Left Ventricular Dynamics During Exercise in Endurance Athletes

MILENA SUNDSTEDT
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Abstract

Large quantities of data have described left ventricular adaptation to endurance training, but basic concepts on left ventricular performance during exercise remain controversial. In this thesis, we present the results of studies of left ventricular dynamics during exercise in 89 endurance-trained athletes.

Using radionuclide ventriculography, 35 female and 30 male endurance athletes were studied in supine position. During supine exercise at 70% of the age-expected maximal heart rate, the adjustments in left ventricular volumes were small, suggesting a high preload before exercise. Stroke volume increased by changes in the left ventricular end-diastolic volumes but no changes were observed in the end-systolic volumes. Moreover, no significant differences were noted between male and female athletes.

Contrast echocardiography was utilized when 24 male endurance athletes were studied during upright exercise. An almost linear increase in stroke volume was seen from upright rest to upright exercise at a heart rate of 160 beats per minute. Stroke volume increased by an almost linear increase in end-diastolic volume and showed an initial small decrease in end-systolic volume. The left ventricular cavity became geometrically more spherical with the largest increase in the left ventricular end-diastolic short-axis cavity diameters in the mid and apical part of the left ventricle. Left ventricular long-axis length obtained from the epicardial apex to the middle of the mitral annulus at end-diastole showed no significant change from rest to exercise. The mitral annulus motion contributed to more than 50% of the stroke volume during exercise with no significant difference between septal and lateral annular motion at peak exercise. Major changes were observed in left ventricular filling indices during upright exercise. The mean transmitral pressure gradient showed a linear increase and increased several times as the mean diastolic time decreased, with large reductions in mean left ventricular filling time. Despite the shortened filling time, the heart was able to increase the filling rate (measured as volume per time) five times. This observation verifies that the heart has large reserves at rest and reveals the increase in capacity during exercise.

Keywords: athletes, exercise, left ventricular dynamics, stroke volume, mitral annular motion

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Det krävs ett helt nytt sätt att tänka för att lösa de problem vi skapat med det gamla sättet att tänka.

Albert Einstein
Cover image by Amanda Sundstedt, 9 years old.
List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.


V. Henriksen E, Sundstedt M, Hedberg P. Left ventricular end-diastolic geometrical adjustments during exercise in endurance athletes. *Clinical Physiology and Functional Imaging* (accepted)

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats per minute</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>H+</td>
<td>Hydrogen ions</td>
</tr>
<tr>
<td>PCO₂</td>
<td>Partial pressure of carbon dioxide</td>
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<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<tr>
<td>RNV</td>
<td>Radionuclide ventriculography</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>LA</td>
<td>Left atrial</td>
</tr>
<tr>
<td>AV-plane</td>
<td>Atrioventricular plane</td>
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</table>
Elis Henschen wrote “Big hearts win races!” one hundred years ago when he first described the athlete’s heart. Athletic training induces morphological changes in the left ventricle (LV) in endurance athletes. Regular training causes the heart to enlarge, with a combination of LV cavity enlargement, increased wall thickness and mass. This physiological adaptation is often referred to as the athlete’s heart. Athletes participating in dynamic exercise develop predominantly increased LV chamber size with a proportional increase in wall thickness (eccentric hypertrophy) that is caused by increased volume load associated with the high cardiac output of endurance training. The extent to which absolute LV cavity dimensions is increased by systematic training is modest in most athletes but may be substantial in others.

During exercise, cardiac output must increase to match the need for increased oxygen supply to the working muscles. A cardiac output between 34-42 l/min has been reported during maximal upright exercise in elite endurance-trained athletes. To reach a cardiac output in this range a large stroke volume is needed. All researchers agree that stroke volume increases above resting values during exercise, but how and in what range stroke volume changes during exercise in fit endurance athletes is debatable. Reports from the 1960s and 1980s suggest a plateau in stroke volume at workloads of approximately 50% of maximal oxygen uptake, whereas recent research suggests that stroke volume increases progressively from rest to maximal exercise. Neither during upright nor during supine exercise has a marked increase in LV end-diastolic volume or a decrease in end-systolic volume previously been possible to measure. Therefore, no one has been capable of explaining the predicted, almost 100%, increase in stroke volume from upright rest to upright exercise in endurance athletes.

Despite an increase in stroke volume during exercise, the heart cycle is shortened. During maximal exercise, the LV filling and ejection take no more than 300 ms at a heart rate of 200 beats per minute (bpm), suggesting a large LV capacity, being able to uphold a fine balance between maintaining optimal filling and ejection despite a large stroke volume. In what way the LV is able to maintain this balance is not known.
History

In the late 19th century, Otto Frank used isolated frog hearts to ascertain that the strength of ventricular contraction was increased when the ventricle was filled with increasing volumes 18. The greater the initial volume, the more rapid the rate of increase, the higher the peak pressure reached and the faster the rate of relaxation. This observation was extended by the studies of Ernest Starling and colleagues in the early 20th century. Starling found that, in dogs, increasing venous return, and therefore the filling pressure of the ventricle, led to increased stroke volume by a more rapid and forceful contraction 19. Ernst Starling described this relationship in his Linacre Lecture, which was given at Cambridge University in 1915 and published in 1918 20. These findings of Frank and Starling are often referred to as the Frank-Starling mechanism or Starling’s Law of the heart, but there is evidence that the essential features of this mechanism were discovered earlier 18.

The Scandinavian contribution to exercise physiology has been substantial during the 20th century 1. In 1941, Hohwu-Christensen, a Danish physiologist, moved to Stockholm and became the first physiology professor of the College of Physical Education at Gymnastik- och Idrottshöskolan (GIH) 21. Hohwu-Christensen had studied at the Harvard Fatigue Laboratory in 1930s. This laboratory trained most of those who became world leaders in exercise physiology during the 1950s and 1960s, performing research primarily on general problems of exercise, nutrition and health 21. Hohwu-Christensen introduced Per-Olof Åstrand to the field of exercise physiology, as well as Bengt Saltin, two well-known Swedish physiologists. For more than one hundred years ago, the Swedish professor Elis Henschen was the first to recognize the athlete’s heart. He concluded “skiing causes an enlargement of the heart and that this enlarged heart can perform more than the normal heart. There is, therefore, a physiological enlargement of the heart due to athletic activity: The athlete’s heart” 1.

Physical exercise

Exercise can be divided into two types: isotonic and isometric exercise. Isotonic or dynamic exercise is when there is a change in muscle length, with little or no change in tension (for example running). Isometric or static exercise is defined as little or no change in muscle length but an increase in tension (for example weight lifting). An important difference between the two types of exercise is the amount of muscles involved: in running large muscle groups are involved, whereas in weight-lifting small muscle groups are affected. In the following text only isotonic exercise will be discussed.
Increased muscle activity requires increased oxygen delivery to the working muscles to produce more energy. Oxygen uptake is the product of cardiac output and the difference in oxygen content in the arteries and veins (or the arterio-mixed venous oxygen difference). Cardiac output is the product of heart rate and stroke volume. The heart rate increases during exercise because of an early withdrawal of the normal vagal inhibition followed by beta-adrenergic stimulation, which also increases contractility. Stroke volume is dependent on preload (the LV volume at the end of diastole), afterload (the resistance against the ejection of blood) and the contractile state of the myocardium. Because of venous return that is caused by the pumping action of the exercising muscles and redistribution of the blood volume, LV preload increases during dynamic exercise. This action leads to increased force of contraction and therefore increased stroke volume according to the Frank-Starling mechanism.

The oxygen is transported by the blood that is either bound to hemoglobin in the red blood cells (greater than 98%) or dissolved in the blood plasma (less than 2%) \(^{23}\). With repetitive training, the blood volume and number of red blood cells increase, making the blood more efficient as an oxygen carrier. The capillary density increases in the muscles, which facilitates the delivery of oxygen to the muscles, resulting in an increased maximal oxygen uptake in the working muscles.

The arterio-mixed venous oxygen difference can increase during exercise by increasing oxygen extraction from the blood to the working muscles and by redirecting the blood to where it is needed. During heavy endurance exercise, muscles receive up to 80% or more of the available blood \(^{23}\). This shift in blood flow to the muscles is accomplished primarily by reducing the blood flow to less active organs such as the kidneys and intestines by the sympathetic nervous system regulation \(^{23}\). In the skeletal muscles, exercise induces metabolic dilatation of arterioles resulting in a decrease in total peripheral resistance, leading to a decrease in diastolic blood pressure during exercise \(^{22}\). As the blood with low oxygen content from working muscles mixes with oxygen-rich venous blood from the rather inactive organs, there is a limitation of oxygen utilization to approximately 75% of the total oxygen content in blood. The arterio-mixed venous oxygen difference increases by approximately a factor of three from rest to maximal exercise \(^{23}\).

The stroke volume in the right ventricle (RV) must increase to the same extent as the stroke volume in the LV during exercise. Blood flow in the lungs increases primarily through recruiting new, earlier poorly perfused lung segments (with an increased depth of inspiration), followed by a continuous and gradual increase in the rate of breathing in proportion to the body’s metabolic needs \(^{23}\). The increased ventilation and blood flow volume
in the lungs increase oxygen uptake. Gas exchanges occur between the air in the alveoli and the blood in the capillaries, where the H⁺ concentration and PCO₂ in the blood continuously affect respiratory activity through the respiratory Center in the brain. During heavy exercise, the anaerobic contribution to energy generates a large production of H⁺, which is why ventilation increases proportionally more than the oxygen uptake in order to adjust the acid-base balance. Ventilation in athletes is usually not a limiting factor for performance, even during maximal effort.

The heart cycle
There are certain ways of describing the heart cycle. In physiological terms the heart cycle is often described as follows.

Systole
Systole, the contracting phase, starts with isovolumetric contraction. This is when LV pressure exceeds the atrial pressure and increases to the same extent as the pressure in the aorta, without any change in LV volume. As pressure in the LV increases above the pressure in aorta, the aortic valve opens and the LV ejects blood, the stroke volume. It is a complex process involving coordination between the different muscle layers in the heart, with circumferentially fibers in the mid-wall and the base of the ventricle and longitudinal fibers in the subendocardial and subepicardial free wall. The shortening of muscle fibers results in a thickening of the ventricular walls, as well as a movement of the mitral annulus towards the LV apex. The systolic function is determined by the contractility (the capacity of the myocardium to contract), preload (LV volume at the end of diastole, i.e. the degree to which myocardial fibers are stretched by filling) and afterload (the resistance against the ejected blood). During exercise, an increased venous return results in an increased preload and an increased contractility by the Frank-Starling mechanism and beta-adrenergic stimulation.

Diastole
Diastole starts from the time when aortic flow begins to decline, i.e. when more and more myofibers enter the state of relaxation. The relaxation is an energy-depending process for uptake of calcium into the sarcoplasmatic reticulum. When aortic valve closes (LV pressure is less than the aortic pressure), the isovolumetric relaxation time starts. LV pressure decreases without any change in LV volume. When LV pressure is below the atrial pressure, the mitral valve opens and diastole continues with the rapid filling phase followed by diastasis and atrial contraction. Diastole is dependent on
the elastic properties of the myocardium (compliance) and different loading conditions, as well as efficient atrial contraction. The most widely used method for evaluating the diastolic function is Doppler-echocardiography 26-29.
Aims

This thesis presents the results of studies of LV hemodynamics in endurance-trained athletes. The specific objectives of the studies were:

- to evaluate the relative LV volumes and the changes in LV ejection fraction (LVEF) from rest to exercise in supine position in male and female endurance athletes.

- to examine whether there were gender differences regarding the LV volume reply and LVEF changes with supine exercise in endurance athletes.

- to examine how LV stroke volume and LV end-diastolic and end-systolic volumes change from upright rest to upright exercise in male endurance athletes.

- to describe the changes in Doppler LV filling and ejection indices from upright rest to upright bicycle exercise in male endurance athletes.

- to quantify the LV longitudinal motion during exercise by assessing the relative mitral annular excursion and to evaluate the absolute LV longitudinal axis at end-diastole and end-systole in male endurance athletes at upright rest and during upright exercise.

- to investigate LV end-diastolic geometrical alterations from upright rest to upright exercise in male endurance athletes.
Methods

Study population
Before the examinations, the 89 endurance athletes included in the study completed a questionnaire about their past and present health status and sports activities. No participant was a habitual smoker or on medication for cardiovascular disease. Furthermore, none of the participants had a history or echocardiographic evidence of heart disease. There were no major abnormalities in the electrocardiograms. One athlete had blood pressure of 145/90 mmHg but no previous history of hypertension. The blood pressure in the other athletes was below 140/90 mmHg.

All participants gave their informed consent and received a detailed explanation on the study and procedures used. The study was approved by the ethics committee at the University of Uppsala, Sweden.

Paper I
The orienteerers in paper I were the participants in an in-depth medical examination of young Swedish male elite orienteerers studied extensively because of 16 identified cases of sudden unexpected cardiac deaths occurring between 1979-1992. The participants, 35 female and 30 male orienteerers, were all well trained young endurance athletes, the majority attending special upper secondary sport schools for orienteerers. Because of their young age (16-30 years, mean 20 years), most athletes had been endurance performers for only a few years at the time of the study. The year before the examination the training load had been 300-500 hours/year of running, predominantly in forest terrain. Because of the increased death rate in the male elite orienteerers, both male and the female orienteerers were recommended to decrease their training intensity and training load during the six-month period of the investigation. We do not know to what extent the athletes followed these recommendations, however.

Papers II-IV
The study group in papers II-IV included 24 male endurance athletes (mean age 26 years, range 19-38 years). The participants had various backgrounds from competitive exercise activities and intensities of training: long-distance
runners (n = 9), cyclists (n = 10), cross-country skiers (n = 3) multi-sport athletes (cycling, running, climbing, n = 2). All the athletes were high-level competitors (mean number of years of competition 9 years, range 4 to 20 years). Before the examination, the training load for the cyclists was 700-1,000 hours/year of cycling, while the training load for the long-distance runners, cross-country skiers and multi-sport athletes was 200-500 hours/year, with mainly running and skiing.

Paper V
A priori power calculation in the study of geometrical adjustments in the LV during exercise indicated that we would need to study 14 athletes to find a significant change in the LV short-axis diameters. The assumptions made were that a short-axis diameter of 55 mm would increase 5 mm from rest to exercise at a heart rate of 160 bpm and that the study would be able to detect, within 80% probability with a two-sided 5% level of significance, a true increase in the short-axis diameter. Therefore, the study group in paper V included 15 randomly selected athletes from the group of 24 male athletes from papers II-IV. The selected athletes included five long distance runners, eight cyclists and two multi-sport athletes.

Radionuclide ventriculography
In paper I, an in vivo intravenous technique was used. Twenty minutes after administration of tin pyrophosphate (Amersham stannous red blood cell agent) the erythrocytes were labeled with 650 MBq Tc-99m pertechnetate. Electrocardiogram-gated imaging was performed using a General Electric AC 400 gamma camera with a low energy general-purpose parallel-hole collimator. To achieve optimal separation between the LV and RV the camera head was positioned in the left anterior oblique position with a slight 15° craniocaudal tilt. The position of the camera and the athlete were kept unchanged after being set for the acquisition at rest. After 10 minutes of tracer equilibration, supine multigated blood pool imaging at rest was performed. A General Electric (eNTEGRA) software system was used for image acquisition and data analysis. Totally, 600 beats were collected both at rest and during exercise with 24 frames per heart cycle in 64 x 64 matrix size.

The relative LV volumes were estimated using the number of counts in diastole and systole. Because the LV volume is proportional to the LV counts and because the counts per frame are proportional to the time per frame, the exercise images were adjusted for the shorter frame duration time and for the time activity delay between the two acquisitions:
Adjusted counts per frame = \( \frac{\text{mean RR interval at rest} \times \text{counts}}{\text{mean RR interval during exercise} \times 24 \text{ frames}} \)

An experienced operator outlined LV end-diastolic and end-systolic silhouettes manually. The automatic adjustments produced by the software system were used for background correction (bc). The LVEF at rest and during exercise was calculated as \( \frac{\text{LVEDC(bc)} - \text{LVESC(bc)}}{\text{LVEDC(bc)}} \). LVEDC(bc) = background corrected LV end-diastolic counts; LVESC(bc) = background corrected LV end-systolic counts. The relative stroke volumes were estimated as LVEDC(bc) - LVESC(bc).

Echocardiographic examination

In papers II - V, echocardiographic examinations were performed using an Acuson Sequoia 512 system, version 5.0 (Acuson, Mountain View, CA, USA), with a harmonic 3.6 MHz transducer recorded with a simultaneous electrocardiogram. All the examinations were stored on videotapes for subsequent analysis. Immediately before exercise, all participants were studied in the left lateral recumbent position, and the echocardiograms were recorded in the standard parasternal, apical and subcostal views. Measurements and recordings at rest were made during normal breathing. The two-dimensional diastolic measurements of the left cavity and wall dimensions were performed using the leading edge-to-edge principle according to the recommendation of the American Society of Echocardiography (ASE) \(^{32}\). The measurements were made from end-diastolic frames defined as the frame closest to the onset of the QRS complex. End-systole was defined as the smallest internal diameter close to the mitral valve opening. The LV mass was estimated with the ASE-recommended formula \(^{33}\).

In addition, echocardiographic measurements were performed from each participant at rest in the upright position and at three levels of upright exercise (heart rate 100, 130 and 160 bpm). The volume measurements and the short-axis diameters (papers II and V) were obtained from the apical view using contrast echocardiography. By administering the contrast agent octafluoropropan (Optison®, Mallinckrodt Medical, Inc., St. Louis, MO, USA) intravenously, LV boundary detection was improved. A dose of 0.2 ml of Optison® was injected in an antecubital vein at rest in the upright position and at the different levels of upright exercise. LV volume was obtained using the biplane disc summation method (modified Simpson’s rule) \(^{34,35}\). The disc summation method assumes that the 2-dimensional slices pass directly through the central axis of the LV cavity. Foreshortening of the LV axis will inevitably lead to an underestimation of the true volume. To avoid shortening of the true major LV axis the images representing the largest possible cavity length were used.
The LV short-axis end-diastolic diameters were made from endocard to endocard from apical four- and two chamber-views and the short-axis diameters were made perpendicular to the LV axis. The first short-axis diameter (1) was obtained close to the mitral valve annulus and the diameter closest to the LV apex (6) one cm below the endocardial apical border. Depending on the LV axial cavity length, the remaining four measurements were obtained at intervals of 14-17 mm. The LV longitudinal axis at end-diastole (0) was measured from the endocardial apex to the middle of the mitral annulus. To minimize the risk of an anterior-posterior imaging plane that deviates from the LV central axis causing an underestimation of the true diameters the apical four- and two-chamber short axis measurements at equivalent levels were averaged.

For Doppler measurements (paper III), echocardiography was performed from the four- and five-chamber apical views. To determine the peak velocities both the transmitral and aortic velocities were measured at the highest velocity spectra in the most distinct spectral envelopes. The cursor was lined up parallel to the LV inflow and outflow in order to minimize the angle. The sample volume was positioned at the tips of the mitral leaflets when pulsed Doppler echocardiography was performed. The Doppler recordings were made at a speed of 50 mm/s. The following Doppler indices were measured or calculated:

- Peak transmitral flow velocity in early diastole (E-wave) was measured with pulsed Doppler. During exercise, the peak diastolic flow velocity was calculated since the E- and A-wave fuse from a heart rate of approximately 100 bpm.
- Using the modified Bernouilli equation, the mean transmitral pressure gradient was derived with pulsed Doppler from measurements of flow velocity across the mitral valve. The velocity time integral of mitral flow was obtained by tracing the velocity curve contour.
- The peak aortic flow velocity through the aortic valve was measured with continuous Doppler.
- The diastolic filling time was obtained from the beginning to the end of the transmitral inflow.
- The isovolumetric relaxation time was measured from the onset of the QRS complex to the beginning of the transmitral inflow subtracted from the onset of the QRS complex to the end of the aortic flow.
- The LV ejection time was measured from the beginning to the end of the aortic flow.

Mitral annulus motion was registered with M-mode at two sites of the mitral annulus (paper IV). From the 4-chamber view, the cursor was drawn
from the apex through the mitral valve immediately adjacent to the valve placed in the septal and lateral regions of the mitral annulus perpendicular to the direction of movement. Mitral annulus motion was defined as the vertical distance between the point of the annulus most distant from the apex and a point closest to the apex, representing the total motion at that point during systole, in the apical direction. The method is similar to that described by Höglund et al. The absolute LV longitudinal axis from the epicardial apex to the middle of the mitral annulus at end-systole and end-diastole was measured from the 4-chamber view with two-dimensional echocardiography (paper IV).

The same investigator performed all the examinations and measurements. Each parameter value was averaged over three cardiac cycles, except for the LV volumes and LV short- and long-axis end-diastolic measurements, in which case one representative cardiac cycle with the largest possible LV cavity length was chosen.

Exercise protocols
The subjects in paper I were subjected to supine bicycle exercise. To prevent motion artifacts while maintaining vigorous exercise we used handlebars to stabilize the chest. Heart rate and electrocardiogram were constantly recorded during exercise. The initial workload was 100 Watts, followed by increments of 50 Watts every two minutes for male athletes and 80 Watts followed by increments of 40 Watts for female athletes. When the athletes estimated 15 on the Borg exhaustion scale (a scale ranging from 6 to 20, where 15 is hard and 19 is very, very hard), the workload was maintained and data acquisition started. This level of exercise was chosen to ensure that the participants were able to continue exercise for about five minutes (600 heart cycles) during data acquisition. The mean heart rate during data recording was 139 bpm, which is 70% of the age-expected maximal heart rate.

The endurance athletes in papers II - V participated in three upright bicycle exercise studies. Two exercise tests were sub-maximum, where images for volume and geometric measurements (the first submaximal test) and Doppler and mitral annulus motion measurements (the second submaximal test) were obtained at three levels of exercise. The initial workload was 80 watts, followed by increments of 10 watts until the desired heart rates of 100, 130 and 160 bpm were reached. During echocardiography, the workload was maintained for one to two minutes to ensure a steady heart rate. The submaximal tests were done on two separate days.

During the third exercise test, the maximum oxygen uptake was measured. A cardiopulmonary exercise test was used with ventilatory gas ex-
change analysis in which expired gases were collected breath by breath through a mouthpiece during exercise using an analyzer (Oxycon Alpha, Jaeger, Wurzburg, Germany). Heart rate and electrocardiogram were constantly recorded and oxygen consumption was constantly calculated during exercise. The initial workload was 100 watts followed by increments of 20 watts every minute up to 200 watts, followed by increments of 10 watts every minute until complete exhaustion was reached. The maximal test was done after one of the submaximal tests, with a minimum of one hour of rest between the tests.

Reliability

Paper I

The variability for LVEF measured by radionuclide ventriculography (RNV) has previously been described in our laboratory. Two separate acquisitions were used with the shortest possible time between the registrations. The 95% confidence interval for the differences between two measurements were ± 0.04 units for the LVEF at rest. Therefore, an increase or decrease of > 0.04 units in LVEF from rest to exercise was considered as a statistically significant change.

Paper II

The intraobserver variability in volume measurements in paper II was assessed in 10 randomly selected athletes at rest and during exercise at a heart rate of 160 bpm. These measurements were obtained from the videotapes on different occasions and therefore most probably on different heart cycles. The mean differences in end-diastolic volumes were 17 ml (standard deviation (SD) 13) at rest and 9.3 ml (SD 22) during exercise. The mean differences in end-systolic volumes were 8.9 ml (SD 17) at rest and 13.6 ml (SD 19) during exercise.

Paper III

The intra- and interobserver variability for Doppler measurements was tested in 20 athletes at rest and during exercise at a heart rate of 160 bpm. These measurements were obtained on different occasions and therefore most probably on different heart cycles, but each parameter value was averaged over three cardiac cycles. At rest, the mean difference for the calculated mean transmitral pressure gradient was 0.00 mmHg (SD 0.07) for the same observer and 0.05 mmHg (SD 0.08) between two observers. During exercise
at a heart rate of 160 bpm, the corresponding figures were 0.16 mmHg (SD 0.69) and 0.09 mmHg (SD 0.69), respectively.

For the same observer, the mean difference for the LV filling time at rest was 3 ms (SD 30) and 16 ms (SD 46) between two observers. During exercise, the mean difference for the same observer was 9 ms (SD 12) and 21 ms (SD 19) between two observers.

Paper IV
The intra- and interobserver variability for measurement of the mitral annular motion was tested in 20 athletes at rest and during exercise at a heart rate of 160 bpm. These measurements were also obtained on different occasions and therefore most probably on different heart cycles, but each parameter value was averaged over three cardiac cycles. At rest, the mean difference in the septal wall was 0.2 mm (SD 0.6) for the same observer and 0.6 mm (SD 1.1) between two observers, and in the lateral wall 0.6 mm (SD 1.5) for the same observer and 0.5 mm (SD 0.9) between two observers. During exercise at a heart rate of 160 bpm, the corresponding figures in the septal wall were 1.1 mm (SD 1.3) and 0.5 mm (SD 1.5), respectively and in the lateral wall 0.4 mm (SD 0.9) for the same observer and 0.2 mm (SD 1.1) between two observers.

For the same observer, the mean difference for the LV long-axis length at end-diastole at rest was 1.1 mm (SD 3.3) and 2.8 mm (SD 4.5) between two observers. During exercise, the mean difference for the same observer was 3.1 mm (SD 4.1) and 4.0 mm (SD 5.4) between two observers.

Paper V
The intra- and interobserver variability for short-axis measurements was tested during exercise at a heart rate of 160 bpm. Twenty-four short-axis diameters in four athletes were measured. For the same observer, the mean difference for the LV short-axis diameter at end-diastole during exercise was 1.8 mm (SD 1.7) and 1.7 mm (SD 2.4) between two observers.

Validity
The validity of our ultrasound systems is regularly evaluated at our laboratory. Doppler is tested using a moving string target DP1 (BBS Medical, Sweden)\textsuperscript{38}. During the years when the study was performed, the average error for measured velocities in pulsed and continuous wave Doppler was less than 1%. For distance measurements in B- and M-mode, the error was less than 2% as measured with the RMI 403GS Grey Scale Phantom (GammaxRMI, Middleton, WI, USA). The mean error for the time scale was less
than 0.5% using the ECG pulse generator System 80 (H. Sundström, Sweden).

A calibration of the gas analyzer for the cardiopulmonary exercise test was performed before each test. The inaccuracy of the oxygen analyzer is less than 0.25% (Erich Jaeger GmbH, Hoechberg, Germany).

Statistical analysis

Measurements were expressed as mean values (± SD). The unpaired (two-tailed) t-test was used to study differences between men and women in paper I and the paired (two-tailed) t-test was used for studying individual changes between rest and exercise in papers I, II and V and to determine differences between the lateral and septal mitral annulus motion in paper IV. Continuous variables had principally a normal distribution on visual inspection of frequency histograms. Comparisons between continuous variables were therefore calculated by t-tests and analyses of variance (ANOVA). However, because of the relative small material non-parametric calculations were also done (Friedman ANOVA and Wilcoxon matched pairs test), which showed comparable results.

Pearson’s correlation coefficient was used to evaluate the correlations between LVEF at rest and the change in LVEF from rest to exercise (paper I) and between oxygen uptake and cardiac output at rest and during exercise (paper II). Cardiac output at maximal exercise was extrapolated from the linear regression equation between cardiac output and oxygen uptake at the lower workloads. Repeated-measures ANOVA was used to compare data groups in papers III-IV. Scheffé test was used for post-hoc comparisons. The level of statistical significance used was p < 0.05.
Results

Characteristics of the participants

Characteristics of the participants are presented in Tables 1-2. Significant differences were noted between male and female athletes in paper I on weight and length but not in age.

Table 1. General characteristics in the 30 male and 35 female orienteerers in paper I.

<table>
<thead>
<tr>
<th></th>
<th>Male orienteerers</th>
<th>Female orienteerers</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
<td>21 ± 3.9</td>
<td>20 ± 2.5</td>
<td>ns</td>
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<tr>
<td>Height (cm)</td>
<td>181 ± 7.0</td>
<td>170 ± 5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>68 ± 6.2</td>
<td>57 ± 4.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.87 ± 0.12</td>
<td>1.66 ± 0.07</td>
<td>&lt;0.001</td>
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Table 2. General characteristics of the 24 endurance athletes in papers II-V.

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<tr>
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<th>Range</th>
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<tr>
<td>Age (years)</td>
<td>26.2 ± 4.6</td>
<td>19 - 38</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181 ± 5</td>
<td>171 - 189</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>71.9 ± 7.5</td>
<td>55 - 85</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.91 ± 0.11</td>
<td>1.64 – 2.12</td>
</tr>
</tbody>
</table>

The maximum oxygen uptake in the 24 endurance athletes in papers II-V ranged from 56 to 78 ml/kg/min, with a mean maximum uptake of 67 ± 6 ml/kg/min.
Paper I

The results of the relative LV volumes and the changes in LVEF measured with RNV are given in Table 3. The heart rate increased from 55 ± 9 bpm at rest to 139 ± 13 bpm during exercise when the acquisition was performed.

Table 3. Data from the radionuclide ventriculography method in the 30 male and 35 female orienteers at supine rest and during supine exercise.

<table>
<thead>
<tr>
<th></th>
<th>Male orienteers</th>
<th>Female orienteers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.67 ± 0.05</td>
<td>0.69 ± 0.05</td>
<td>ns</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.72 ± 0.06</td>
<td>0.73 ± 0.05</td>
<td>ns</td>
</tr>
<tr>
<td>Difference</td>
<td>0.05 ± 0.05</td>
<td>0.04 ± 0.05</td>
<td>ns</td>
</tr>
<tr>
<td>EDC (counts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>24 025 ± 3 576</td>
<td>20 450 ± 8 231</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exercise</td>
<td>26 683 ± 4 794</td>
<td>23 579 ± 8 062</td>
<td>ns</td>
</tr>
<tr>
<td>Difference</td>
<td>2 658 ± 2 703</td>
<td>3 129 ± 3 049</td>
<td>ns</td>
</tr>
<tr>
<td>ESC (counts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>8 006 ± 2 018</td>
<td>6 328 ± 2 484</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Exercise</td>
<td>7 612 ± 2 353</td>
<td>6 360 ± 2 752</td>
<td>0.055</td>
</tr>
<tr>
<td>Difference</td>
<td>-394 ± 1 589</td>
<td>32 ± 1 838</td>
<td>ns</td>
</tr>
<tr>
<td>SC (counts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>16 018 ± 2 144</td>
<td>14 121 ± 5 949</td>
<td>ns</td>
</tr>
<tr>
<td>Exercise</td>
<td>19 071 ± 3 293</td>
<td>17 218 ± 5 817</td>
<td>ns</td>
</tr>
<tr>
<td>Difference</td>
<td>3 052 ± 2 496</td>
<td>3 096 ± 2 303</td>
<td>ns</td>
</tr>
</tbody>
</table>

EDC = end-diastolic counts; ESC = end-systolic counts. SC = stroke counts.

End-diastolic counts increased significantly in both female (15%) and male athletes (11%). The difference between males and females regarding the increase in end-diastolic counts was not statistically significant. In the total study population, end-diastolic counts increased by 13% (p<0.001). End-systolic counts showed no significant change from rest to exercise (Figure 1).
Stroke counts were found to increase by 21% (p<0.001). The increase in stroke counts showed no gender disparities.

In 54% of the athletes the LVEF showed a significant increase with exercise (>0.04 units); in 42% of the athletes, however, there was no change in LVEF. A significant decrease was seen in 5% of the athletes (one male and two females). A significant negative correlation (\( r = -0.38, \ p = 0.002 \)) was found between LVEF at rest and the change in LVEF from rest to exercise. There were no gender differences in LVEF at rest or during exercise.

Paper II

The echocardiographic findings in volume measurements at rest are presented in Table 4. Three athletes had a LVEF at rest between 0.40 and 0.50, but their LVEF increased with exercise to values above 0.65.
Table 4. Echocardiographic scan data in 24 endurance athletes at rest, sitting upright on the bicycle.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>53 ± 4</td>
<td>48 - 61</td>
</tr>
<tr>
<td>LV septum thickness (mm)</td>
<td>10.5 ± 1.5</td>
<td>7 - 14</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>175 ± 34</td>
<td>127 - 275</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>70 ± 25</td>
<td>38 - 130</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>105 ± 24</td>
<td>59 - 148</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.61 ± 0.10</td>
<td>0.40 – 0.77</td>
</tr>
</tbody>
</table>

LVEDD= left ventricular end-diastolic diameter; LVEDV= left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume.

LV end-diastolic volume was found to increase by 18% from upright rest to upright peak exercise at a heart rate of 160 bpm. The increase in end-diastolic volume contributed to 73% of the increase in stroke volume from rest to peak exercise and to more than 90% of the increase in stroke volume from a heart rate of 100 bpm up to 160 bpm (Figure 2).

Figure 2. Left ventricular end-diastolic and end-systolic volumes measured using the disc summation method at upright rest and during upright exercise in 24 endurance athletes (mean value and 95% confidence intervals of the mean).
The LV end-systolic volume decreased by 21% from rest to peak exercise. The main decrease in end-systolic volume was observed from rest to exercise at a heart rate of 100 bpm, representing 38% of the increase in stroke volume.

Stroke volume showed an almost linear 45% increase from rest to peak exercise. The oxygen pulse (oxygen uptake/heart rate) was also used to calculate stroke volume. The arterial-mixed venous oxygen difference has been reported to be close to 15 ml/100 ml blood (± 2 ml /100 ml) between a heart rate of 130 bpm up to maximal exercise 39-41. Consequently, we approximated the arterial-mixed venous oxygen difference to 15 ml /100 ml blood from a heart rate of 130 bpm up to maximal exercise. The stroke volume at a heart rate of 130 and 160 bpm estimated using the disc summation method showed no significant differences from the stroke volume estimated using the oxygen pulse (Figure 3).

Figure 3. Stroke volume at upright rest and during upright exercise in 24 endurance athletes measured using the disc summation method and stroke volume calculated from the oxygen pulse divided by the estimated arterial-mixed oxygen difference of 15 ml /100 ml blood (mean value and 95% confidence intervals of the mean).
The increase in cardiac output from rest to exercise was 3.3 times at a heart rate of 160 bpm. Using the linear regression equation (r = 0.87, p = 0.002) between cardiac output estimated using the disc summation method and oxygen uptake (cardiac output = 3.62 + oxygen uptake /159), the maximal estimated cardiac output at maximal oxygen uptake was 33 ± 3 l/min, an increase of 4.4 times from rest to maximal exercise.

Paper III

The findings regarding Doppler measurements at upright rest and during upright exercise are outlined in Table 5.

Table 5. Doppler measurements at upright rest and during upright exercise in 24 endurance athletes.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>100 bpm</th>
<th>130 bpm</th>
<th>160 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak transmitral flow velocity (m/s)</td>
<td>0.62 ± 0.13</td>
<td>0.97 ± 0.11***</td>
<td>1.20 ± 0.18***</td>
<td>1.43 ± 0.22***</td>
</tr>
<tr>
<td>Mean transmitral flow velocity (m/s)</td>
<td>0.28 ± 0.07</td>
<td>0.66 ± 0.11***</td>
<td>0.84 ± 0.10***</td>
<td>1.02 ± 0.15***</td>
</tr>
<tr>
<td>Peak transaortic flow velocity (m/s)</td>
<td>1.14 ± 0.17</td>
<td>1.64 ± 0.20***</td>
<td>1.96 ± 0.32***</td>
<td>2.20 ± 0.27***</td>
</tr>
<tr>
<td>Transmitral mean pressure gradient (mmHg)</td>
<td>0.54 ± 0.36</td>
<td>2.35 ± 0.58***</td>
<td>3.84 ± 1.27***</td>
<td>5.42 ± 1.77***</td>
</tr>
<tr>
<td>Ejection time (ms)</td>
<td>268 ± 22</td>
<td>237 ± 15***</td>
<td>199 ± 20***</td>
<td>184 ± 17*</td>
</tr>
<tr>
<td>Filling time (ms)</td>
<td>588 ± 93</td>
<td>197 ± 26***</td>
<td>175 ± 22</td>
<td>156 ± 19</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>76 ± 31</td>
<td>41 ± 15***</td>
<td>30 ± 12</td>
<td>29 ± 14</td>
</tr>
</tbody>
</table>

IVRT= isovolumetric relaxation time. Level of significance compared with rest or previous exercise level: * = p < 0.05, *** = p < 0.001

Both peak diastolic and systolic flow velocities increased linearly during exercise. At peak exercise (heart rate of 160 bpm), the maximum transmitral flow velocity had more than doubled and the peak aortic flow velocity had nearly doubled. The calculated transmitral mean pressure gradient showed a significant and linear increase at each level of exercise. From rest to peak exercise, the calculated mean transmitral pressure gradient showed a tenfold increase from 0.54 mmHg to 5.42 mmHg (Figure 4).
Figure 4. The transmitral peak flow velocity and the calculated mean pressure gradient at upright rest and during upright exercise in 24 endurance athletes (mean value and 95% confidence intervals of the mean).

The ejection time declined as exercise intensity increased, with a significant decrease at each level of exercise (Table 5, Figure 5). From rest to peak exercise, the mean ejection time was shortened by 31%, from 268 ± 22 ms to 184 ± 17 ms. The filling time decreased markedly during early exercise. At a heart rate of 100 bpm the mean filling time had decreased by 66%, from 588 ± 93 ms to 197 ± 26 ms. There was no further significant decrease in filling time at subsequent heart rate levels. From rest to peak exercise, the mean filling time was shortened by 73% (Table 5, Figure 5).
Figure 5. Left ventricular filling time and ejection time at upright rest and during upright exercise in 24 endurance athletes (mean value and 95% confidence intervals of the mean).

The mean decrease in isovolumetric relaxation time was 46% from rest to exercise at a heart rate of 100 bpm (from 76 ± 31 ms to 41 ± 15 ms). However, with greater exercise intensity and a higher heart rate, the isovolumetric relaxation time showed a slight but non-significant decline between the different exercise levels. From rest to peak exercise, the isovolumetric relaxation time was shortened by 62%.

The filling rate, i.e. volume per time, was calculated by dividing the stroke volume (assessed from paper II) by the filling time. The filling rate was 185 ± 62 ml/sec at rest and increased significantly (p < 0.05) at each level of exercise to 986 ± 192 ml/sec at peak exercise (Figure 6).
**Figure 6.** Left ventricular filling rate measured as stroke volume per filling time in the upright position at rest and during exercise in 24 endurance athletes (mean value and 95% confidence intervals of the mean).

**Paper IV**

The mitral annular motion at upright rest and during upright exercise is outlined in Table 6.
Table 6. Mitral annular motion in 24 male endurance athletes at upright rest and during upright exercise.

<table>
<thead>
<tr>
<th></th>
<th>Rest Mean ± SD</th>
<th>100 bpm Mean ± SD</th>
<th>130 bpm Mean ± SD</th>
<th>160 bpm Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAM, septal wall (mm)</td>
<td>10.9 ± 2.3</td>
<td>16.3 ± 2.4***</td>
<td>17.3 ± 2.2</td>
<td>18.3 ± 2.3</td>
</tr>
<tr>
<td>MAM, lateral wall (mm)</td>
<td>12.4 ± 2.1</td>
<td>17.4 ± 2.1***</td>
<td>18.0 ± 2.3</td>
<td>18.5 ± 1.7</td>
</tr>
<tr>
<td>Mean MAM (mm)</td>
<td>11.6 ± 2.0</td>
<td>16.9 ± 2.1***</td>
<td>17.6 ± 2.0</td>
<td>18.4 ± 1.7</td>
</tr>
</tbody>
</table>

MAM = mitral annulus motion. Level of significance compared with rest or previous exercise level: *** = p < 0.001

At rest, the mitral annular excursion was 13% higher in the lateral wall than in the septal wall (p < 0.001). The mitral annular motion increased significantly during early exercise. At a heart rate of 100 bpm, the amplitude had increased by 49% in the septal wall (p < 0.001) and by 40% in the lateral wall (p < 0.001). However, with further intensity and a higher heart rate, the mitral annular excursion showed only a slight, non-significant increase. From rest to peak exercise at a heart rate of 160 bpm, the amplitude increased in the septal and lateral wall by 68% and 49%, respectively. There was no significant difference between the mitral annular motion in the lateral and septal walls at peak exercise (Figure 7).
Figure 7. M-mode measurements of the septal and lateral parts of the mitral annular motion in 24 male endurance athletes at rest and during exercise (mean value and 95% confidence intervals of the mean).

LV total long-axis length from epicardial apex to the middle of mitral annulus at end-diastole showed no significant change from rest to exercise but the long-axis end-systolic length decreased by 5% compared with resting values at a heart rate of 160 bpm (Figure 8).
Figure 8. Left ventricular total long-axis length in end-diastole and end-systole at upright rest and during upright exercise in 24 male endurance athletes (mean value and 95% confidence intervals of the mean).

Paper V

The LV end-diastolic dimensions at upright rest and during upright exercise measured as the average of apical four- and two-chamber views from endocard to endocard are shown in Table 7. The LV geometrical alterations are presented in Figure 9.
Table 7. Echocardiographic left ventricular end-diastolic inner endocardial long- and short-axis measurements at different levels from the mitral annulus to apex in 15 endurance athletes at upright rest and during upright exercise at a heart rate of 160 bpm.

<table>
<thead>
<tr>
<th></th>
<th>Rest (mm) Mean ± SD</th>
<th>Exercise (mm) Mean ± SD</th>
<th>Change from rest to exercise (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>91 ± 4.7</td>
<td>95 ± 4.7</td>
<td>4</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>1</td>
<td>49 ± 4.2</td>
<td>53 ± 4.1</td>
<td>8</td>
<td>p= 0.003</td>
</tr>
<tr>
<td>2</td>
<td>56 ± 4.8</td>
<td>61 ± 3.6</td>
<td>9</td>
<td>p= 0.004</td>
</tr>
<tr>
<td>3</td>
<td>56 ± 5.5</td>
<td>63 ± 5.0</td>
<td>13</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>4</td>
<td>51 ± 6.0</td>
<td>59 ± 4.0</td>
<td>14</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>5</td>
<td>42 ± 5.3</td>
<td>49 ± 4.7</td>
<td>14</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>6</td>
<td>28 ± 3.5</td>
<td>35 ± 4.0</td>
<td>20</td>
<td>p&lt; 0.001</td>
</tr>
</tbody>
</table>

0 = LV long axis; 1-6 LV short-axis measurements at subsequent levels from mitral annulus to apex.

All short-axis diameters showed a significant increase between 8-20% from rest to exercise at a heart rate of 160 bpm, with the largest increase in the apical part of the LV. The smallest relative increase from rest to exercise in the LV short-axis measurements was observed closest to the mitral valve annulus.

The LV internal long-axis (level 0) showed a significant increase from rest to exercise though the absolute increase in LV cavity length was small (4%).
Figure 9. Echocardiographic LV end-diastolic inner geometry at upright rest (broken line) and during upright exercise at a heart rate of 160 bpm (unbroken line) in 15 male endurance athletes. The figure is constructed from measurements averaged from apical four- and two-chamber views.
Discussion

Stroke volume

Large amounts of data have illustrated how long–term endurance training is associated with morphological cardiac alterations such as increased cavity dimensions, wall thickness and LV mass. It has been suggested that these changes represent hemodynamic adaptations to intensive and prolonged exercise. Despite the large quantity of studies on LV performance in endurance athletes at rest, data regarding basic physiological concepts during exercise are conflicting.

In the 1960s, Åstrand et al. demonstrated that during upright exercise cardiac stroke volume reached its upper limit at a heart rate of approximately 110 bpm, indicating that stroke volume achieved its upper limit at a low exercise level. Since then, it has generally been accepted that during incremental exercise stroke volume plateaus at approximately 50% of maximal oxygen uptake. However, as the maximal heart rate in athletes is equal to the maximal heart rate in sedentary subjects, the high cardiac output seen in endurance athletes can only be explained by a large stroke volume. Using cardiac catheterization, Ekblom and Hermansen found that during upright exercise an almost 100% increase in stroke volume is required to explain the large increase in cardiac output in fit endurance athletes. We demonstrated an almost linear increase in stroke volume by 45% from upright rest to upright sub-maximal exercise at a heart rate of 160 bpm. The increase in end-diastolic volume explained 73% of the total increase in stroke volume. The stroke volume assessed by contrast echocardiography and the stroke volume predicted from the cardiopulmonary exercise test showed an almost linear relationship with increased intensity of exercise. An increase in end-diastolic volume has been suggested to be the major contributing factor augmenting LV stroke volume during upright exercise. The increase in ejected stroke volume may be partly explained by the Frank-Starling mechanism stating that, within physiological limits, the force generated by the contracting muscle is greater if the muscle has been previously stretched.

In modern textbooks of heart physiology it is still the recognized “truth” that stroke volume increases initially, followed by a near-plateau at higher exercise levels. These assumptions are largely based on the early findings
from invasive studies with the dye-dilution techniques. Ekblom and Hermansen and Åstrand et al. reported that stroke volume progressively increases to approximately 50% of maximal oxygen uptake \(^9,10\). However, in the paper of Ekblom and Hermansen nine of the 13 well-trained athletes reached their maximal stroke volume at maximal exercise \(^9\). Furthermore, in the data presented by Åstrand et al. \(^11\) of the 23 well-trained students reached maximal stroke volume at maximal exercise \(^10\). Unfortunately, these findings were ignored and it became a physiological paradigm that stroke volume plateaus during incremental upright exercise.

Mitral annulus motion and its contribution to stroke volume

A small number of studies have examined mitral annular motion during and after exercise \(^46-48\) but to our knowledge no one has examined individuals at upright rest followed by upright exercise. At upright rest, the mean mitral annulus motion is less compared with supine rest, probably because of a lower preload in the upright position \(^49\). The mean mitral annulus motion in our athletes was 11.6 mm, slightly higher than the mitral annulus excursion seen in 10 normal individuals studied by Sundblad et al. \(^49\). It is well known that at rest the lateral part of the annulus has a significantly larger amplitude of motion than the septal \(^50-52\). It has been suggested that the reason for this difference is that the LV lateral free wall is relatively more stretched during LV filling \(^49\). Other possible explanations are the presence of prominent longitudinally arranged fibers in the lateral LV wall or a discrepancy in papillary muscle contraction dynamics. Our data confirm that at rest the motion of the lateral part of the mitral annulus has larger amplitude than the septal part. However, during peak exercise, the septal and lateral excursions showed no differences in amplitude. Further, the axial end-diastolic length measured from the epicardial apex to the middle of the mitral annulus remained unchanged from upright rest to upright exercise. A further increase in LV end-diastolic volume should therefore be explained by mainly an increase in the LV short-axis diameters. This explanation was confirmed in paper V. Overall the LV end-diastolic configuration becomes more spherical during exercise with the largest increase in the short-axis diameters in the mid and apical parts of the LV. The increase in the LV short-axis diameters was smallest the closer to the mitral annulus. This observation is probably explained by the relative rigid fibrous ring protecting the annulus from dilating to avoid mitral regurgitation during heavy exercise.

The LV length response during exercise found in the present study is similar to the findings of Sundblad and Wranne, who examined the effects of posture on LV cavity dimensions \(^49\). They found no increase in LV end-
diastolic total axial length from upright to supine position but an increased axial LV shortening at end-systole and an increase of the short-axis diameter from upright to supine position. Our data suggest a similar LV response from upright rest to upright exercise as from upright to supine position, i.e. a geometrically more spherical LV during exercise.

Previous studies have illustrated that the mitral annular excursion plays an important role in the systolic pump function of the normal human heart at rest\(^36,53-56\). The mitral annular motion has been shown to be higher in trained than untrained individuals at rest, suggesting that the mitral annular excursion is important in the understanding of cardiac dynamics in athletes\(^57,58\). The contribution of mitral annulus motion to stroke volume can be approximately calculated by multiplying the mitral annulus motion by the epicardial short-axis area. Contraction of the longitudinal fibers causes shortening of the LV chamber along its longitudinal axis. As the outer LV diameter during the cardiac cycle is almost unchanged and the myocardial tissue volume nearly non-compressible, an axial shortening will inevitably cause a reduced radial inner diameter during systole\(^49,54,59\). Therefore, the epicardial diameter should be used when calculating the area. Because the short-axis areas vary by the range of mitral annulus motion, we used the mean of the largest and shortest short-axis area from the internal cavity measurements of the base of the LV, presuming that the LV wall was 10 mm in diameter. The calculated contribution from mitral annulus motion to stroke volume was approximately 50-60\% of the stroke volume at a heart rate of 160 bpm.

**Stroke volume during maximal exercise**

Because the LV volumes were not assessed during maximal exercise, we can only speculate on the volume response during maximal endurance exercise. Using the linear regression relation between cardiac output and maximal oxygen uptake, the predicted stroke volume calculated at maximal exercise was found to increase by almost 70\%. The data show an almost linear increase in stroke volume with increased intensity of exercise. Moreover, the increase in stroke volume from a heart rate of 100 bpm up to 160 bpm was to more than 90\% explained by an increase in end-diastolic volume. It is conceivable that the mechanism for achieving a further increment in stroke volume during intensive exercise is a further increase in end-diastolic volume. Whether this adaptation can be explained by the Frank-Starling mechanism or a poorly understood inflow/outflow auto regulation remains to be discovered.
Stroke volume during supine exercise

When measured by RNV, we were able to demonstrate during exercise in the supine position an increase in stroke volume by 21% with a relative increase in LV end-diastolic volume of 13%. Jensen-Urstad et al. reported comparable results, finding a 14% increase in end-diastolic volume and a 25% increase in stroke volume with exercise in athletes. Compared with paper II where the exercise tests were performed at the upright position, the maximal heart rate at the supine position was less during image acquisition (70% of the age-expected maximal heart rate in contrast with 82% during upright exercise).

A reclining position allowed improved venous return, which leads to increased stroke volume before exercise. Therefore, because of the increased preload at rest, a large increase in LV end-diastolic volume during exercise is not expected. The present investigation suggests that the adjustments in LV volumes during supine exercise are small, implicating a balance between filling volumes and ejection before exercise.

Disparities between exercise in the upright and supine position in preload settings noted during mild or moderate exercise may, however, be less pronounced during maximal exercise and the volume reply may even be similar for both supine and upright exercise.

Filling dynamics

During heavy exercise, LV filling is rapid and efficient, emphasizing the stroke volume as a delicate balance between maintaining an optimal filling and ejection. Assuming that the postulation of Frank-Starling in the intact human heart is correct, optimal filling is a necessity for optimal ejection, suggesting that the LV is a preload-dependent pump with closely linked filling and ejection. To our knowledge, no one has been able to explain the physiology underlying the efficient, fast LV loading during exercise. Few studies have focused on the diastolic filling dynamics in athletes during upright exercise.

Ventricular relaxation is a complex energy-dependent process in which the contractile elements are deactivated and the myocytes return to their precontraction state. LV relaxation starts in mid-systole and ends during the first part of the early filling period. The isovolumetric relaxation time is a part of LV relaxation and is measured from the end of aortic flow to the beginning of LV inflow. The LV ejection time, isovolumetric relaxation time and diastolic filling time are all reduced during exercise, suggesting that the duration of the biochemical relaxation is shortened during exercise. Libonati demonstrated an inverse correlation between peak treadmill time and LV isovolumetric relaxation time in men at rest. Furthermore, Vanoverschelde
et al. reported a reduction in isovolumetric relaxation time in persons with higher exercise capacity compared with persons with lower exercise capacity. Faster LV relaxation may increase the early transmitral pressure gradient and facilitate the “suction” of blood into the LV during early filling. These data are supported by Nixon et al., who showed that peak filling velocity was significantly higher in athletes compared with sedentary men in supine exercise from a heart rate of 140 bpm, suggesting that the filling is altered by training. An additional physiological explanation for the decrease in isovolumetric relaxation time during exercise is that the increase in the transmitral mean pressure gradient advances the mitral valve opening and thereby reduces the isovolumetric relaxation time.

We demonstrated an almost linear increase in the transmitral mean pressure gradient from 0.5 mmHg at rest to 5 mmHg at peak exercise at a heart rate of 160 bpm. There are several limitations to transmitral Doppler measurements during exercise (see study limitation). The absolute values should be interpreted with caution but may illustrate the relative changes in the mean transmitral pressure gradient during exercise, i.e. a linear increase during incremental exercise.

The mean transmitral pressure gradient acts as a driving force that propels blood into the ventricle. The increase in the transmitral mean pressure gradient during exercise indicates an increase in left atrial (LA) pressure and/or a decrease in LV filling pressure. Previous studies have shown an increase in the pulmonary capillary wedge pressure from 4-7 mmHg from upright rest to upright exercise, reflecting an augment in the mean LA pressure. Udelson et al. reported that an isoproterenol infusion (simulating the adrenergic stimulation of the myocardium by exercise) lowered the LV pressure in diastole (range -0.5 to -2.4 mmHg) and increased transmitral flow velocity in seven of eight sedentary men and women. Thus, the increased mean pressure gradient is probably best explained by both an increase in LA pressure and a decrease in LV filling pressure creating an increased driving force between LA and LV during exercise.

The increase in the transmitral pressure gradient is necessary to achieve the substantial increase in the LV filling rate measured as volume per time during exercise. By dividing the stroke volume by filling time, filling rate was assessed. The calculated filling rate was 185 ± 62 ml/s at rest and it increased to 986 ± 192 ml/s at peak exercise. Despite an increase in heart rate and a reduction in filling time by 73%, the filling rate measured as volume per time increased five times from rest to peak exercise, suggesting a large filling capacity in the normal endurance athlete’s heart.
Theories of LV filling dynamics during exercise

The physiology behind the ultra-fast and efficient LV loading during exercise is poorly understood. The axial shortening during systole is a complex motion consisting of both axial and torsion deformation. It has been suggested that the ultra-fast untwisting recoil stored in the myoelastic elements during systole may be an important source of energy for maintaining a rapid early filling \(^{69}\). An increased shortening observed during exercise may increase the stored energy in the myoelastic untwisting elements. The energy stored in the myoelastic elements during ventricular systole and the force created by atrial contraction may be two potential sources of energy for displacement of the atrioventricular (AV) plane and expansion of the LV cavity during LV filling.

Applying the hydrodynamic model (when mechanical energy is converted to fluid energy and fluid energy back to mechanical energy) on the circulatory system, i.e. the contraction force in LV is converted to fluid energy (pressurized fluid) and into blood flow during ventricular contraction, is of no controversy. However, there is no general agreement that hydraulic forces play a key role during LV loading. As the AV-plane moves towards apex during systole, the LA size increases and blood is sucked from the pulmonary veins into LA. To maintain efficient filling during heavy exercise (a filling time of no more than 150 ms) it is reasonable to assume that a large blood pool close to the mitral valve in late systole is required. To avoid a high backward pressure in late ventricular systole the LA is mainly enlarged by an increased systolic AV-plane excursion. Furthermore, in late ventricular systole the fluid energy in LA increases in parallel with an increase in mean pulmonary wedge pressure from rest to maximal upright exercise by 4-7 mmHg \(^{66,67}\) (reflecting an increased LA pressure) and, subsequently, an increase in the trans-mitral driving pressure and blood volume. The transformation of fluid power to flow and mechanical power may be potential forces serving to comprehend the ultra fast LV loading during exercise. It further suggests that the systolic AV-plane excursion is crucial for the optimal and ultra fast low pressure LV filling during exercise. As the hydraulic forces progressively increase during exercise, the LV loading will, within physiological limits, become increasingly efficient. Because an optimal LV filling is necessary for an optimal ejection, the LV filling and ejection are closely linked through the AV-plane excursion, i.e. a potential LV AV-plane in -and output auto regulation.
Radionuclide ventriculography for measuring stroke volume

RNV as a method for measuring heart volume has been validated in several investigations\(^7^0^-^7^2\). The end-diastolic volume and end-systolic volume can be determined because the counts within the image area are directly proportional to volume. The investigations have reported good correlations. Sorensen et al. compared RNV with the Fick method in 9 healthy male volunteers during maximal supine exercise\(^7^1\). They reported no difference between the cardiac output derived from the different methods. In another report Melin et al. showed that radionuclide technique underestimated cardiac output\(^7^3\). Melin et al. compared the direct Fick method with RNV during rest and submaximal exercise in 9 healthy volunteers and 10 patients with hypertension. They found a good correlation between the two methods but RNV consistently underestimated cardiac output\(^7^3\). The important methodological limitations are the long acquisition time in which the number of unlabeled erythrocytes increases with time and that a correct background subtraction is crucial for correct volume measurements\(^7^4\).

Echocardiography for obtaining heart volumes

Although stress echocardiography has been shown to be a reasonable sensitive method for detection of myocardial ischemia\(^7^5^-^7^7\), little information is available on LV cavity or volume changes during exercise in normal persons or in patients with heart disease.

The modified Simpson’s formula is an established method for LV volume determination\(^3^4,^3^5\). Fundamental two-dimensional apical echocardiographic imaging has been shown to produce a systematic underestimation of LV volumes when compared with cineventriculography\(^7^8\). This underestimation may be due to an outlining of the inner contour of the LV trabeculation or difficulties in obtaining the true LV axis. Using transpulmonary contrast imaging, a more distal outlining can be achieved in that the contrast agent enters the space between the trabeculations. A large amount of data has been reported on the use of second harmonic imaging and contrast echocardiography\(^7^9^-^8^1\). Contrast echocardiographic opacification of the LV has been shown to increase the overall endocardial border depiction and improve measurement variability and wall motion enhancement. In one study, Hundley and co-workers compared two-dimensional fundamental contrast echocardiography with magnetic resonance imaging for LV volume determination\(^8^2\). The LV volume assessments in patients with normal LVEF showed good agreement between the methods, with no significant differences in end-diastolic or end-systolic volumes.
Ejection fraction

Stroke volume normalized for the LV end-diastolic volume (the LVEF) is the most commonly used index of systolic function. In paper I, 54% of the athletes had a significant increase in LVEF and 5% displayed a significant decrease in LVEF from rest to exercise. There was a negative correlation between LVEF at rest and the change with exercise. Thus, all athletes showing a decrease in LVEF with exercise had LVEF values above 0.6 units at rest. In a study in which LVEF was determined by echocardiography, Fisman et al. found that 41% of the athletes had less than a 0.05-unit increase or even a slight decrease in LVEF. The increase in LVEF from rest to exercise was lower in athletes as compared with untrained persons. Employing RNV Rerych et al. observed a significant decrease in LVEF at rest after exercise, but a larger increase in LVEF from rest to exercise in trained individuals as compared with untrained individuals. One explanation for the inconsistencies in LVEF response during exercise is the measurement variability, which varies considerably depending on the method used (i.e. RNV versus echocardiography). The differences between two measurements in our laboratory have previously been shown to be ± 0.04 units (95% confidence interval) for LVEF at rest as measured using RNV and 0.12 units (two standard deviations) as measured by echocardiography. Similar reproducibility has been shown in other reports. When comparing the variation in LVEF as measured by echocardiography and RNV in 34 patients at our laboratory, the mean difference between the methods was 0.05 units (SD 9.2) (unpublished data).

LVEF is influenced by the inotropic state and disparate load settings (consequently different inotropic and different pre-and afterload conditions), which are additional explanations to the inconsistencies in LVEF response. Furthermore, our study demonstrates that the increase in LV end-diastolic volume is the major factor contributing to the increase in stroke volume. In view of the fact that LVEF is stroke volume normalized for the end-diastolic volume, LVEF is a poor variable for studying LV hemodynamics. Therefore, LVEF should be used with caution as a predictor of cardiovascular functional state in endurance athletes.

The right ventricle

The evidence for diastolic ventricular interaction between the right and left side is indisputable and it is well documented that the pericardium enhances the interaction between the ventricles. As both ventricles are encircled by the same muscle fibers, share the septal wall and are enclosed within the pericardium, an increase in end-diastolic volumes during exercise would inevitably cause a deterioration of the ventricular filling properties. However,
ever, we have illustrated that the LV filling rate increased almost linearly to a heart rate of 160 bpm, suggesting that the LV filling does not plateau or decline at this level of exercise. Furthermore, as the absolute axial annular excursion increased more in the septal than in the lateral part of the annulus and the axial end diastolic length (measured from epicardial apex to mitral annulus) remained unchanged during exercise, it is, according to the Frank-Starling mechanism, reasonable to expect that during exercise the relative increase in septal short-axis stretch is greater than the stretch produced in the lateral free wall. These findings may suggest that the expansion of the LV toward the RV is somewhat larger than the extension of the LV free wall toward the pericardium. Assuming that the RV end-diastolic volume remains unchanged or increases during exercise and that a given amount of exercise demands similar cardiac output in both the RV and LV, a septal shift toward the right would decrease the filling properties in a normal athlete’s RV. A possible solution to this physiological enigma is disparate LV and RV end-diastolic responses to exercise. Data provided by Morrison et al. illustrate that the RV ejection fraction increased more than the LVEF during supine exercise. As the RV and LV must increase the stroke volume to the same extent, their suggestion is that there is a decrease in RV end-diastolic volume and, consequently, an even larger decrease in end-systolic RV volume during exercise. The data of Morrison et al. further illustrate that RV systolic function is afterload-dependent as the RV ejection fraction showed a close inverse relation to total pulmonary vascular resistance. These data indicate disparate dynamic responses for increasing cardiac output during exercise in the LV and RV, i.e. a preload-dependent LV and an afterload-dependent RV. This reasoning also explains how the LV end-diastolic volume may increase during exercise without a deterioration of the filling properties in the normal athlete’s heart.

Methodological considerations and study limitations.

Some of the discrepancies found when exploring LV volume changes from rest to exercise can be reasonably explained by differences in study populations, type of activity, workload, level of training and upright versus supine exercise. Difficulties in analyzing the data may also be due to measurement variability. However, several limitations of this study need to be carefully considered:

1. The data acquisitions from the RNV and the echocardiographic imaging were not obtained during maximal exercise. Therefore, our data are only valid for endurance athletes during submaximal exercise.
2. To minimize rotational and imaging plane errors (such as missing the true LV axis during the echocardiographic examinations) the images representing the largest possible cavity length were used in both apical four- and two-chamber views. In apical four-chamber view there is a risk of an anterior-posterior imaging plane that deviates from the LV central axis causing an underestimation of the true LV axis and several short-axis measurements. However, these potential errors should not influence the relative volume alterations from upright rest to upright exercise.

3. As a contrast agent was administrated during exercise color flow mapping could not be performed. Therefore, we cannot exclude that mitral regurgitation during exercise may have implied a volume load contributing to the LV end-diastolic cavity enlargement. However, at rest in supine position no participant had a mild, moderate or severe mitral regurgitation.

4. The images were not obtained in a specific part of the respiratory cycle. The present report does not provide any information excluding the power of large and rapid alterations in the intrathoracic pressure during exercise. These respiratory-induced alterations may increase the ventricular interdependence and generate a larger beat to beat variation in the LV end-diastolic volume during exercise as compared with resting conditions.

5. Because invasive measurements were not performed, the arterial-mixed venous oxygen difference was not assessed. Thus, several investigators have shown that oxygen uptake and the arterial-mixed venous oxygen difference during incremental exercise are related by a curvilinear function, i.e. with an initial marked increase in the arterial-mixed venous oxygen difference followed by a small increase during heavy exercise. The arterial-mixed venous oxygen difference has been reported to be close to 15 ml/100 ml blood (+ 2 ml /100 ml) between a heart rate of 130 bpm up to maximal exercise, which is the rationale for the approximation of the arterial-mixed venous oxygen difference to 15 ml/100 ml blood.

6. Because of the motion of the heart during exercise and the heavy respiration, the transducer position cannot be standardized. The Doppler echocardiographic method might therefore not be expected to be a highly precise indicator of changes in transmirtal and aortic flow velocities. Nevertheless, the identification of mitral and aortic curves was not difficult.

7. There are two potential errors in measuring velocities and pressure gradients with spectral Doppler: Doppler angle misalignment and spectral
broadening. Doppler spectrum is not a single frequency, but is broadened because of the geometry of the ultrasound beam. This effect is termed spectral broadening and is attributed to two effects: the transit time of the scatter across the sample volume and the range of angles over which the scatter receives pulses from the transducer and reflects them back. The minimum and maximum velocities will decrease and increase, respectively, as the Doppler spectrum broadens. Thus, because of spectral broadening, the true maximum velocities are always overestimated. During exercise, there was a large spectral broadening. Therefore, the true aortic and mitral flow velocities may be overestimated. This gives a potential larger overestimation of the transmitral mean pressure gradient in that the velocity is squared in the equation for measuring the pressure gradient. However, these potential errors should not influence the relative changes between the different levels of exercise.

8. The transmitral mean gradient was calculated according to the simplified Bernouilli equation neglecting the subvalvular velocity V1. As V1 may increase during exercise, the mean transmitral pressure gradient could be overestimated.

9. The Doppler measurements were performed at a speed of 50 mm/s. Consequently, when calculating short-time intervals at high heart rates, the temporal resolution is low. Therefore, the isovolumetric relaxation time measurements during exercise should be interpreted with caution.

10. We did not obtain either anterior or posterior mitral annular excursion. These measurements might have improved the measurement of the true mitral annular excursion.
Conclusions

- We found only small changes in LV volumes with supine submaximal exercise in male and female endurance athletes, suggesting a high preload before exercise. The LV end-diastolic volumes increased but no change in end-systolic volumes was observed.

- There were no gender disparities concerning the LV volume and LVEF reply during supine submaximal exercise in endurance athletes.

- Using transpulmonary contrast echocardiography, we demonstrated an almost linear increase in stroke volume during increased intensity of upright exercise in male endurance athletes. This was explained by a linear increase in end-diastolic volume and an initial small decrease in end-systolic volume.

- We found major changes in LV diastolic filling indices during upright exercise in male endurance athletes. The mean transmitral pressure gradient increased linearly as the mean diastolic time decreased, with large reductions in mean LV filling time and isovolumetric relaxation time. Despite the shortened filling time, the LV is able to increase the filling rate (measured as volume per time) five times, suggesting that the LV has a large filling capacity in endurance athletes.

- At upright rest, mitral annular motion was significantly higher in the lateral than in the septal border. During upright exercise, mitral annular motion increased with no difference between septal and lateral annular motion at peak exercise in male endurance athletes. Furthermore, the increase in LV end-diastolic volume seen during exercise could not be explained by an augmentation of the absolute total end-diastolic axial length.

- LV end-diastolic internal cavity measurements increased during upright exercise in male endurance athletes. LV cavity became geometrically more spherical, with the largest increase in the LV end-diastolic short-axis cavity diameters in the mid and apical parts of the LV during exercise.
Populärvetenskaplig sammanfattning

I litteraturen finns omfattande dokumentation avseende vänster kammares anpassning till långvarig fysisk träning. Denna anpassning benämns ofta som ”idrottshjärta”. Det är dock omdiskuterat hur vänster kammare arbetar under ansträngning. Denna avhandling redovisar resultaten av studier på vänster kammare under pågående arbete hos 89 uthållighetsidrottare, flera på elitnivå.

Under liggande cykling undersöcktes 35 kvinnliga och 30 manliga orienterare med radionuklidangiografi. Vänster kammar studerades i sin fyllnadsfas (diastole) och i sin tömningsfas (systole). Vänster kammarens slagvolym ökade genom en ökning av fyllnadsvolymen från vila till arbete vid 70 % av maximal hjärtfrekvens. Förändringarna i vänster kammarens fyllnad jämfört med vila var dock små. Detta talar för att vänster kammare är välfylld redan i vila i liggande ställning. Ingen skillnad kunde ses mellan kvinnor och män.

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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)