventricular dimensions. We measured right and left ventricular septal to free wall diameter and area in diastole as well as left ventricular end-systolic area. Left ventricular volumes were calculated using the single plane method of discs [52]. Pulse wave doppler recordings of mitral, tricuspid and pulmonary venous flow were made between 30 seconds and 1 minute of each pressure stage. From the Doppler recordings peak flow velocities of early and atrial filling were measured. Peak systolic, diastolic, and reverse flow were measured from the right pulmonary vein. At each pressure stage following the doppler recordings, 4 cardiac cycles in the apical 2-chamber view were obtained so as to capture the left

ventricular volume and diameter from an anterior to posterior perspective. Lastly, the sonographer returned to the apical 4-chamber view to record four additional cardiac cycles in a steady state situation (at approximately 3 minutes into the pressure challenge). All echocardiography data was recorded on to a high quality VHS tape and analyzed by a single trained observer follow the experiment.

Breathing frequency was not controlled for in this investigation; however, lower body pressure was always initiated at peak inspiration. This meant that the first beats during pressure were always during expiration. An automated sphygmomanometer was used to monitor blood pressure during each of the pressure challenges. Heart rate was monitored continuously using an ECG.

Data Analysis

Data is presented as means and standard deviations, unless otherwise stated. A three way repeated measures analysis of variance was run using STATISTICA software to compare differences between groups, between different pressures, and at different times following the onset of pressure with Tukey post-hoc comparisons. For all stages, apical 4-chamber view data was analyzed as resting (the average of at least four cardiac cycles prior to the onset of pressure), ten beats immediately following the onset of pressure (beat-by-beat measures), and at minute three of each pressure challenge (average of 4 cardiac cycles). The apical 2-chamber and doppler recordings were an average of 4 cardiac cycles prior to the start of the first pressure, and at each pressure stage. An independent t-test was used to establish group differences for physical characteristics. Values of statistical significance were set at $p < 0.05$ a priori.

Results

Participant characteristics

The normally active and endurance-trained participants did not differ in height, weight, or age (Table 1, page 38). By design, the endurance-trained athletes had significantly higher relative (65.4 ± 5.7 mL·kg^{-1}·min^{-1} vs. 45.1 ± 6.0 mL·kg^{-1}·min^{-1}) and absolute VO_2 max values (4.7 ± 0.7 L·min^{-1} vs. 3.3 ± 0.5 L·min^{-1}), and exercised for significantly more hours per week (15.3 hours vs. 6.1 hours, $p<0.05$) on average. Left ventricular mass, and resting LVEDV and SV were all higher in the endurance-trained group at rest, but not statistically higher (Table 2, page 39). Total cardiac volume was significantly higher (885.3 ± 143.1 mL vs. 722.3 ± 158.5 mL) in the endurance-trained group. Heart rate was elevated in the normally active individuals (64.6 ± 14.9 vs. 54 ± 8.4 beats·min^{-1}), but not statistically different. There was no difference in resting mean arterial blood pressure between the two groups.

Orthostatic Tolerance Test

Seven out of the eight endurance-trained individuals did not reach or complete the final stage (-80 mmHg) of the orthostatic tolerance test. The tests were stopped because of falling arterial blood pressure and/or lightheadedness or dizziness. All eight normally active individuals were able to complete the entire orthostatic challenge without any signs or symptoms of presyncope.

Since the majority of the endurance-trained individuals did not complete the final pressure stage, we could only make statistical comparisons between the groups from rest through to -60 mmHg. Heart rate progressively increased during the orthostatic challenge and it did so to the same extent in both groups. Stroke volume decreased in

both groups, however, it was decreased to a greater degree in the endurance-trained athletes ($p < 0.05$, See figure 5, page 40). Cardiac output was decreased in both groups, but due to the greater decrease in SV seen in the endurance athletes, cardiac output was decreased to a greater extent in the endurance-trained group ($p < 0.05$).

Echocardiogram Data

Four participants from each group underwent positive pressure first, and four completed the negative pressure challenge first. There was no order effect found regardless of which task was completed first.

Right ventricular end-diastolic area and LVEDV were reduced incrementally with decreasing levels of negative pressure, and incrementally increased as positive pressure was increased. We report RV area because we and others [16] believe it to be a more reliable and valid measure than calculated RV volume.

Right ventricular end-diastolic area (apical 4-chamber view) was reduced during negative pressure and increased during positive pressure from rest to the same degree in both the normally active and endurance-trained groups (See figure 6, page 41 and figure 7 on page 42). There was also no difference between the two groups in the response of RV end-diastolic septal to free-wall diameter during negative (both decreased to the same extent) and positive pressures (both increased to the same extent). Overall, the RV responded to the lower body pressures in the same manner for both groups.

Left ventricular end-diastolic volume in the apical 4-chamber view was decreased progressively (with negative pressure) or increased (with positive pressure) from resting levels in both groups, however there was a greater responsiveness to the

pressures in the endurance-trained group (p<0.05). In summary, during negative pressures the endurance-trained group had a greater reduction in LVEDV, and during positive pressure they exhibited a greater increase in LVEDV (see figure 8 and figure 9 on pages 43 and 44 respectively). Left ventricular end-diastolic septal to free-wall diameter progressively decreased during negative pressure and progressively increased during positive pressure; however the overall group responses did not differ statistically (p=0.067).

Stroke volume, as calculated from apical 4-chamber derived LVEDV minus left ventricular end-systolic volume, was reduced in both groups during negative pressure and was increased during positive pressure. Again, the endurance-trained individuals were more sensitive to the changes resulting in greater decreases in SV during negative pressure and larger increases during positive pressure when compared to the normally active individuals (p<0.05).

Heart rates were consistently, but not statistically higher in the normally active individuals at rest and throughout the pressure challenges. There was no statistical difference in the way in which the groups' heart rates responded to the pressure challenges.

Cardiac output was calculated as SV obtained from the apical 4-chamber view multiplied by heart rate. Cardiac output responded to the pressures as one would expect, with the highest cardiac outputs coming from the highest positive pressures and vice versa. Largely owing to the differences in SV, there were also differences in the response of cardiac output between the groups (p<0.05).

There was an interesting temporal response seen in both groups and in both ventricles. During negative pressure there was an initial decrease in end-diastolic volume, however, the heart and circulation compensated (or attempted to compensate) for this decrease. This is evident by an increase in end-diastolic volumes, almost back to resting values, at approximately 3-6 beats (depending on the pressure). After approximately beat 6 or 7, the brief compensations were no longer sufficient allowing end-diastolic volume to decrease again. This finding was particularly evident in the endurance-trained individuals (see figures 6 through 9).

There was a differential response in ejection fraction (calculated as SV/LVEDV) between the two groups (p<0.05). The endurance-trained group was consistently lower at all negative pressures and higher during all positive pressures. Not only were the endurance-trained individuals consistently lower (or higher), but they had larger changes for a given change in pressure, with a particularly large drop in ejection fraction at -80 mmHg (p<0.05) (see figure 10, page 45). The normally active individuals were able to maintain a higher SV for a given end-diastolic volume throughout the negative pressures.

Similarly contractility (systolic blood pressure/end-systolic volume) of the groups responded differently to the lower body pressures (p<0.05). Interestingly the endurance-trained individuals showed almost no response to negative pressure while the normally active individuals progressively increased their contractility throughout negative pressure (see figure 11, page 46).

Left ventricular end-diastolic volume was also calculated from the apical 2-chamber view. The endurance athletes had larger changes in LVEDV with positive

and negative pressure; however the difference between the groups was not statistically significant. Anterior to posterior diameter of the LV was also measured in the apical 2-chamber view. The diameter changed minimally with positive pressure, but it did decrease, particularly at high negative pressures. There was no difference between groups in the way the anterior to posterior dimensions were altered. These findings indicate that the intracardiac changes caused by the lower body pressures occurred to a greater extent in the free-wall to septal plane than they did in the anterior-posterior plane.

Early tricuspid peak flow velocity was significantly altered by the lower body pressures, whereas late or atrial tricuspid filling velocity was not statistically altered by lower body pressure. There were no differences between the groups in the way they responded to the pressures in either early, atrial or the early to atrial ratio for tricuspid peak flow velocity.

Early and late mitral peak filling velocities were both affected by the pressure challenges. However, the endurance-trained group showed greater decreases in peak flow velocity with negative pressure and larger increases with positive pressure during early mitral filling, and in the early to atrial filling ratio ($p < 0.05$). There was no group difference in late mitral filling.

Systolic and diastolic pulmonary venous flow velocities were both significantly decreased with negative pressure and increased with positive pressure; however there were no differences in the way the groups responded. Peak pulmonary reverse flow velocity increased incrementally with the application of negative pressure and decreased with positive pressure, however the groups did not respond differently.

Discussion

Responses to lower body negative pressure

Both groups exhibited decreases in LVEDV, SV, and Q progressively throughout LBNP, with the endurance-trained group exhibiting greater decreases in all variables. This finding is in accordance with Levine et al. who reported that endurance-trained individuals have greater decreases in end-diastolic volume and SV for a given drop in PCWP [30]. In both the present study (7 out of 8 athletes) and that of Levine et al. [30] (6 out of 7 athletes) the greater decreases in LV volume were related to presyncopal symptoms during LBNP. A substantial reduction in LVEDV, SV and Q ultimately leads to falling arterial pressures and a reduced cerebral blood flow. Insufficient cerebral and retinal blood flow results in symptoms of lightheadedness and/or presyncope. Reduced orthostatic tolerance has also been found by numerous investigators in many endurance-trained athletes [39-43].

In the present investigation we simultaneously obtained RV area in conjunction with measures of LV dimensions. Since there was no difference in the RV response to LBNP, our data indicates that although there may be differences in LV compliance, these diastolic differences between the groups may not exist (or exist to a lesser extent) on the right side of the heart. The RV was primarily affected by the alterations in venous return caused by the lower body pressures as a result of being in series with the circulation. However, the LV may have had direct influences in the form of diastolic ventricular interaction in addition to alterations in the filling pressure [11]. This may be the reason why there were divergent responses between the groups on the left but not the right side of the heart.

We propose that diastolic ventricular interaction may play a significant role in explaining the ability of the normally active individuals to maintain their LV volumes to a greater extent despite a similar reduction in RV area. The effective filling of the left ventricle, or LV transmural pressure, is calculated by subtracting right atrial pressure from pulmonary capillary wedge pressure. Early transmitral filling pressure is the difference between left atrial pressure and LV pressure [53, 54]. Both the transmural and transmitral filling gradients may contribute to the differences observed in the present investigation. By reducing preload with LBNP, right atrial (or pericardial pressure, [20]) is reduced and the transmural filling gradient is increased. This would be particularly evident in the normally active individuals who may have higher resting pericardial pressures. It may also be plausible that LV pressure may be reduced to a greater degree in the normally active group (with falling left atrial pressures in both groups) resulting in a greater maintenance of transmitral filling pressure and ultimately LVEDV.

It has been shown that 30 to 40% of LV pressure is created by forces external to the LV itself [55]. These external pressures include pericardial tension and ventricular interaction with the RV [55]. With LBNP, RV area was reduced as was the pressure it was exerting on the LV. Since pericardial pressure is related to total cardiac volume, a reduction in total cardiac volume would result in a reduction, though slight as it may be, in pericardial pressure as well [4]. The partial removal of these external constraints on the LV would intern lower right atrial and LV pressure and in fact increase the transmural and early transmitral filling gradient, allowing the LV to fill to a greater extent [53, 54]. However, sustained LBNP also reduces PCWP

and left atrial filling pressures [54], resulting in a net LV filling pressure reduction. By reducing the right atrial and LV pressures (by removing external constraints) as well as the PCWP and left atrial pressure, the overall transmural and transmitral filling gradients would be reduced, but to a lesser extent in the normally active individuals. Research from heart failure patients further supports this theory. Atherton et al. showed that with reductions in RV volume, LVEDV was paradoxically increased [17]. This finding in patients with heart failure was attributed to increased LV compliance, likely due to the reduction of external constraints, namely the pericardium and RV, on the LV. It has been shown that right ventricular haemodynamics can alter the LV pressure-volume relationship [56, 57]. Two separate investigations have shown that decreasing RV preload leads to a shift in the pressure-volume relationship of the LV down and to the left. A downward shift of the pressure-volume curve means that a given end-diastolic volume can be attained at a lower pressure, indicating a more compliant ventricle. These increases in compliance could also be attributed to the removal of external constraints. The theory of increased LV compliance and greater maintenance of LVEDV has also been supported by others studying healthy individuals using head up tilt [48]. Gauzzi et al.'s findings are congruent with ours and can also be explained by a reduction in RV volume causing a temporary increase in LV compliance, ultimately maintaining the early diastolic filling gradient and a larger LV volume [48].

Our proposed explanation is also supported by the fact that the greater difference in the LV between the two groups was seen in septal to free-wall diameter as opposed to the anterior-posterior diameter. Although the difference did not attain statistical

significance (p=0.067), there was likely a physiologically relevant difference (leading to the difference in calculated volume) between the two groups in septal to free-wall diameter. This physiological difference between the groups could then be explained by diastolic ventricular interaction and the movement or altered compliance of the interventricular septum and LV. Again, as RV volume was reduced and constraints on the LV were diminished in the normally active individuals, the septum was able to move towards the RV contributing to a temporary increase in LV compliance allowing for LV volume to be maintained to a greater degree.

This theory is further supported by the doppler peak flow velocities obtained during LBNP. Early mitral peak flow velocity was maintained to a greater extent in the normally active individuals, supporting the notion that their LV filling pressure gradient was maintained to a greater extent [53, 54]. This divergent response was seen despite similar reductions in early tricuspid peak velocities and pulmonary venous systolic and diastolic peak velocities in both groups. The fact that pulmonary venous inflow velocity was affected to the same degree implies that left atrial filling was altered to the same degree. This would again lend evidence to the theory that as a result of the removal of external constraints to the LV [55], right atrial and LV pressures were reduced in the normally active individuals, resulting in a greater maintenance of transmural and transmitral filling pressures, LVEDV and SV.

To our knowledge, our finding of increased contractility in the normally active group during LBNP has not been previously discovered. Gauzzi et al. [48] found no changes in contractility during head-up tilt, but this may be explained by the degree of tilting they used (up to 60 degrees), compared with the high levels of LBNP we

used in this investigation (up to -80 mmHg). It has been reported that standing upright (or the equivilant of 90 degrees tilt) places the same amount of stress on the cardiovascular system as -50 mmHg of LBNP [46]. This argument makes sense because it is at the higher pressures, particularly -80 mmHg where we saw the largest increases in contractility in the normally active group. Increased contractility would enable the normally active individuals to preserve their SV and Q to a greater extent than the endurance-trained individuals. Increased contractility may also increase the diastolic filling gradient by increasing diastolic suction [58]. In fact, following reductions of LVEDV, diastolic suction has been shown to be augmented by an increase in the contractile state and by low end-systolic volumes, both of which were seen during every negative pressure in the normally active group [58]. Therefore, diastolic suction may also play a role in aiding the normally active individuals to maintain their LVEDV and SV to a greater extent.

The ability of the normally active individuals to increase their contractile state during LBNP enabled them to maintain their ejection fraction to a greater degree than the endurance-trained athletes. Partially due to almost no change in their contractility from baseline, the endurance athletes exhibited a reduction in ejection fraction, with a particularly large decrease at -80 mmHg. It is interesting to note that this large decrease in ejection fraction coincides with the negative pressure which ultimately resulted in presyncope in seven out of eight athletes.

The reasons why contractility and ultimately ejection fraction were not increased in the endurance-trained group in response to reductions in preload are uncertain. We propose two plausible hypotheses: 1) there was a suppressed inotropic response to

circulating catecholamines, and 2) arterial baroreptors in the aorta and the carotid sinus did not respond to the extent necessary in response to reductions in blood pressure. It is possible that due to chronically high levels of circulating catecholamines during years of exercise training, the beta-receptors responsible for initiating an increase in contractility have become desensitized. This would not be advantageous during exercise, and would be contrary to the belief that endurance athletes have superior cardiac performance during exercise. However, the receptors may require higher concentrations of catecholamines (as seen during exercise) to stimulate the necessary gains in contractility. The first hypothesis has some potential merit, although it has not yet been substantiated. The second hypothesis has been supported to a certain degree (i.e. endurance-trained athletes have a reduced baroreflex in response to volume unloading), but the effects of the baroreflex in endurance athletes have predominantly been examined with relation to heart rate and blood pressure regulation as opposed to contractility [43, 59]. Arterial baroreflexes can alter cardiac function via a chronotropic or inotropic response, as well as changing peripheral vascular resistance [43]. In fact, it has been shown in animal models that reduced carotid artery pressure causes reflex increases in contractility [60, 61]. It has been hypothesized that high vagal tone and/or a "resetting" of the baroreceptors (i.e. a higher or lower pressure required to trigger a response) in endurance-trained individuals suppresses their compensatory mechanisms for reductions in blood pressure seen during LBNP [62, 63].

The most plausible explanation for greater reductions of LVEDV and SV in endurance-trained individuals might be that there are contributions from numerous factors most notably diastolic ventricular interaction and baroreceptor responsiveness.

Response to lower body positive pressure

The same explanation for the group differences during positive pressure as during negative pressure is appropriate, only in opposite directions. The RV increased in area to the same extent in both groups; however LVEDV was increased to a greater degree in the endurance-trained group. In the normally active group, we propose that as RV area increased the amount of external constraint put on the LV did as well [55]. More specifically, when the RV is enlarged the portion of the pericardium that is attached to its free wall is stretched outwards, whereas the pericardial tissue on the LV free wall is pulled inward acting to reduce LV size and compliance [18]. Increased RV volume could increase pressure on the LV in two ways: 1) an increase in RV volume increases total cardiac volume and therefore pericardial pressure 2) increases in RV volume can shift the interventricular septum towards the LV, making the LV temporarily less compliant [23]. Both of these effects likely contributed to increasing ventricular interaction and not allowing the LV to increase to the same degree as in the endurance-trained group. We propose that the LV of the endurance-trained individuals has less external constraint on it than the LV of the normally active individuals. Therefore, by increasing RV volume the constraint to filling in the LV increases in both groups but would still be less in the endurance-trained group. Again, the findings of the changes in LV and RV areas are supported by the diameter and doppler recordings as they were during negative pressure.

Ventricular compliance and the pericardium

We believe that a more compliant left ventricle in endurance athletes contributes significantly to the differences seen in this investigation. Left ventricular compliance can be affected by the pericardium. The pericardium has been shown to mediate diastolic ventricular interactions during changing ventricular volumes [24]. Gibbons-Kroeker et al. found that following an injection of blood into an atria in the canine heart, there was a compensatory reduction in the contralateral side of the heart [24]. Diastolic ventricular interaction was also seen with the removal of fluid, whereby the opposite side of the heart would momentarily increase in volume; likely a result of the removal of pericardial pressure and/or increased septal compliance. All ventricular interaction was lost following the removal of the pericardium [24]. The animal model of Gibbons-Kroeker et al. suggests that a certain amount of pericardial tension, or ventricular stiffness, is required for ventricular interaction [24]. In the present study, there was a greater degree of ventricular interaction in the normally active group, perhaps implicating either a less compliant pericardium, or simply a less compliant myocardium.

The investigation by Gibbons-Kroeker et al. [24] tracked beat-by-beat changes in volume following a change in preload; however, their study differed from the present investigation in that they altered preload for only one cardiac cycle and then examined the following heart beats. In comparison, in the present study the lower body pressure was applied for three continuous minutes. Therefore, our beat-by-beat response differed from the one observed in the Gibbons-Kroeker study in some aspects. The time course of the response observed during several of the pressures in

both the right and left ventricle mimics the response humans encounter during daily life when going from a seated or supine position to an upright one. We observed an immediate decrease in end-diastolic volume, followed by a momentary compensation, and then depending on the group and pressure, either a continuation of the compensation or a lack of compensation. In everyday life when we go from being seated or supine to an upright position we would expect to see the same cardiovascular response as we did during the LBNP. Temporal compensation to the decrease in preload would aid in the prevention of orthostatic intolerance (e.g. lightheadedness) while a reduced compensation may lead to symptoms of orthostatic intolerance.

Interestingly, in five out of eight normally active participants we observed a momentary paradoxical increase in LVEDV following the onset of low levels of LBNP (-20 and -40 mmHg) similar to the response found by others [17, 24]. This provides further evidence for a greater degree of pericardial-mediated diastolic ventricular interaction in the normally active individuals [17, 24].

The pericardium has been shown to play a major role in setting the diastolic limits of the heart [4, 7]. Together the heart and the pericardium exhibit a J-shaped pressure-volume relationship, whereby small initial increases in pericardial volume are met with small increases in pressure, but further increases in ventricular volume are met with large increases in pressure [6, 19-22]. When the pericardium is removed from the heart, this relationship shifts to the right, allowing for enhanced myocardial filling at lower pressures [19]. Interestingly, the diastolic pressure-volume curves of normally active individuals and endurance athletes developed in the experiment by

Levine et al. [30] correspond directly with the pressure-volume relationships of the intact canine heart and the canine heart following pericardiectomy respectively [10, 19, 24].

To summarize, the endurance-trained individuals exhibit a pressure-LVEDV curve similar to a canine heart following pericardiectomy, whereas the pressure-volume curve of the untrained individual mirrors the intact heart and pericardium curve of the canine. As well, following alterations in right ventricular preload, the heart of normally active individuals displays more diastolic ventricular interaction as seen in intact hearts, whereas the endurance athletes exhibit less interaction; resembling the canine heart following pericardiectomy. Further evidence that endurance-trained athletes have an altered pericardium comes from the fact that their enhanced filling capacity and ability to increase stroke volume to a greater degree during exercise compared to untrained individuals [27-35] parallels the increases in LVEDV, stroke volume and exercise capacity seen in animal models during exercise following pericardiectomy [8, 26].

There is evidence to suggest that chronically trained endurance athletes may provide a case in which pericardial compliance can be altered. Research in dogs has suggested that a chronic increase in ventricular filling can stimulate pericardial growth [36, 37]. Following nine weeks of an elevated right atrial preload (as a result of grafting a blood vessel between the aorta and inferior vena cava) the pericardium increased in both size and mass, but retained its stress-strain relationship [36]. Both an increase in pericardial mass and the maintenance of compliance indicate that pericardial growth (rather than stretch) occurred. An increase in pericardial size with

maintenance of the stress-strain relationship would produce the rightward shift that is evident in the pressure-volume relationship of the LV of endurance-trained athletes [30]. The necessary stimulus may be present in endurance athletes to provoke pericardial remodeling in the form of exercise-induced hypervolemia and years of exercising at high LVEDV [24, 36].

Ventricular compliance and diastolic function across the health span

The present investigation, coupled with others [16, 17, 48, 64] suggest that there may be an inverse relationship between the degree of diastolic ventricular interaction in an individual, and the ventricular compliance or diastolic function of the individual. Whereby heart failure patients exhibit large degrees of ventricular interaction and poor diastolic function, endurance-trained individuals exhibit minimal diastolic ventricular interaction and superior diastolic function. There may also be optimal degrees of diastolic ventricular interaction depending on the physiological challenge. For example, during an orthostatic challenge it is detrimental to have minimal ventricular interaction owing to the potential for greater reductions in LVEDV and SV. However during exercise, minimal diastolic ventricular interaction is desirable allowing stroke volume to increase with relatively small changes in filling pressures, whereas, those individuals with high levels of diastolic ventricular interaction often have markedly reduced exercise tolerance [17, 64].

Limitations

Echocardiography provides a two dimensional image of a three dimensional organ. We were able to acquire the third dimension of the LV with the apical 2-chamber view but not simultaneously. It is also technically difficult to acquire clear images of

the RV; however extra care was taken by our experienced sonographer to provide clear images of both sides of the heart.

All of the measures made in this study were non-invasive, and therefore we cannot identify true cardiac or pericardial pressures. However, we feel that the invasive results of previous investigations provide strong theoretical evidence to allow our non-invasive findings to be substantiated.

A further limitation is that our increases in cardiac volume (with positive pressure) may replicate alterations at the cardiac level but the accompanying chemical, hormonal, mechanical and thermal changes that are normally seen during exercise were not present in this investigation.

Conclusion

The results of this investigation imply that the enhanced ventricular compliance which allows endurance-trained athletes to perform in a superior manner during exercise may be detrimental to them during conditions of orthostatic stress. Our findings also indicate that endurance-trained individuals may have less diastolic ventricular interaction when compared to normally active individuals. Large reductions in contractility and ejection fraction in the endurance athletes during negative pressure were interesting and unexpected findings, and they may play an important role in future investigations involving orthostatic tolerance.

Future investigations should include examining the effects of a long term aerobic training program on diastolic ventricular interaction, simultaneous assessment of baroreceptor responsiveness and diastolic ventricular interaction and the use of
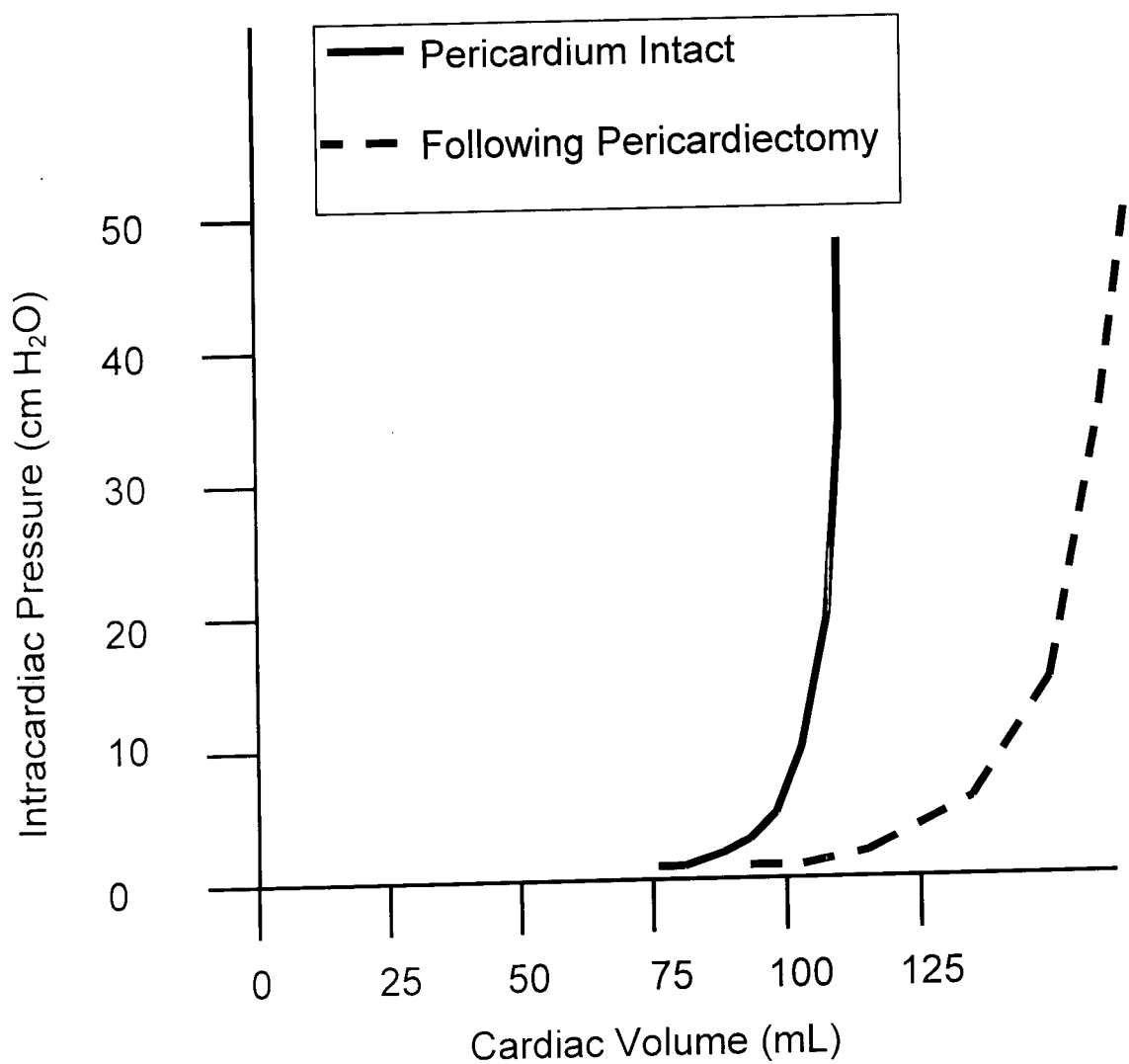
magnetic resonance imaging to assess diastolic ventricular interaction and pericardial

surface area. .

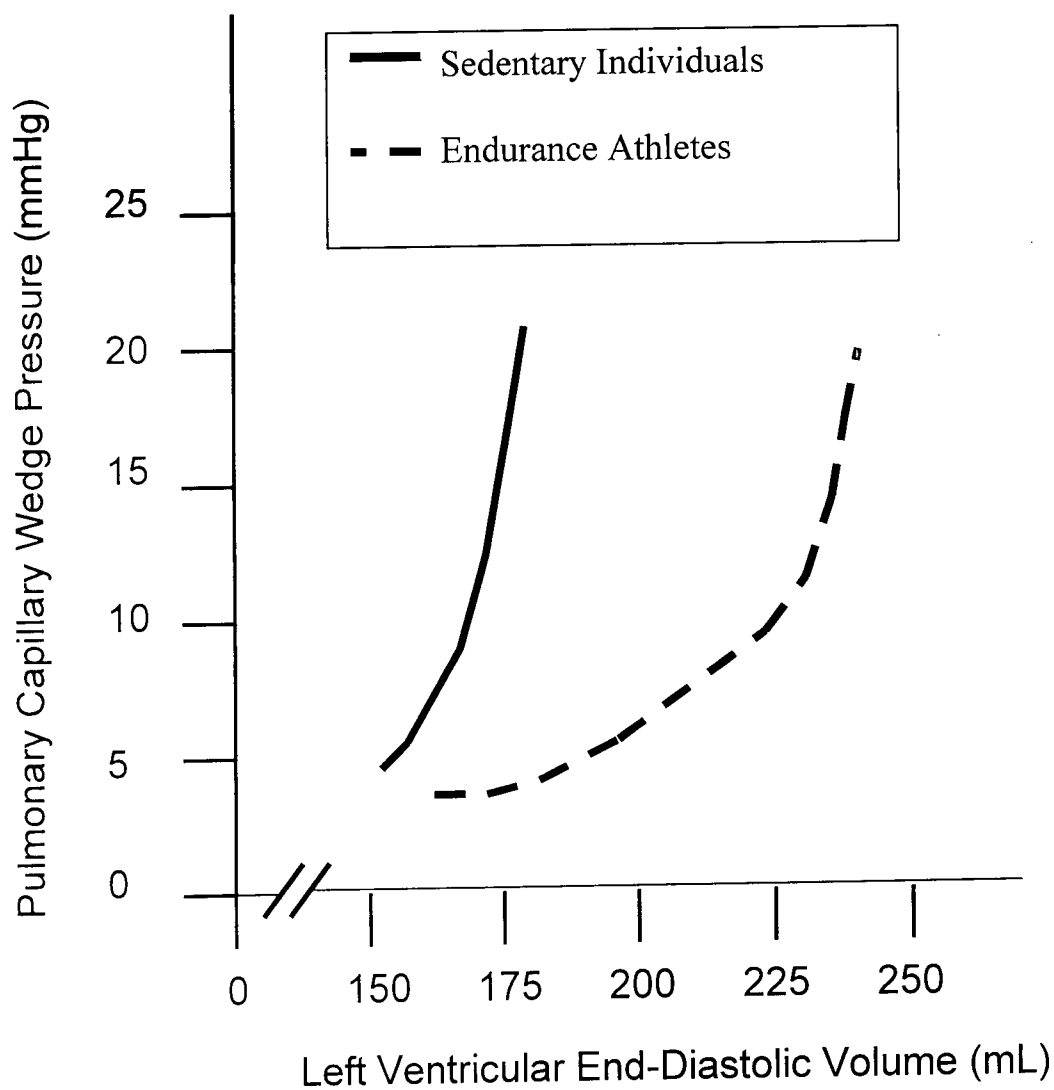Figure 1: Pericardial compliance curve.

The J-shaped pressure-volume relationship of a canine heart with an intact pericardium. *Adapted from Holt et al. 1970 [4].*

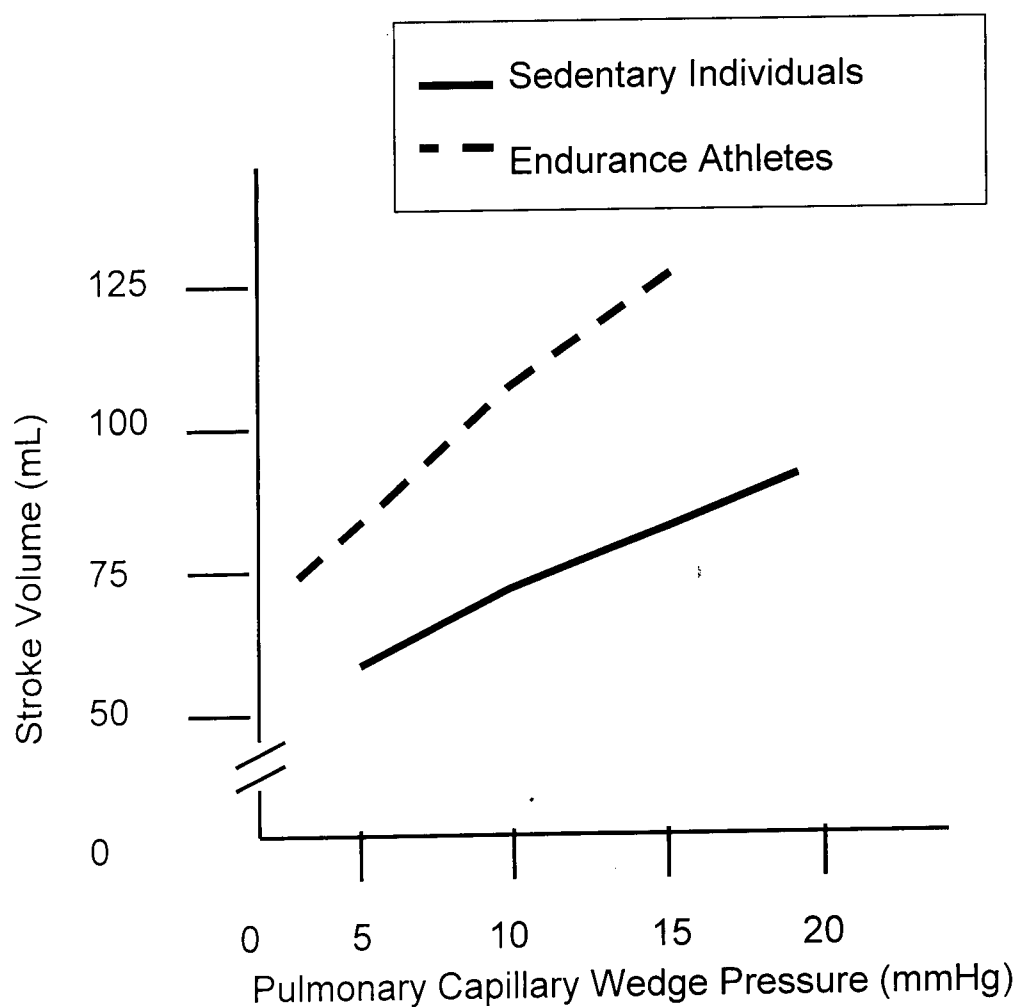Figure 2: Cardiac compliance without and without the pericardium.

The pressure-volume relationship of a canine heart with the pericardium intact (solid line), and with the pericardium removed (dashed line). *Adapted from Holt et al. 1970 [4].*

Figure 3: Left ventricular compliance curves in trained and untrained individuals.

End-diastolic pressure-volume relationships between endurance-trained (dashed line) and sedentary (solid line) humans. *Adapted from Levine et al. 1991 [30].*

Figure 4: Starling curves in sedentary and endurance athletes.

The relationship between PCWP and SV in sedentary (solid line) and endurance-trained humans (dashed lines). *Adapted from Levine et al. 1991 [30].*

Table 1: Participant Characteristics

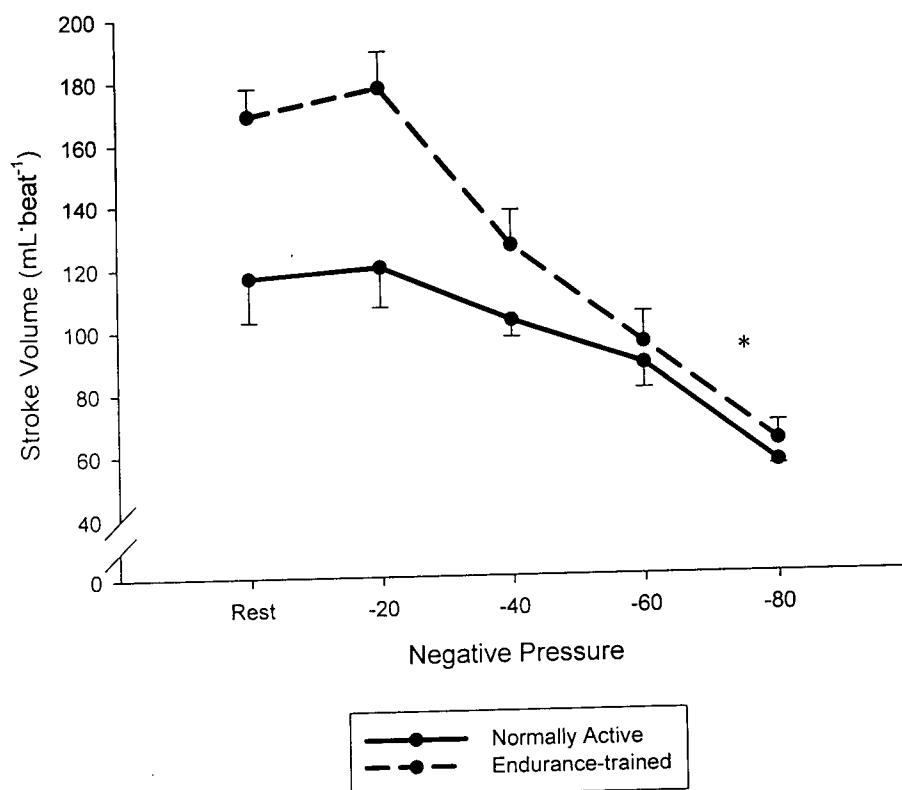|	Normally Active Individuals	Endurance-trained Individuals
Height (cm)	179.1 ± 5.2	181.8 ± 6.6
Weight (kg)	73.5 ± 6.8	72.3 ± 9.4
Age (years)	25.3 ± 4.0	25.8 ± 3.8
Relative VO_2 max $(mL \cdot kg^{-1} \cdot min^{-1})$	45.1 ± 6.0	$65.4 \pm 5.7*$
Absolute VO_2 max $(L \cdot min^{-1})$	3.3 ± 0.5	$4.7 \pm 0.7*$
Hours of Physical Activity Per Week	6.1 ± 2.9	$15.3 \pm 1.9*$

The physical characteristics for the normally active and endurance-trained individuals. Values are means plus or minus the standard deviation (n=8 for both groups). Group differences (*) were significant using the student's t-test (p<0.05).

Table 2: Resting Haemodynamic and Cardiac Characteristics.

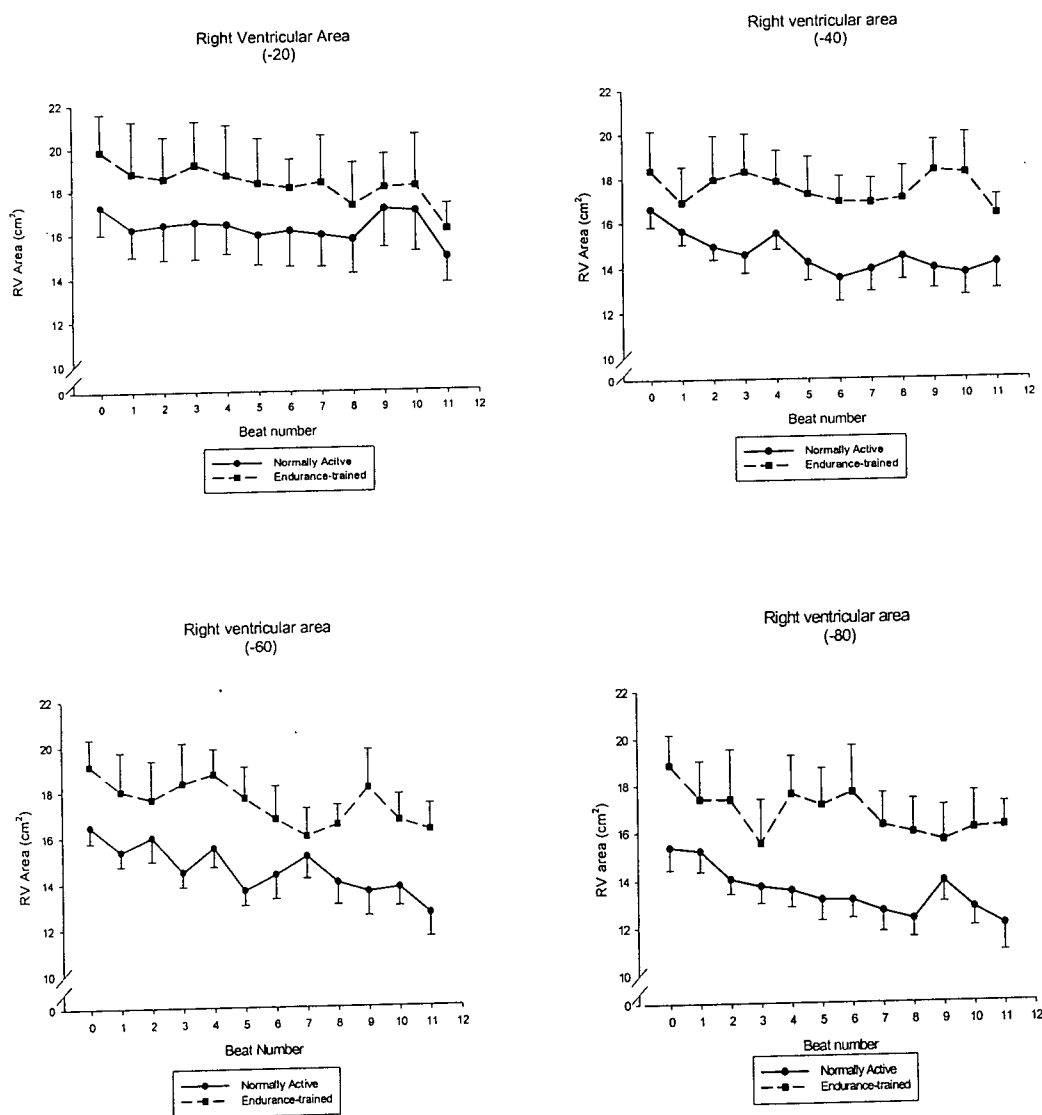|	Normally Active Individuals	Endurance-trained Individuals
Left Ventricular End-Diastolic Volume (mL·beat^{-1})	94.9 ± 25.4	112.0 ± 18.0
Stroke Volume (mL·beat^{-1})	65.0 ± 15.5	78.0 ± 16.6
Heart Rate (beats·min^{-1})	64.6 ± 14.9	54.0 ± 8.4
Cardiac Output (L·min^{-1})	4.1 ± 0.9	4.3 ± 1.3
Ejection Fraction (%)	68.9 ± 5.1	69.7 ± 4.4
Contractility (mmHg·mL^{-1})	4.39 ± 1.5	3.65 ± 0.5
Right Ventricular Area (cm^2)	16.6 ± 3.1	18.6 ± 3.9
Mean Arterial Pressure (mmHg)	81.0 ± 7.7	82.0 ± 6.7
Left Ventricular Mass (g)	251.2 ± 77.8	306.0 ± 68.0
Total Cardiac Volume (mL)	722.3 ± 158.5	885.3 ± 143.1*

A comparison of the resting haemodynamic and cardiac characteristics of the normally active and endurance-trained individuals. Values are means plus or minus the standard deviation (n=8 for both groups). Group differences (*) were significant using the student's t-test (p<0.05).

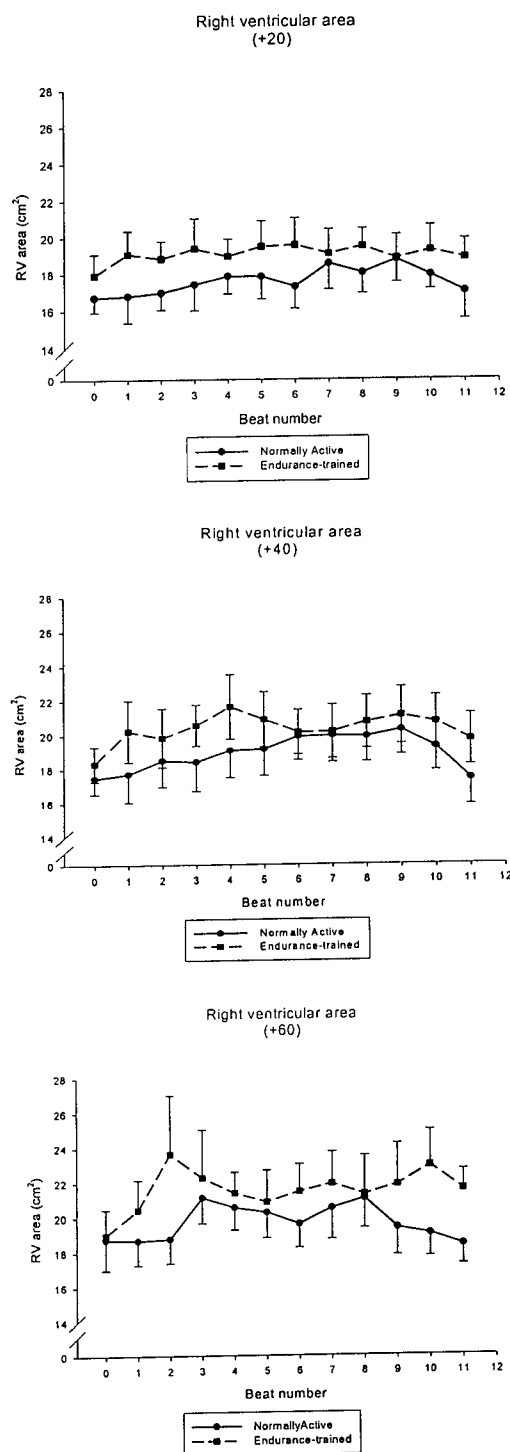Figure 5: Stroke volume response to lower body negative pressure.

Stroke volume response to LBNP in the normally active group (solid line), and endurance-trained group (dashed line). Stroke volume was measures on experimental day two using the acetylene single breath-hold technique. A statistically significant interaction effect (group x pressure) occurred in the stroke volume response to negative pressure.

Figure 6: Changes in right ventricular area during lower body negative pressure.
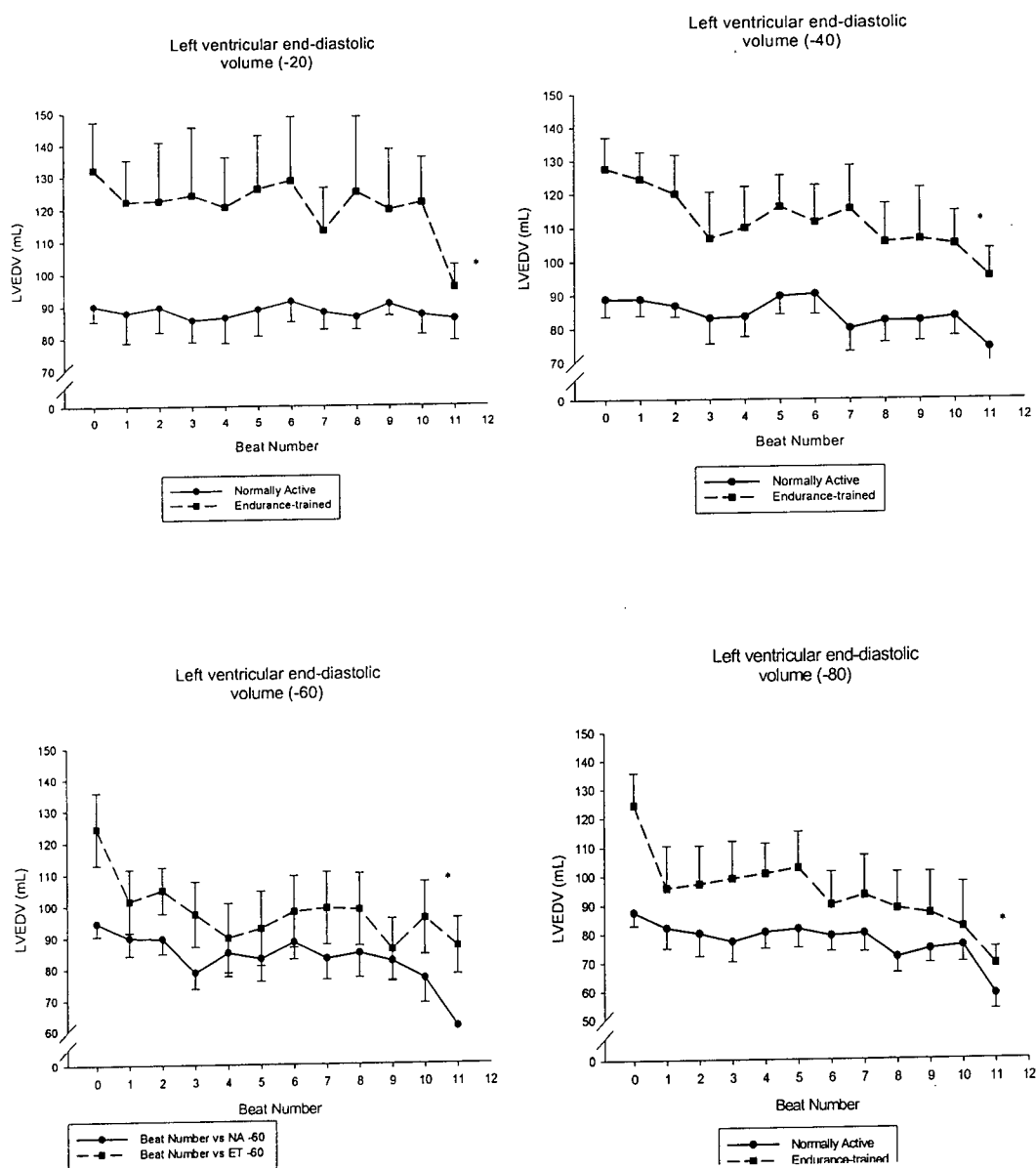

The right ventricular area response to lower body negative pressure on experimental day three as measured by echocardiography. Values are presented as group means ± the standard error of the mean. Beat zero refers to the resting average, beats 1-10 are immediately following the onset of pressure, and beat 11 is the 3 minute average.

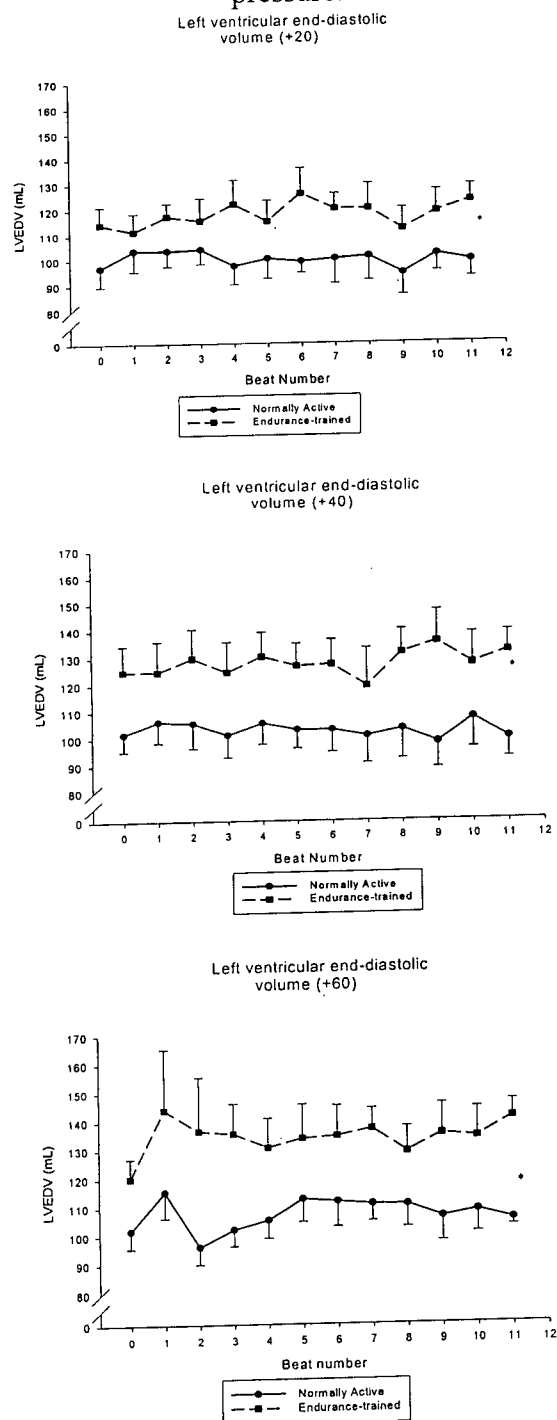Figure 7: Changes in right ventricular area during lower body positive pressure.

Right ventricular area
(+20)

Right ventricular area
(+40)

Right ventricular area
(+60)

The right ventricular area response to lower body positive pressure on experimental day three as assed by echocardiography. Values are presented as group means ± the standard error of the mean. Beat zero is the resting average, beats 1-10 are immediately following the onset of pressure, and beat 11 is the 3 minute average.

Figure 8: Changes in left ventricular end-diastolic volume during lower body negative pressure.
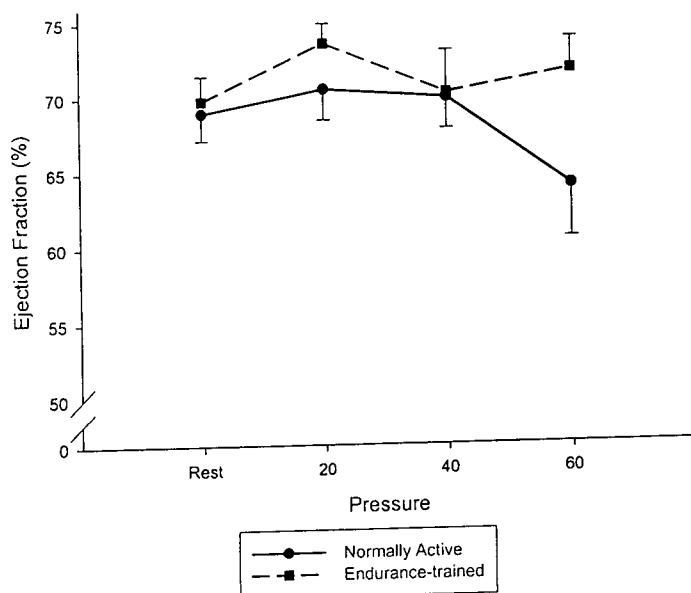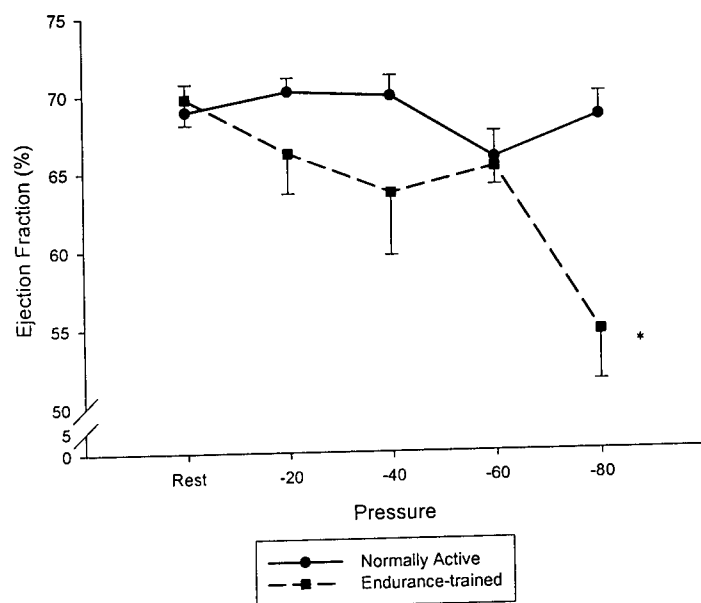

The left ventricular volume response to lower body negative pressure on experimental day three as assessed by echocardiography. There was a statistically significant interaction effect (pressure x beat x group) (p<0.05). Values are presented as group means ± the standard error of the mean. Beat zero is the resting average, beats 1-10 are immediately following the onset of pressure, and beat 11 is the 3 minute average.

Figure 9: Changes in left ventricular end-diastolic volume during lower body positive pressure.

Left ventricular end-diastolic
volume (+20)

Left ventricular end-diastolic
volume (+40)

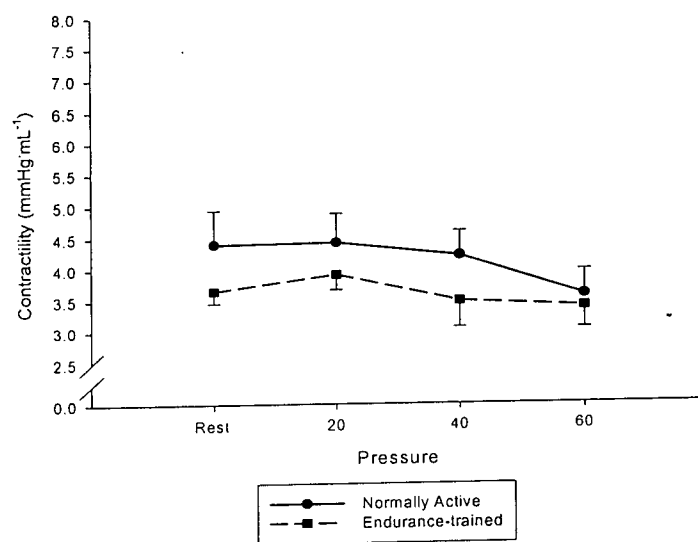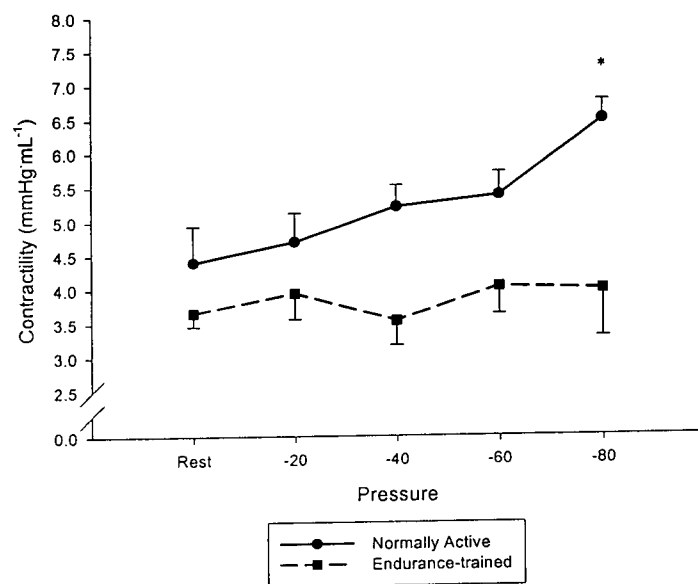Left ventricular end-diastolic
volume (+60)

The left ventricular volume response to lower body negative pressure on experimental day three as assessed by echocardiography. There was a statistically significant interaction effect (pressure x beat x group) (p<0.05). Values are presented as group means ± the standard error of the mean. Beat zero is the resting average, beats 1-10 are immediately following the onset of pressure, and beat 11 is the 3 minute average.

Figure 10: Changes in ejection fraction during lower body pressure.

The ejection fraction response to lower body negative (top) and positive pressure (bottom) on experimental day three. The values are group means ± standard error of the mean. Values are measured at rest and during the third minute of pressure. There is a statistical difference between the groups at -80 mmHg.

Figure 11: Changes in contractility during lower body pressure.

The contractility response to lower body negative (top) and positive pressure (bottom) on experimental day three. The values are group means ± standard error of the mean. Values are measured at rest and during the third minute of pressure. The normally active group had an increase at -80 mmHg from rest.

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