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2010

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Citation for published version (APA):

Steding Ehrenborg, K. (2010). *Exercise physiology and cardiac function. Aspects on determinants of maximal oxygen uptake*. [Doctoral Thesis (compilation), Clinical Physiology (Lund)]. Department of Clinical Physiology, Lund University.

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Lund University, Faculty of Medicine Doctoral Dissertation Series
2010:90

Exercise physiology and cardiac function

Aspects on determinants of maximal oxygen
uptake

KATARINA STEDING



LUND UNIVERSITY

Doctoral Thesis
2010

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The public defense of this thesis for the degree Doctor of Philosophy in Medicine will, with due permission from the Faculty of Medicine at Lund University, take place in Föreläsningssal 3, Skåne University Hospital, Lund, on 15 October 2010.

Cover:

Long-axis images in 4 ch view of a female control, male control, female triathlete and male triathlete. This figure illustrates the increase in cardiac dimensions with endurance training. Note that the female triathlete (height 1.80 m, weight 70 kg) has a larger heart than the male control subject (height 1.81 m, weight 80 kg).

ISSN 1652-8220

Department of Clinical Physiology, Lund University

ISBN 978-91-86671-06-8

SE-221 85 LUND, Sweden

A full text electronic version of this thesis is available at
<http://www.lu.se/forskning/avhandlingar-och-publikationer/avhandlingar>

Typeset using L^AT_EX and the template lumedthesis.cls ver 1.2,
available at <http://www.hedstrom.name/lumedthesis>

Printed by: Mediatryck, Lund, Sweden

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*I have a dream, a song to sing
to help me cope with anything
If you see the wonder of a fairy tale
you can take the future even if you fail
I believe in angels
something good in everything I see
I believe in angels
when I know the time is right for me
I cross the stream, I have a dream*
—B. ANDERSSON AND B. ULVAEUS

*To wear your heart on your sleeve isn't a very good plan. You should wear it
inside, where it functions best.*
—MARGARET THATCHER

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List of Publications

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

- I. **Steding K**, Engblom H, Buhre T, Carlsson M, Mosén H, Wohlfart B, Arheden H. Relation between cardiac dimensions and peak oxygen uptake. *Journal of Cardiovascular Magnetic Resonance* 2010 Feb 1;12(1):8.
- II. Engblom H, **Steding K**, Carlsson M, Mosén H, Hedén B, Buhre T, Ekmeahag B, Arheden H. Cardiac reserve index as a novel method for diagnosing heart failure: MR imaging and peak oxygen uptake in heart failure patients, healthy volunteers and athletes. Submitted.
- III. **Steding K**, Buhre T, Arheden H, Wohlfart B. Respiratory indices by gas analysis and fat metabolism by indirect calorimetry in normal subjects and triathletes. *Clinical Physiology and Functional Imaging* 2010, 30(2):146-151
- IV. **Steding K**, Carlsson M, Arheden H. Cardiac pumping in athletes and normal subjects. Manuscript.

Summary

Already in 1899, Henschen in Sweden investigated the relationship between cardiac size and success in cross country skiing. The cardiac size was then determined from chest percussion. Today, cardiac volumes and mass can be determined with high accuracy from cardiovascular magnetic resonance imaging (CMR). Although the athlete's heart has been of interest for many researchers for over 100 years, further characterization of the athlete's heart is needed in order to understand how training affects cardiac dimensions and function. Few studies have investigated the effects of training in female athletes and few have compared males and females. Therefore, the overall aim of this thesis is to characterize the physiologically enlarged athlete's heart and the healthy respiratory response to exercise in both males and females, in order to facilitate the differentiation between the physiologically enlarged heart and the pathologically enlarged heart.

Paper I showed that the total heart volume (THV) increase with training in both males and females, with a balanced enlargement of the left and right ventricle. Furthermore, THV was a strong, independent predictor of peak oxygen uptake ($\dot{V}O_{2peak}$). Males had a larger left ventricular mass (LVM) normalized to THV when compared to females of similar fitness level.

In **Paper II**, THV in relation to $\dot{V}O_{2peak}$ was compared between 31 patients diagnosed with heart failure and a control group consisting of athletes and normal subjects. The ratio between $\dot{V}O_{2peak}$ and THV ($\dot{V}O_{2peak}/THV$) was defined as the cardiac reserve index. Cardiac reserve index was significantly lower in patients when compared to athletes and controls. This difference also remained when only patients with normal ejection fraction were compared with the control group.

Paper III investigated three different respiratory indices (Dx, Px and Pq) in triathletes and controls. The sequence in which the indices occurred during an incremental exercise test differed between well trained subjects and untrained subjects. This difference was shown to be caused by the well trained subjects' ability to metabolize fat at high workloads.

In **Paper IV** cardiac pumping mechanics was compared between athletes and controls matched for age and gender. Cardiac pumping was divided into longi-

tudinal pumping - the movement of the atrioventricular plane towards the apex during systole and towards the base during diastole, and radial pumping - the inward movement of the myocardium. Except for the longitudinal contribution to the left ventricular stroke volume in males, the results of **Paper IV** showed that there essentially was no difference in cardiac pumping mechanics between male and female athletes and controls, emphasizing the conclusion from **Paper I** that it is the total heart volume that is the dominant determinant for cardiac pumping performance.

In summary, this thesis shows that long term training increases the total heart volume in both males and females, with a balanced enlargement between the left and right ventricle. By performing an exercise test with gas analysis to obtain $\dot{V}O_2peak$, the athlete's heart can be distinguished from a pathologically enlarged heart. Fit individuals can metabolize fat at high workloads, which will affect the respiratory indices determined during an exercise test. Finally, there seems to be essentially no differences in cardiac pumping between athletes and controls, and between males and females at rest. Thus, the main reason for the larger stroke volume and high $\dot{V}O_2peak$ in athletes seems to be the large total heart volume.

Populärvetenskaplig sammanfattning

Redan 1899 i Sverige undersökte Henschen sambandet mellan hjärtstorlek och framgång inom längdskidåkning. Han uppskattade då hjärtstorleken genom att knacka och lyssna mot skidåkarnas bröstorg. Idag kan vi bestämma hjärtats storlek, muskelmassa och blodvolym mycket exakt med hjälp av magnetkamera (MR). Vi kan även göra filmer som visar hur hjärtat rör sig när det pumpar. Syftet med denna avhandling är att med hjälp av magnetkamera beskriva det friska, fysiologiskt förstorade idrottshjärtats form och funktion hos både män och kvinnor. Vidare är syftet att undersöka skillnader i mjölksyretrösklar mellan friska normalpersoner och elitidrottare.

Delarbete I visade att hjärtstorleken ökar med träning hos både män och kvinnor, och storleksökningen påverkar höger och vänster kammare lika mycket. Studien visade också ett starkt samband mellan hjärtstorlek och kondition, mätt som maximalt syreupptag ($\dot{V}O_2peak$). I en jämförelse mellan män och kvinnor visades det att för en given hjärtstorlek har män en större muskelmassa i vänster kammare. Detta kan bero på att män har högre halter testosteron vilket är stimulerande för muskeltillväxt i hela kroppen.

I **delarbete II** jämfördes 31 patienter med hjärtsvikt med elitidrottare och normaler från delarbete I avseende hjärtstorlek i relation till $\dot{V}O_2peak$. Kvoten mellan $\dot{V}O_2peak$ och total hjärtvolym (THV) kallas cardiac reserve index. Cardiac reserve index var signifikant lägre för patienter med hjärtsvikt jämfört med övriga försökspersoner, även för de patienter som hade normal ejektionsfraktion. Denna studie introducerar således en möjlig ny hjärtsviktsmarkör.

I **delarbete III** visades det att förmågan att använda fett som bränsle under arbete påverkar i vilken ordning tre olika mjölksyretrösklar passerar under ett konditionstest. Vältränade individer kan förbränna fett även under höga belastningar, vilket gör att vissa trösklar passerar senare hos idrottare. Detta är fördelaktigt då det sparar på kroppens kolhydrater som bara finns i begränsad mängd. Genom att undersöka när trösklarna passerar kan man ge mer individanpassade träningsråd.

I **delarbete IV** jämfördes hjärtats pumpning hos 32 elitidrottare med den hos 32 ålders- och könsmatchade normalpersoner för att undersöka om träningen påverkar hjärtats pumpmekanik. Pumprörelsen kan delas in i två komponenter; den longitudinella pumpningen där hjärtats klaff-plan rör sig uppifrån och ner, och den radiella pumpningen där hjärtväggen rör sig utifrån och in. Resultaten visade att i vila finns det inga större skillnader i hjärtats pumpning mellan män och kvinnor, eller mellan idrottare och normalpersoner.

Sammanfattningsvis visar denna avhandling att träning ger en större hjärtvolym hos både män och kvinnor, och med hjälp av konditionstest kan man skilja det friska idrottshjärtat från ett sjukt förstorat hjärta. Resultaten visar även på skillnader i vilken ordning tre olika mjölksyretrösklar passeras under ett konditionstest samt att hjärtats pumpning i vila inte skiljer sig mellan manliga och kvinnliga idrottare och normalpersoner.

Abbreviations

2 ch	two chamber
3 ch	three chamber
4 ch	four chamber
ATP	adenosine triphosphate
AVPD	atrioventricular plane displacement
AV-plane	atrioventricular plane
CMR	cardiac magnetic resonance imaging
CO	cardiac output
CO ₂	carbon dioxide
Dx	derivative crossing
ECG	electrocardiogram
EDV	end-diastolic volume
ESV	end-systolic volume
FAD	flavin adenine dinucleotide
¹ H	hydrogen
HCO ₃ ⁻	bicarbonate
H ₂ CO ₃	carbonic acid
H ₂ O	water
HR	heart rate
LV	left ventricle
LVM	left ventricular mass
LVSV	left ventricular stroke volume
MRI	magnetic resonance imaging
NAD ⁺	nicotinamide adenine dinucleotide
Pq	respiratory compensation point
Px	point of crossing
RER	respiratory exchange ratio
RV	right ventricle

$\dot{R}VSV$	right ventricular stroke volume
SA	short axis
SV	stroke volume
THV	total heart volume
THVV	total heart volume variation
TSV	total stroke volume (LVSV+RVSV)
TSV_{rad}	total stroke volume generated by radial pumping
TSV_{long}	total stroke volume generated by longitudinal pumping
$\dot{V}CO_2$	carbon dioxide elimination
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_{2max}$	maximal oxygen uptake
$\dot{V}O_{2peak}$	peak oxygen uptake

Chapter 1

Introduction

1.1 The heart

To be able to deliver the appropriate volume of blood to the tissues over a lifetime, the heart must be extremely adjustable and sustainable. With every heartbeat, the normal healthy heart at rest typically pumps 70ml of blood out into the systemic circulation. At a heart rate of 70 beats per minute, approximately 5 litres of blood is ejected from the heart every minute.⁷⁰ During exercise, the stroke volume and heart rate increases and the heart of an elite athlete can pump over 200ml of blood with every beat during exercise (i.e 40 litres/min at a heart rate of 200).³²

The heart consists of four chambers; the left and right atria and the left and right ventricle. The atria and ventricles are separated by the atrioventricular plane (AV-plane), a fibrous structure where the valves are inserted. The mitral valve separates the left atria and ventricle, and the tricuspid valve separates the right atria and ventricle. Venous blood, low on oxygen, enters the right ventricle (RV) through the right atria. The blood is pumped into the pulmonary circulation where it is oxygenated and transported to the left atria and the left ventricle (LV). The left ventricle pumps the blood through the aorta into the systemic circulation, supplying the whole body with oxygen (Figure 1.1).

The pressure in the pulmonary circulation is low (24/8mmHg)¹⁰⁴ and the right ventricle can easily overcome this pressure gradient. Therefore, the myocardial wall of the right ventricle is thin compared to the left ventricular wall. The left ventricle needs to overcome a much larger pressure (120/70mmHg)¹⁰⁴ in order to eject blood into the systemic circulation. Therefore, the left ventricular myocardial wall is thick and able to create a high pressure.

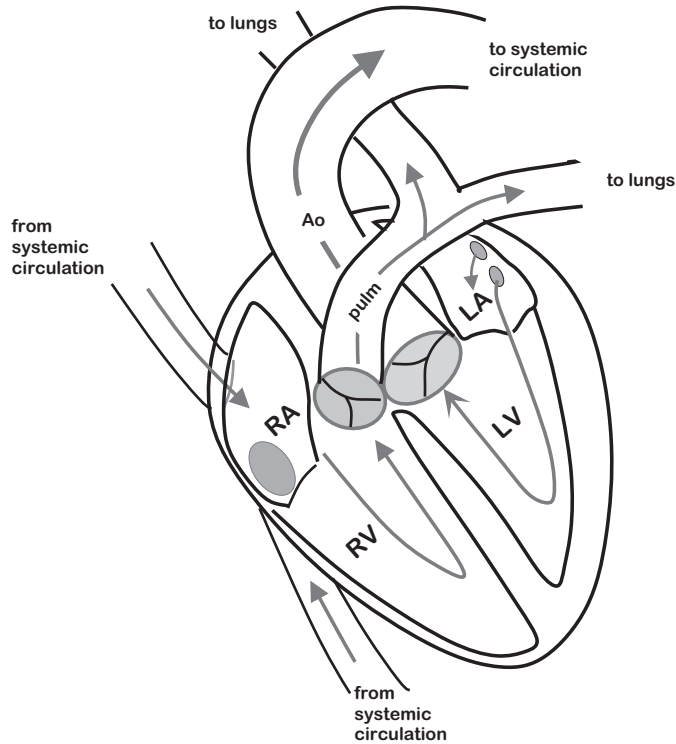


FIGURE 1.1 Schematic image of the heart in four-chamber view. *Ao = aorta, Pulm = pulmonary trunk, LA = left atrium, RA = right atrium, LV = left ventricle, RV = right ventricle*

1.2 Cardiac pumping

Cardiac pumping can be divided into two phases separated in time; diastole - the relaxation/filling phase, and systole - the contraction/ejection phase. Furthermore, the pumping can also be divided into two different modes of pumping; longitudinal pumping - the movement of the AV-plane towards the apex during systole and towards the base during diastole, and radial pumping - the inward movement of the myocardium.

Diastole and Systole

During ventricular systole, the atria fill with blood. Ventricular diastole begins when the myocardium relaxes and the atrioventricular valves (AV-valves) open, allowing blood to flow from the atria into the ventricles. Just before the AV-valves close again, the atria contract and an additional volume of blood enters the ventricles. A period of isovolumic contraction occurs before the aortic and pulmonary valves open and blood is ejected. When the aortic and pulmonary valves close there is a period of isovolumic relaxation before the AV-valves open and diastole begins.⁴¹

The filling and ejection of the ventricles can be affected in the presence of cardiac pathologies^{11,34,61} but also from training, as seen in elite athletes.^{6,55} The rate of filling and emptying of the ventricles is therefore often used to measure diastolic and systolic function.^{6,11,34,55,61}

Longitudinal pumping and Radial pumping

Physiology textbooks often describe cardiac pumping as a squeezing motion, taking only radial pumping into consideration.^{78,113} The knowledge about longitudinal pumping is not new, but was described already by Leonardo Da Vinci (1452-1519) who concluded that the ventricles shorten in systole and lengthen in diastole.¹⁰⁵ The longitudinal pumping has later been described by several studies using different modalities such as chest x-rays,^{42,51} computer tomography,⁴⁸ echocardiography^{2,33,85} and cardiac magnetic resonance imaging (CMR).^{20,21,89}

A few studies have tried to quantify the relationship between longitudinal and radial pumping.^{16,20,33,89,100} Emilsson et al.³³ used echocardiography and defined the longitudinal contribution as the volume encompassed by the mitral annular longitudinal motion multiplied by the LV epicardial cross-sectional area at the onset of systole. Their estimation of the longitudinal contribution to the left ventricular stroke volume (LVSV) was 82%. In a study by Carhäll et al.,¹⁶ the longitudinal contribution defined as the volume generated by the mitral annular motion was found to be 19%. In a CMR study by Carlsson et al.²⁰ the longitudinal contribution was defined as the atrioventricular plane displacement (AVPD) multiplied by the short-axis epicardial area encompassed by the AVPD. The longitudinal contribution to the LVSV was found to be approximately 60% and the radial contribution approximately 40%. Furthermore, the right ventricular stroke volume (RVSV) was 80% longitudinal and 20% radial. Thus, there are differences in methodology and definitions complicating a comparison of the different studies. Using echocardiography it can be difficult to place the short-axis plane perpendicular to the long-axis plane. This may cause an overestimation of the cross-sectional area and subsequently an overestimation of the longitudi-

nal contribution to the LVSV. However, CMR is considered gold standard for determining cardiac volumes and mass,⁸¹ and the placement of the short-axis perpendicular to the long axis is better obtained using CMR, thereby reducing the risks of overestimation when quantifying longitudinal and radial pumping.

Atrioventricular plane displacement

Left ventricular AVPD is one of the variables affecting longitudinal pumping and is often used as a measurement of cardiac function.^{1,50,90,106,114,115} The AVPD is caused by both the ventricular contraction, pulling the AV-plane towards the apex, and the atrial contraction, pulling the AV-plane towards the base. Previous studies have shown that the AVPD is increased with increased heart rate during exercise.^{96,101} The heart rate can also increase from the stress caused by undergoing a cardiac examination with echocardiography or CMR. Furthermore, heart rate is closely related to the cardiac output (CO) which in turn is related to the metabolism. Therefore, there is a need to consider factors such as heart rate and CO when assessing cardiac function using AVPD.

Total heart volume variation

When the AV-plane moves down towards the apex during systole, the atria fill reciprocally.^{38,42,48} Thus, the volume of blood leaving the heart and the volume of blood entering the heart due to longitudinal pumping is approximately the same, and therefore the longitudinal pumping does not cause any outer volume change of the heart.^{19,20} The radial pumping, however, causes a small change in total heart volume (THV) over the cardiac cycle. The difference in THV over the cardiac cycle has been defined as the total heart volume variation (THVV).¹⁹ By using mainly longitudinal pumping, the heart is kept energy efficient.^{42,48,49,66} If the heart pumped using mainly radial pumping, it would not only need energy to move the blood forward but also it would need to use energy to pull on the surrounding tissues that attach to the pericardial sac.

In a study by Hamilton and Rompf,⁴² the heart volume was found to be relatively constant in frogs, turtles and dogs over the cardiac cycle. Later studies in cats, monkeys³⁸ and dogs^{48,49} found similar results. Gauer³⁸ concluded that the filling of the atria during ventricular systole is larger in small animals with small hearts compared to larger animals with large hearts. Thus, a larger THVV can be expected in large hearts. Previous studies in humans have shown that the radial contribution to the total stroke volume (TSV_{rad}) explains the major part of THVV.²⁰ Therefore, by measuring the THVV, TSV_{rad} can be estimated.

1.3 Athlete's heart

Athlete's heart is a term used to describe the physiologically enlarged heart seen in athletes, as a result from long term training. Already in 1899, Henschen in Sweden estimated the heart size of cross country skiers using chest percussion.⁴⁶ Since then, the size of the heart in athletes has been studied using several different modalities such as bi-planar chest x-rays,^{32,77} echocardiography^{6,63,75,79,80,111} and CMR.^{72,82,88,93,94,111,117}

The heart has been shown to adjust to long term training with increased ventricular volumes and mass. It has been suggested that there are two forms of hypertrophy as a result from intense training, termed eccentric hypertrophy and concentric hypertrophy. Eccentric hypertrophy is thought to be seen predominantly in endurance athletes. Theoretically, endurance exercise causes a large volume load on the heart which leads to an enlargement of the left ventricular diameter, and a proportional increase in wall thickness. In strength trained athletes, the increased pressure load on the heart when the athlete is lifting heavy weights is thought to stimulate hypertrophy of the myocardium without a concomitant increase in left ventricular internal diameter, causing concentric hypertrophy. These two kinds of hypertrophy were first suggested by Morganroth et al. in 1975,⁷⁵ and they have been both confirmed^{6,26,83} and refuted.^{44,58,111} However, due to the combination of endurance- and strength training performed by most elite athletes today, the concept of the endurance trained and the strength trained heart can not be considered absolute but is rather relative.

Gender aspects

Few studies have focused on the gender aspects of training and few have investigated the differences between males and females. This may in some part be explained by the fact that females have not, until recently, trained and competed at elite level. Furthermore, females are often excluded from studies because of the monthly hormonal changes that may affect the results.

Several studies have shown that males have larger absolute cardiac dimensions when compared to females.^{28,79,93,98,99} However, the question whether training affects the male and female heart differently is not yet clear. Petersen et al.⁸² found no sex-specific adaptive structural and functional changes to exercise training in elite athletes. In contrast, other studies have found a larger left ventricular mass (LVM) normalized for body weight (g/kg)¹¹¹ and a larger LVM normalized for body surface area (BSA) (g/m²)^{28,79,93,99} in male athletes when compared to female athletes. The larger LVM in males may in part be explained by their higher systolic blood pressure during exercise.^{40,118} Furthermore, testosterone has been shown to stimulate myocardial growth.^{22,69} Left ventricular cavity size normalized

for BSA,⁷⁹ weight or body mass index⁹⁹ has been found to be smaller,⁹⁸ similar⁹³ and larger^{79,99} in female athletes. Therefore, there is a need for further studies to investigate the gender differences in the response to exercise.

1.4 Heart failure

Heart failure is a combination of signs and symptoms that occur when the heart fails to pump an adequate cardiac output (CO) to meet the demand of the tissues, and not a disease itself. Heart failure can follow as a consequence of cardiac pathologies such as ischemic heart disease, cardiomyopathies and valve insufficiencies or stenosis.

Diastolic and systolic dysfunction

Heart failure is often divided into two categories; diastolic dysfunction - problems with ventricular filling, and systolic dysfunction - problems with ventricular ejection.

In diastolic dysfunction the ventricular wall is abnormally stiff and has reduced ability to fill at normal filling pressures. This leads to a reduced end-diastolic volume (EDV) and consequently a reduced SV and CO. In pure diastolic heart failure, the contractility of the myocardium remains normal. The most common reason for the development of diastolic failure is systemic hypertension. When the left ventricle is forced to pump against a chronically elevated arterial pressure, the ventricular wall hypertrophies. The structural and biochemical changes associated with this hypertrophy makes the ventricle stiff and filling is complicated.

Systolic dysfunction is characterized by a decrease in myocardial contractility. Despite a normal EDV, SV is reduced as reflected by a decrease in ejection fraction (EF%). In many patients both diastolic and systolic dysfunction exists. For example, after a myocardial infarction the chronic loss of contracting myocardium causes a systolic failure. At the same time, the non-distensible fibrous scar tissue that replaces the normal, distensible myocardium causes a diastolic dysfunction.

Diagnosing heart failure

Heart failure is caused by a variety of different pathologies and can present in different ways, making the diagnosis a difficult clinical challenge.^{68,86,87,112} Clinical criteria such as crackles on auscultation, breathlessness, ankle swelling and fatigue^{18,43,71} are used. However, the symptoms can be hard to interpret in several patient groups such as in obese patients, patients with unrecognized symptomatic myocardial ischemia without heart failure, when pulmonary diseases are

present⁸⁷ and in females.¹¹² Therefore, an objective measure of cardiac function is also needed for diagnosis.³⁰

Echocardiography is commonly used to assess diastolic and systolic function in heart failure. When echocardiography at rest does not provide enough information for the diagnosis, stress echocardiography, radionuclide imaging or CMR can be used. Exercise testing is considered of limited value, although a normal exercise test excludes heart failure as a diagnosis. Instead, exercise testing is used to evaluate treatment and for prognostic stratification.¹⁰²

Classification of heart failure

There are several different ways of classifying the severity of heart failure. The New York Heart Association (NYHA) classifies the patients from I-IV, where stage I includes patients with cardiac disease but without limitations of physical activity and stage II includes patients who have cardiac disease resulting in a slight limitation of physical activity but are comfortable at rest. In stage III, patients have cardiac disease with a marked limitation of physical activity but are still comfortable at rest. Stage IV includes patients with cardiac disease resulting in inability to carry on any physical activity without discomfort and symptoms of cardiac insufficiency may be present even at rest.²³

As a complement to the NYHA classification, the American College of Cardiology (ACC) and the American Heart Association (AHA) identified four stages (A-D) of heart failure, where the first two stages involves patient groups that are not yet in heart failure and therefore not included in the NYHA classification.

According to the ACC/AHA classification, stage A includes patients with high risk of developing heart failure, but with no structural or functional abnormalities and who have not shown any signs or symptoms of heart failure. In stage B, structural heart disease has developed but there are no signs of heart failure. Stage C includes patients who have current or prior symptoms of heart failure associated with an underlying structural heart disease. Finally, stage D includes patients with advanced structural heart disease with marked symptoms of heart failure at rest despite therapy.⁵⁴

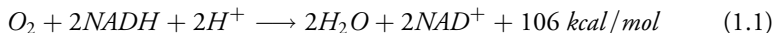
1.5 Exercise physiology

Exercise physiology has emerged from more traditional fields of anatomy, physiology and medicine. It has a unique focus on functional dynamics and consequences of movement. Not only the heart, but the whole body is extremely adjustable to increasing external work. In order to understand what determines maximal work capacity in health and disease, several aspects such as cellular metabolism, oxy-

gen saturation, hemoglobin levels, alveolar diffusion, ventilation as well as cardiac function and morphology need to be considered.

Metabolism

There are three different, but linked, metabolic pathways; the glycolysis, Krebs cycle and oxidative phosphorylation. In the glycolysis, carbohydrates (mainly glucose) are catabolized to form the cells' "energy currency" - adenosine triphosphate (ATP). These reactions takes place in the cytosol and no oxygen is needed. Reactions without oxygen are termed *anaerobic*. The end product from the glycolysis is pyruvate and if no oxygen is present, pyruvate is converted into lactate (the ionized form of lactic acid) by a single enzyme-mediated step. If oxygen is present, pyruvate enters the Krebs cycle inside the mitochondria. In Krebs cycle, molecular fragments formed during carbohydrate, fat and protein breakdown are catabolized into carbon dioxide (CO₂), hydrogen (H) and small amounts of ATP. The H is transferred to the coenzymes NAD⁺ and FAD to form NADH and FADH₂ which enter the oxidative phosphorylation. In the oxidative phosphorylation, cytochromes form an electron transport chain and NADH and FADH₂ releases H⁺ and electrons. The electrons from the H⁺ are transferred via the different compounds of the chain, and at each step of the chain, a small amount of energy is released. This energy is used to move H⁺ from the matrix into the compartment between the inner and outer mitochondrial membranes. This provides a source of potential energy by producing a H⁺ gradient across the membrane. At three points along the chain, H⁺ can flow back to the matrix side. The flow of H⁺ transfers energy which is used to form ATP. At the end of the transport chain, the electrons combine with H⁺ and oxygen (O₂) to form water (H₂O). The oxidative phosphorylation is necessary for the regeneration of the hydrogen-free form of NAD⁺ and FAD. Therefore, the Krebs cycle can only operate when oxygen is present, under so called *aerobic* conditions.

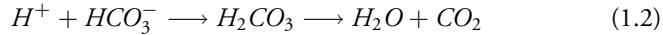


The oxidative phosphorylation is the quantitatively most important mechanism for the production of ATP.¹⁰⁴

Exercise

At rest or low-intensity exercise there is a sufficient oxygen supply for Krebs cycle and the oxidative phosphorylation to operate. With increased exercise intensity, the energy demand increases. If the increasing demand for ATP cannot be met by aerobic metabolism exclusively, anaerobic processes will compensate and lactic

acid is formed. In order to maintain pH, the H^+ from the lactic acid is buffered by bicarbonate (HCO_3^-), and via carbonic acid (H_2CO_3), water (H_2O) and carbon dioxide (CO_2) are formed:¹⁰⁴



The ventilation increases in order to blow off CO_2 and maintain pH.^{31,104}

Determining the exercise capacity

Maximal oxygen uptake ($\dot{V}O_{2max}$) represents the maximum capacity of the body to utilize oxygen to meet an increasing energy demand during heavy exercise. As described by Hill and Lupton in 1923:⁴⁷

"However much the speed be increased beyond this limit, no further increase in oxygen intake can occur: the heart, lungs, circulation, and the diffusion of oxygen to the active muscle-fibers have attained their maximal activity."

$\dot{V}O_{2max}$ is usually lower in females compared to males¹⁵ and decreases with age^{110,119} and physical inactivity.⁹² When determining $\dot{V}O_{2max}$, incremental exercise testing where the work rate gradually increases until exhaustion is often used. The value reached at the end of exercise may not show the true $\dot{V}O_{2max}$ and therefore peak oxygen uptake ($\dot{V}O_{2peak}$) is used to describe the highest value reached in paper I, II and IV.

Several different criteria are used to determine when $\dot{V}O_{2peak}$ can be considered reached, e.g. a leveling off in $\dot{V}O_2$, a respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) exceeding 1.0 and reaching maximal heart rate. Borg's Rating of Perceived Exertion (RPE) scale¹³ can also be used to ensure maximal effort during exercise testing.

Determining anaerobic thresholds

The anaerobic threshold is a theoretical point when muscle tissue goes from aerobic to anaerobic metabolism. All tissues do not switch from aerobic to anaerobic processes simultaneously and therefore the process is better described as a transition rather than a threshold. During dynamic exercise, the increase in lactic acid becomes greater as the work rate increases, resulting in a metabolic acidosis. The point where lactate starts to accumulate has been labeled differently in the literature; e.g. anaerobic- or aerobic threshold and onset of blood accumulation (OBLA).^{3,10,14,35,107} Above this point the time that work can be sustained will be limited.¹⁰⁸

Regular physical exercise can increase the threshold^{37,62,84} and enhance an individuals capability to perform submaximal activities. The anaerobic threshold has been shown to correlate well with performance at endurance events.^{8,14,27,29,35,95} For example, for a given $\dot{V}O_2max$, an athlete that can run at a work rate of 85% of $\dot{V}O_2max$ without accumulation of lactate will be able to run a marathon faster than an athlete with a threshold occurring at 60% of $\dot{V}O_2max$.

Anaerobic metabolism can be measured from lactate levels in blood.^{9,37,76,91,97} It can also be measured non-invasively during an exercise test with gas analysis.^{10,37,97,107} As mentioned above, the H^+ from the lactic acid produced during anaerobic metabolism is buffered by HCO_3^- which results in an increase of non-metabolic CO_2 . Ventilation increases in order to blow off CO_2 and maintain pH.^{31,104} The changes in metabolism and ventilation are reflected by different respiratory thresholds, or indices. The term respiratory indices will be used in this thesis to describe the transition points where the metabolism goes from aerobic to anaerobic.

1.6 Exercise testing with gas analysis

Exercise testing is commonly used to assess patients with heart or lung disease in order to diagnose, estimate prognosis, determine functional capacity, plan future treatment or evaluate treatment.⁵⁶ It can also be used to determine maximal working capacity in healthy subjects, e.g. to assess fitness status in athletes or for certain professions such as firemen. In Sweden, the exercise test is normally performed on an ergometer cycle, but also treadmill and, when necessary, arm cycling, can be used. The exercise test can be complemented with gas analysis, where maximal oxygen uptake ($\dot{V}O_2max$) as well as respiratory indices can be determined. The term peak oxygen uptake ($\dot{V}O_2peak$) is often used instead of $\dot{V}O_2max$ as it can be difficult to reach the true maximum during an exercise test.

Incremental ergometer cycle test

The protocol for the exercise test is adjusted to yield an exercise duration of approximately 8-12 minutes.⁴ The starting load and the ramp of the exercise test is chosen with respect to the patients age, weight and self estimated fitness. ECG and heart rate is monitored continuously throughout the test, and blood pressure is measured typically every two minutes. The Rating of Perceived Exertion Scale (RPE) by Borg¹³ is used to follow the patients' subjective feeling of exertion, and in the case of chest pain, the Borg Category Ratio, CR-10 scale,¹³ is used.

Gas analysis

Exercise testing with gas analysis can be used to determine whether the exercise capacity is normal or pathologically limited.¹⁰⁸ Gas analysis is clinically used in the assessment of heart failure patients for evaluation of prognosis¹⁰⁹ and in consideration of a heart transplant.⁶⁷ In healthy subjects and athletes, the gas analysis can be used to assess fitness status and evaluate training results.

For the gas analysis, a facemask covering the mouth and nose is placed on the patient. The oxygen (O₂) inspired and carbon dioxide (CO₂) expired during the exercise test is continuously measured breath by breath and the results can be followed on a computer screen. From the gas analysis, measurements such as minute ventilation ($\dot{V}E$), O₂ uptake ($\dot{V}O_2$), CO₂ elimination ($\dot{V}CO_2$) and the respiratory exchange ratio (RER) are obtained.

1.7 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can be used to obtain images of the body in any given imaging plane. It is free of ionizing radiation and is therefore suitable for repeated examinations. The MRI technique allows for flexible contrast manipulation and is very well adapted for quantitative imaging of soft tissues. The MRI scanner consist of a main magnet, responsible for the main magnetic field, radio frequency coils which are used to transmit and receive radiofrequency pulses, and a gradient system, used to encode properties of the MR signal such as position or speed.

Basic principles

The physics behind MRI relies on particle spin. All protons have spin and therefore the electrical charge of the protons move. A moving electrical charge is an electrical current, and an electrical current induces a magnetic field. Thus, each proton can be considered a tiny magnet. The spin of the proton will move around the external magnetic field B in a movement called precession, like when a spinning top moves around an axis. The frequency of the precession ω_0 is equal to:

$$\omega_0 = -\gamma B_0 \quad (1.3)$$

where γ is the gyromagnetic ratio and B_0 is the magnetic field. The gyromagnetic ratio is constant for each element. Hence, the nuclear spin, ω_0 , called the *Larmor frequency*, is proportional to the magnetic field.⁶⁰

The main magnet

The main magnet consists of a metal wire, most often wrapped around a circular gantry. The wire is cooled by liquid helium which makes it superconductive and the resistance is approximately zero. The electrical current through the metal wire generates a strong magnetic field, typically 1–3 Tesla (T). By comparison, the earth's magnetic field strength is 30–60 μ T. The typical field strength for cardiac imaging is 1.5T. As the patient is placed in the magnet, the proton spins start to precess around the axis of the main magnetic field (B_0). Local field fluctuations will allow the system to reach its thermal equilibrium state, where the resulting magnetization from all spins in the sample M_0 is aligned along B_0 . M_0 is the signal we want to measure.

Radio frequency coils

When B_0 and M_0 are aligned in the same direction, M_0 cannot be detected. In order to make the the vector M_0 deviate from the direction of the magnetic field B_0 , a radio frequency (RF) pulse is sent into the patient using a RF-transmitter coil. When the frequency of the transmitted RF pulse matches the Larmor frequency, the energy can be absorbed by the protons within the body. This is called resonance (as in magnetic resonance imaging). The added energy causes M_0 to deviate from B_0 by a given angle. The magnetic vector M_0 precess around the B_0 axis, inducing an electrical current in the RF-receiver coil. The peaks of the signal amplitude are called echoes and are proportional to the number of ^1H protons that were excited by the RF-pulse. The amounts of ^1H are different for different tissues, which give rise to some of the contrast between different tissues in MRI.

The gradient system

The gradient coils are used to introduce linear magnetic field gradients, a variation of the magnetic field with regard to position. As mentioned above, the Larmor frequency is directly proportional to the magnetic field. By applying linear magnetic field gradients, it is possible to excite only the specific slices of the body in which the Larmor frequency is in resonance with the given RF-pulse. Thus, the gradient system can e.g. be used to spatially locate the MR signal and when conducting flow measurements.

K-space

Signal is sampled in lines of raw data which are ordered in k-space. In k-space the signal is still encoded according to phase and frequency and not to anatomical

landmarks. Before the signal is transformed into anatomical landmarks, corrections and manipulations can be made in k-space. The number of lines and the position of the lines determine the spatial or, if dynamic imaging is employed, temporal resolution of the final image. Once the k-space contains enough information (enough lines), a mathematical operation called Fourier transform is applied to derive excellent anatomical images, well suited for diagnostic and research purposes.

Cardiac Imaging

Cardiac magnetic resonance imaging (CMR) can be used for static anatomical imaging as well as dynamic imaging of the heart and is considered gold standard for assessing the myocardial volumes and mass.^{12,57,64} Cardiac MR can also be used for non-invasive flow measurements in both large vessels^{5,53,103} and in small vessels down to the size of the coronary arteries.⁶⁵

ECG triggering

Magnetic resonance imaging is sensitive to motion, and respiration and the intrinsic movement of the heart makes CMR challenging. The respiration is commonly compensated by imaging during breath holding. To compensate for the intrinsic cardiac movement over the heart cycle, ECG triggering is used. ECG triggering can be used either prospectively or retrospectively. With prospective ECG triggering the MR scanner automatically detects the R-wave and image acquisition begins at that point, or after a predetermined delay, and continues for a determined length of time. The RR interval determines the time available for image acquisition but often the last part of the cardiac cycle, the atrial contraction, is not imaged. With retrospective ECG triggering it is possible to image the entire cardiac cycle. This is done by continuous image acquisition and parallel detection of the ECG. After image acquisition, the images are arranged in the appropriate part of the RR interval, thus ensuring coverage of the complete cardiac cycle.

Chapter 2

Aims of the Work

In order to understand what determines maximal work capacity in health and disease, several aspects such as cellular metabolism, oxygen saturation, hemoglobin levels, alveolar diffusion, ventilation as well as cardiac function and morphology need to be considered. The aim of this thesis was to highlight some of these aspects by studying exercise physiology and cardiac pumping mechanics in male and female athletes compared to normal subjects and patients with heart failure.

The specific aim for each paper was:

- I. To study the relationship between maximal work capacity and cardiac morphology by testing the hypothesis that the total heart volume (THV) is an independent predictor of $\dot{V}O_{2peak}$ in males and females and to investigate if the athlete's heart is a physiologically enlarged heart with a balance between the left and right ventricle.
- II. To derive a novel cardiac reserve index by normalizing $\dot{V}O_{2peak}$ to THV and to test the hypothesis that this index can distinguish patients with heart failure from healthy control subjects and athletes.
- III. To determine three respiratory indices and investigate if and why they occur in different sequences in individuals with variable maximal working capacity.
- IV. To study the pumping mechanics of the athlete's heart by comparing the longitudinal and radial contribution to the left ventricular-, right ventricular- and total heart stroke volume between males and females, and between athletes and controls.

Chapter 3

Materials and Methods

3.1 Study populations

All studies were approved by the ethics committee for human research at Lund University, Sweden. Control subjects in Paper I-IV were recruited by advertisement and elite athletes in Paper I-IV were recruited from local elite teams in triathlon, soccer and handball. The patients in Paper II were retrospectively enrolled at Skåne University Hospital, Lund, Sweden. All control subjects, athletes and patients gave their written informed consent to participate in the respective study.

Paper I

Seventy-one athletes, 18 triathletes (6 females), 30 soccer players (12 females) and 23 handball players (12 females) and 60 healthy control subjects (20 females) were included. All athletes were training and competing at national or international level. None of the participants had a history of cardiovascular disease. All of the test subjects were non-smokers and did not use any medications with known cardiovascular effects.

Paper II

Thirty-one patients (5 females) diagnosed with heart failure with varying aetiology were retrospectively enrolled and the study population from Paper I was included as control group.

Paper III

Sixty healthy control subjects (20 female) and 18 triathletes (6 female) were included in order to create a group of individuals with highly variable training activity and maximal working capacity. The subjects were a subgroup from the population also used in Papers I and II.

Paper IV

In Paper IV, 32 athletes (24 soccer players [12 females] and 8 handball players [4 females]) and 32 healthy control subjects (16 females) matched for age and gender were included. The subjects were a subgroup from the population also used in Papers I and II.

3.2 Assessment of cardiac morphology and function

CMR imaging

A 1.5T scanner (Philips Intera CV, Philips, Best, The Netherlands) with a cardiac synergy coil was used to scan all subjects in supine position. Images of the whole heart were acquired using a steady-state free precession MR sequence with retrospective ECG triggering. Repetition time was 2.8ms, echo time 1.4ms, flip angle 60°, spatial resolution of 1.4x1.4mm, temporal resolution typically 30ms and slice thickness 8mm with no slice gap. After defining the long-axis orientation of the heart, short-axis images covering the entire heart from the base of the atria to the apex of the ventricles were obtained using parallel imaging with a SENSE factor of 2.

Image analysis

All morphological analysis was performed in short-axis cine images. Left and right ventricular end-diastolic volumes (LVEDV, RVEDV), end-systolic volumes (LVESV, RVESV) and left- and right ventricular stroke volumes (LVSV, RVSV) and left ventricular mass (LVM) were determined by manual delineation of the endocardial and epicardial border of the ventricles (Figure 3.1).

Total heart volume (THV) was defined as the volume of all structures within the pericardium, including the left and right ventricle, left and right atria, blood pool and the aortic and pulmonary trunk. By manual delineation of the pericardial border in short-axis images in end-diastole, THV was obtained (Figure 3.2). To determine the total heart volume variation (THVV), THV was determined in both end-diastole and end-systole, and THVV was calculated as

$$THVV = THV_{ed} - THV_{es} \quad (3.1)$$

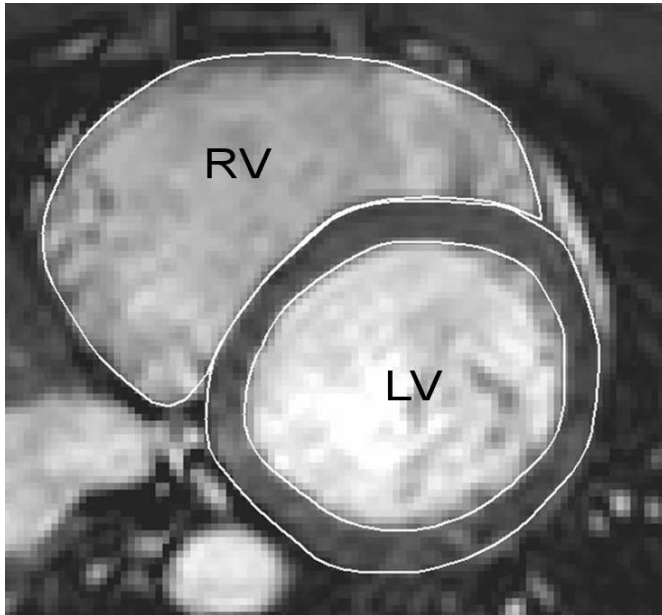


FIGURE 3.1 Example of delineations of the left ventricle (LV) and the right ventricle (RV) in a mid-ventricular short-axis slice. The inner white line of the LV indicates the endocardium and the outer white line indicates the epicardium. In the RV, the white line indicates the epicardium. These delineations were used to obtain volumes and mass for the LV and volumes for the RV.

The atrioventricular plane displacement (AVPD) was defined as the distance between the location of the AV-plane in end-diastole to its location in end-systole. The basal location of the muscular insertion of the ventricles to the AV-plane was manually identified in each of the three long-axis images (Figure 3.3) and a marker was placed. This resulted in six markers for measuring the AVPD in the left ventricle. For the right ventricle, two markers placed on the right ventricular (RV) lateral wall and on the RV outflow tract were used, as well as the mean of two markers on the septum (Figure 3.4). The AVPD was then measured as the distance traveled by the markers placed in end-diastole to end-systole. The contribution of the atrial contraction to the AVPD was measured as the distance traveled by the marker from ventricular diastasis in diastole back to the end-diastolic point.

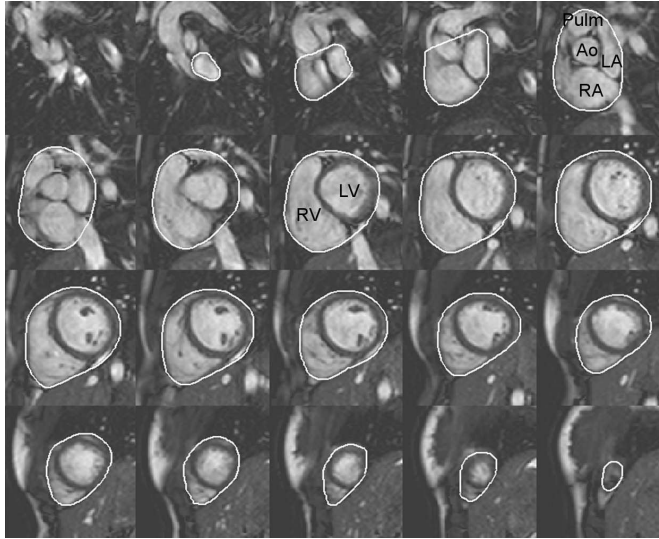


FIGURE 3.2 Example of delineation of the pericardium in short-axis slices to determine the total heart volume (THV). The base of the heart is seen in the upper left corner and the apex in the lower right corner. The THV was defined as the volume of all structures within the pericardium, including myocardium, blood pool, atria and pericardial fluid. This also includes the proximal parts of the great vessels covered by the pericardium. *LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium, Ao = ascending aorta, Pulm = pulmonary artery*

Longitudinal and radial pumping

The longitudinal pumping was defined as

$$SV_{long} = AVPD * mean SA_{epi} \quad (3.2)$$

where SV_{long} is the longitudinal contribution to the SV and $mean SA_{epi}$ is the mean short-axis epicardial area of the two largest slices encompassed by the AVPD. The rationale for using the epicardial border has been described by Carlsson et al.²¹ In short, as the AV-plane moves towards the apex in a piston-like movement during systole, blood is ejected. The myocardium is constant over the cardiac cycle, and therefore there will be a thickening of the myocardium when the ventricle pulls the AV-plane down. This thickening will cause a further ejection of blood. If

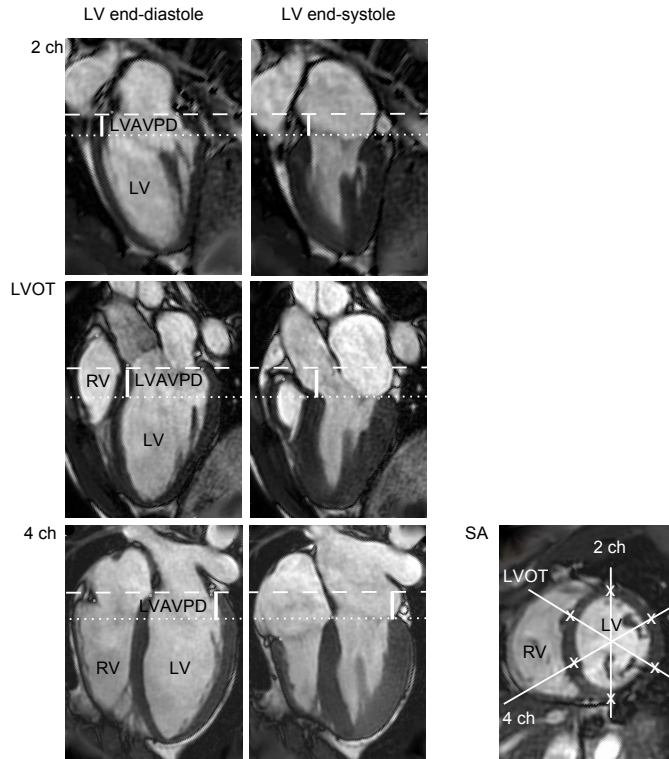


FIGURE 3.3 The left panels show the measurement of the left ventricular atrioventricular plane displacement (LVAVPD) in three long-axis views. To the right, the position of the measurement points for LVAVPD (white x) shown on a short-axis image. In the long-axis images, the white dashed line indicates the position of the AV-plane in end-diastole and the dotted white line indicates the position in end-systole. *LV* = left ventricle, *RV* = right ventricle, *2 ch* = two-chamber view, *LVOT* = left ventricular outflow tract, *4 ch* = four-chamber view, *SA* = short-axis view

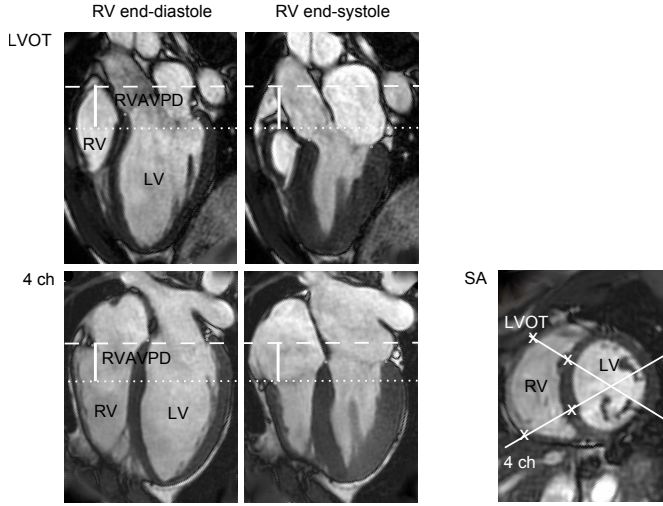


FIGURE 3.4 The left panels show the measurement of the right ventricular atrioventricular plane displacement (RVAVPD) in two long-axis views. To the right, the position of the measurement points for RVAVPD (white x) shown on a short-axis image. For the RVAVPD, the mean of the two septal measurement points was used to determine the septal movement. In the long-axis images, the white dashed line indicates the position of the AV-plane in end-diastole and the dotted white line indicates the position in end-systole. *LV* = left ventricle, *RV* = right ventricle, *LVOT* = left ventricular outflow tract, *4 ch* = four-chamber view, *SA* = short-axis view

endocardial areas are used, the longitudinal contribution will be underestimated as this last volume of blood ejected by the thickening of myocardium will be left out.

The longitudinal contribution to the total stroke volume (TSV_{long}) was calculated from the left and right longitudinal stroke volumes

$$TSV_{long} = LSV_{long} + RSV_{long} \quad (3.3)$$

Previous work has shown that the radial contribution to the total stroke volume (TSV_{rad}) explains the major part of $THVV^{20}$ (Figure 3.5). Therefore, by measuring the $THVV$, TSV_{rad} can be estimated.

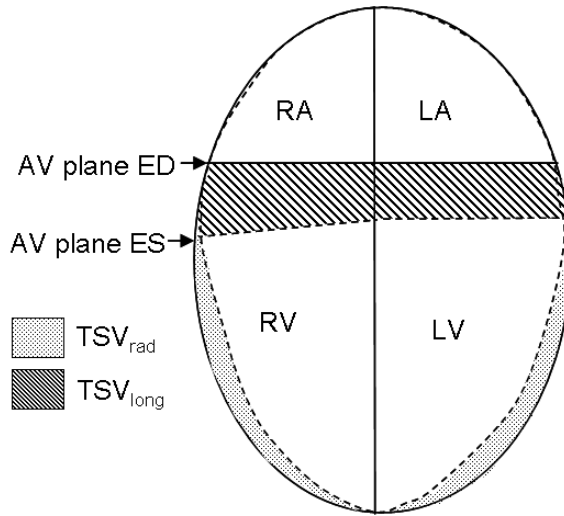


FIGURE 3.5 A schematic view of the heart contours in end-diastole (ED, solid lines) and superimposed in end-systole (ES, broken lines). The striped area shows the longitudinal contribution to the total stroke volume (TSV_{long}) caused by the AV-plane movement. The grey area shows the total heart volume variation (THVV) which is used to estimate the radial contribution to the total stroke volume (TSV_{rad}).

The radial contribution to the left and right stroke volume was calculated according to the formula

$$SV_{rad} = SV - SV_{long} \quad (3.4)$$

In order to determine what factors may affect the LVAVPD, the following equation was used:

$$CO = SV * HR \quad (3.5)$$

SV was decomposed into SV_{long} and SV_{rad} . As shown in equation 3.2, SV_{long} is composed by AVPD multiplied by mean SA_{epi} . This gives the equation

$$CO = HR * (SV_{rad} + AVPD * mean SA_{epi}) \quad (3.6)$$

which can be rearranged into

$$AVPD = CO / (HR * \text{mean } SA_{\text{epi}}) - SV_{\text{rad}} / \text{mean } SA_{\text{epi}} \quad (3.7)$$

Thus, CO, HR, mean SA_{epi} and SV_{rad} can all, theoretically, affect the AVPD.

3.3 Assessment of exercise capacity

$\dot{V}O_2$ peak and respiratory indices

Maximal exercise capacity was determined on an electronically braked ergometer cycle (Siemens Ergomed 940, Upplands Väsby, Sweden) with analysis of inspired and expired air using the gas analysis equipment Oxycon Champion (Jaeger, Hochberg, Germany). Serial $\dot{V}O_2$ values were obtained during the exercise test by calculating the average of all breaths taken during each 10-second period and $\dot{V}O_2$ peak was defined as the highest value reached at the end of exercise. The test continued until exhaustion when test subjects failed to maintain a pedalling rate above 60 revolutions per minute. All normal subjects and athletes reached an respiratory exchange ratio (RER) > 1.15 before termination of the test.

Hemoglobin levels were measured to ensure that test results in normal subjects and athletes were not affected by anaemia and consequently a lowered oxygen transport capacity. In Paper II, the cardiac reserve index was normalized for hemoglobin when comparing healthy subjects with patients.

A computerized method was used to determine three respiratory indices:¹¹⁶

Derivative crossing (Dx) was identified by plotting $\dot{V}CO_2$ against $\dot{V}O_2$ and second degree polynomials were fitted to the curve (Figure 3.6, panel a). The derivative of $\dot{V}CO_2$ and $\dot{V}O_2$ were calculated from the polynomials, and the first point where the derivative exceeded 1.0 was determined.

Point of crossing (Px) was defined as the point where the plotted curve of $\dot{V}CO_2$ crossed the plotted curve of $\dot{V}O_2$ (Figure 3.6, panel a). This point is the equivalent of RER = 1.0 and therefore the point where RER just exceeded 1.0 and all subsequent values exceeded 1.0 was taken as Px.

Respiratory compensation point (Pq) was determined from the end-tidal CO_2 (PET CO_2) plotted against $\dot{V}O_2$. Third degree polynomials were fitted to the curve, and from the polynomials, the first derivative was calculated. The first negative value of the derivative was taken as Pq (Figure 3.6, panel b).

The percentage of $\dot{V}O_2$ peak where Dx, Px and Pq occurred (Dx%, Px%, Pq%) was calculated by dividing the $\dot{V}O_2$ at the given point with $\dot{V}O_2$ peak.

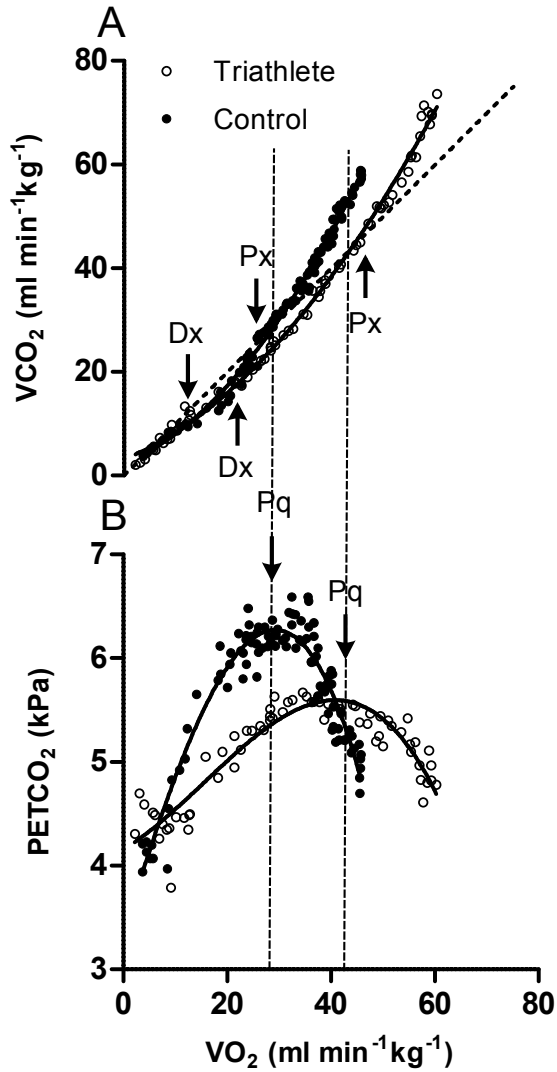


FIGURE 3.6 The indices Dx, Px (panel a) and Pq (panel b) in a female triathlete and a female control subject. The dashed line in panel a is the line of identity. Dx occurs at the lowest $\dot{V}O_2$ of all indices in both the triathlete and the control. In the triathlete, Px occurs at a higher $\dot{V}O_2$ compared to Pq, whilst in the control subject, Px occurs at a lower $\dot{V}O_2$ compared to Pq.

Indirect calorimetry

The fat metabolism at a given $\dot{V}O_2$ can be determined from indirect calorimetry.^{24,36} The equation used in Paper III is from Chèneviere et al.²⁴

$$\text{Fat oxidation rate (g min}^{-1}\text{)} = 1.67VO_2 - 1.67VCO_2 \quad (3.8)$$

Ventilation

In order to compare the ventilation during exercise between subjects, the minute ventilation (VE) was plotted against $\dot{V}CO_2$. Male athletes were compared to male controls and female athletes to female controls.

Statistical analysis

In papers I-III, SPSS 16.0 (Chicago, IL, USA) was used for statistical analysis. For paper IV, PASW Statistics 18 (Chicago, IL, USA) was used. Data are presented as mean \pm standard deviation unless otherwise is specified. A p-value < 0.05 was considered statistically significant. The Mann-Whitney non-parametric test was used in papers I-IV to compare variables where normal distribution could not be assumed. In papers I, II and IV, linear regression was used to assess correlation between variables. Forward stepwise multivariate regression was used in papers I and II to assess independent predictive value of variables. In paper I, receiver operating characteristic (ROC) analysis was performed to test the ability of the cardiac reserve index to distinguish between heart failure patients and controls. In paper III, Fishers exact test was used to determine whether there was a difference in the sequence of respiratory indices between triathletes and controls.

Chapter 4

Results and Comments

4.1 Relation between cardiac dimensions and $\dot{V}O_2peak$ (Paper I)

The relationship between cardiac dimensions and $\dot{V}O_2peak$ are not completely understood and how long term training affect the right ventricle and the THV is not fully elucidated. Furthermore, few studies have included female athletes and the gender aspects of training on cardiac dimensions needs to be further explored.

In Paper I, $\dot{V}O_2peak$ was shown to be significantly correlated to THV (Figure 4.1, panels a-c) and to THV normalized for BSA (Figure 4.1, panels d-f) in both males and females. Thus, for a given BSA, an increased THV is predictive of a higher $\dot{V}O_2peak$. Furthermore, $\dot{V}O_2peak$ was significantly correlated to LVM, LVEDV, RVEDV, BSA and height (Table 4.1). Using multivariable analysis, THV and LVM were shown to be independent predictors of $\dot{V}O_2peak$ ($R^2 = 0.74$, $p < 0.001$ for THV alone, $R^2 = 0.78$, $p < 0.001$ when including LVM), independent of gender. Total heart volume remained an independent predictor when the multivariable analysis was performed after the population was randomly divided into two groups ($R^2 = 0.71$, $p < 0.001$ for group 1 and $R^2 = 0.76$, $p < 0.001$ for group 2). When the study population was divided by gender, there was a significant correlation between $\dot{V}O_2peak$ and all variables studied, except for BSA and height in females. Since there was a strong relationship between the variables entered in the multivariable analysis, multicollinearity needs to be considered when interpreting the results.

To our knowledge, this study is the first to show that THV is a strong predictor of $\dot{V}O_2peak$ in both males and females. In a previous study by Ekblom et al.,³² the relationship between $\dot{V}O_2peak$ and THV determined from chest x-ray was studied in a small group of 13 male endurance athletes, which gave a limited

range of the variables studied. Therefore, the physiological relationship between $\dot{V}O_{2peak}$ and THV was not revealed. To overcome this limitation, the present study, by design, includes a large study population with a continuous increased level of long term endurance training in order to show the physiological relationship between $\dot{V}O_{2peak}$ and THV.

In figure 4.2 the relationship between LVEDV and RVEDV is shown. As LVEDV increased, RVEDV increased in the same order of magnitude ($R^2 = 0.87$, $p < 0.001$), indicating that the athlete's heart is a physiologically enlarged heart with a balance between the left and right ventricle, as previously shown.^{7,82,94}

Cardiac output (CO) is the product of heart rate and stroke volume (SV). In order to obtain a given CO, it is physiologically advantageous for the heart if it can be achieved by a high SV and a low HR. Cardiac performance is commonly assessed by determining CO, which has been shown to be associated with $\dot{V}O_{2peak}$.^{32,73} Maximal CO has been shown to increase by long term endurance training.³² Furthermore, it has previously been shown that the maximal heart rate does not increase by long term endurance training.¹¹¹ Thus, an increased maximal CO induced by endurance training would be explained by an increased SV, due to either an increase in ventricular dimensions or improved pumping mechanics. The results of Paper I suggests that an increase in cardiac dimensions may explain parts of an expected increase in maximal SV leading to an increased CO. To which extent exercise induced changes in pumping mechanics contributes to the increased cardiac performance is not yet fully understood. Previous studies using echocardiography have shown conflicting results of training effects on left ventricular filling, with both improved diastolic filling in athletes as well as no differences between athletes and controls (for review, see George et al.³⁹). With new promising techniques, such as velocity encoded CMR, cardiac pumping in athletes can be further elucidated.

TABLE 4.1
Subject characteristics.

	Group	Number	Age (years)	Height (m)	Weight (kg)	BSA (m ²)	Resting heart rate	Resting SBP	Resting DBP
Males	Control	n=40	34±10	1.81±0.05	81±10	2.00±0.13	61±9	129±9	77±7
	Handball	n=11	25±6**	1.86±0.05**	87±5*	2.10±0.08**	56±6	124±8	70±8**
	Soccer	n=18	24±5***	1.83±0.05	79±5	2.01±0.08	59±6	132±5	75±8
	Triathlon	n=12	35±9	1.84±0.05*	81±6	2.03±0.10	56±8	134±8	75±9
Females	Control	n=20	36±13	1.69±0.06	66±9	1.76±0.12	62±10	121±9	70±8
	Handball	n=12	21±2***	1.72±0.03	68±6	1.80±0.08	60±9	119±5	70±7
	Soccer	n=12	23±4***	1.70±0.06	64±6	1.75±0.11	57±8	119±6	71±6
	Triathlon	n=6	31±5	1.70±0.06	62±5	1.72±0.11	51±7*	121±9	71±9

* p < 0.05 ** p < 0.01 *** p < 0.001 when compared to gender matched control subjects.
DBP = diastolic blood pressure, kg = kilogram, m = metre, SBP = systolic blood pressure.

Gender aspects

Male control subjects, handball players, soccer players and triathletes all had significantly higher THV, LVM, LVEDV and RVEDV when compared to sport-matched females. Figure 4.3 illustrates the difference between males and females and between controls and athletes. All male subject groups had a significantly higher THV/BSA and LVM/THV when compared to females, except for THV/BSA in triathletes. LVEDV/THV did not differ between males and females for any of the groups and RVEDV/THV was significantly different only between male and female triathletes ($p = 0.049$).

The differences between males and females are not only due to gender, but likely also to differences in training. For the soccer players and handball players, the male athletes did more endurance training than female athletes. However, for the triathletes, where there were no differences between males and females in THV/BSA, female athletes had an average of 4 hours/week more endurance training than male athletes, suggesting that endurance training may be of importance for the increase in THV. Paper I is a cross-sectional study and it is therefore not possible to conclude whether the larger THV in athletes is due to training alone, or to other factors as well, such as genetics predisposing for a larger THV. Although there are prospective training studies which show increased cardiac dimensions as a result of training,^{6,59,92} it is likely that genetic factors influence both the THV as well as the cardiac response to training.

Left ventricular mass normalized for THV was significantly higher in all male groups compared to females. It has previously been shown that males have a higher systolic blood pressure during exercise, which may stimulate left ventricular hypertrophy due to increased afterload.^{40,118} Furthermore, the higher level of testosterone in males compared to females may also partly explain the differences in LVM.^{22,69}

4.2 A cardiac reserve index for patients with heart failure (Paper II)

Heart failure is a complex syndrome that can present in a variety of ways and the diagnosis is challenging. The accuracy of diagnosis by clinical means alone is often inadequate.^{86,112} Therefore, the aim of Paper II was to derive a novel cardiac reserve index from $\dot{V}O_{2peak}/THV$ and to test if this index could distinguish between patients with heart failure and healthy controls. The patients in Paper II had different etiologies and different stages of heart failure. This pilot study can be considered a proof-of-the-concept study for diagnosing heart failure, independent of etiology.

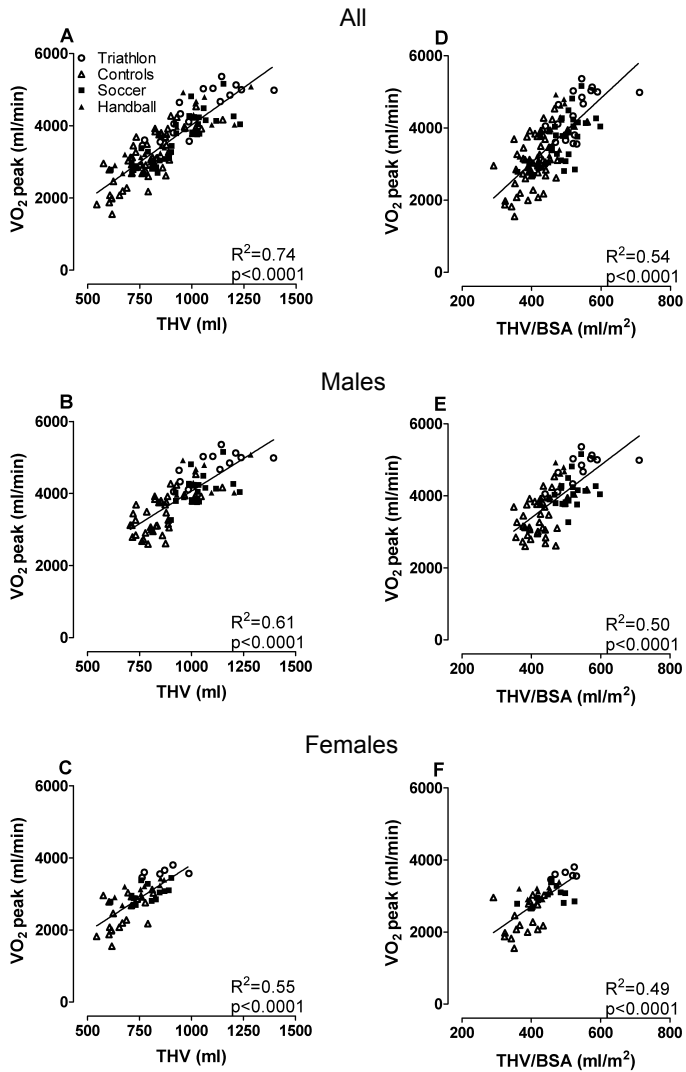


FIGURE 4.1 The relationship between total heart volume (THV) and peak oxygen uptake ($\dot{V}O_2 \text{ peak}$). The left panels show the relationship between absolute THV and $\dot{V}O_2 \text{ peak}$ for a) all subjects, b) males, and c) females. The right panels show the relationship between THV normalized for body surface area (BSA) and $\dot{V}O_2 \text{ peak}$ for d) all subjects, e) males, and f) females. $\dot{V}O_2 \text{ peak}$ was significantly correlated to THV and THV/BSA.

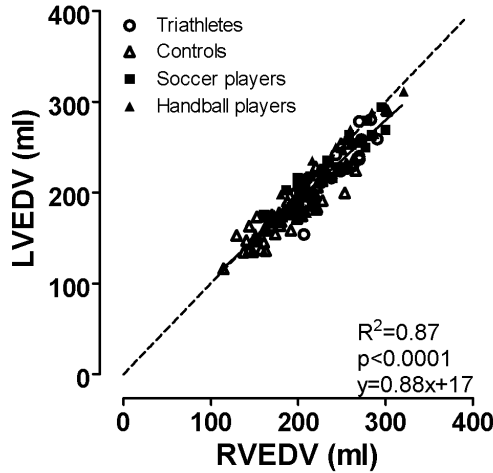


FIGURE 4.2 The relationship between the left ventricular end-diastolic volume (LVEDV) and right ventricular end-diastolic volume (RVEDV) in all subjects.

Figure 4.4a shows a strong correlation between $\dot{V}O_{2peak}$ and THV for the control group consisting of healthy volunteers and athletes ($R^2 = 0.74$, $p < 0.001$) but no correlation for patients with heart failure ($R^2 = 0.0002$, $p = 0.95$). Thus, in the physiologically enlarged heart, $\dot{V}O_{2peak}$ increases as THV increases. In contrast, in the pathologically enlarged heart, $\dot{V}O_{2peak}$ is decreased despite a large THV. In order to determine if a patient is suitable for heart transplantation, $\dot{V}O_{2peak}$ is often normalized to body weight and a cut off-value is used.^{25,67} However, as shown in figure 4.4b, there can be a large variability in $\dot{V}O_{2peak}$ for a given body weight in both healthy subjects and patients. These results suggest that $\dot{V}O_{2peak}$ should be normalized to THV and not to body weight.

In Figure 4.5, the cardiac reserve index ($\dot{V}O_{2peak}/THV$) is shown for each subject group. There was a significantly lower cardiac reserve index in patients ($p < 0.001$) when compared to volunteers and athletes. This difference remained when the index was normalized for hemoglobin levels ($p < 0.001$)(Figure 4.5b). It is expected that the cardiac reserve index drops in the presence of heart failure since cardiac output, and consequently $\dot{V}O_{2peak}$, is disproportional to the metabolic requirements of the peripheral tissues. However, when and in which stage of heart failure the cardiac reserve index decreases is not known.

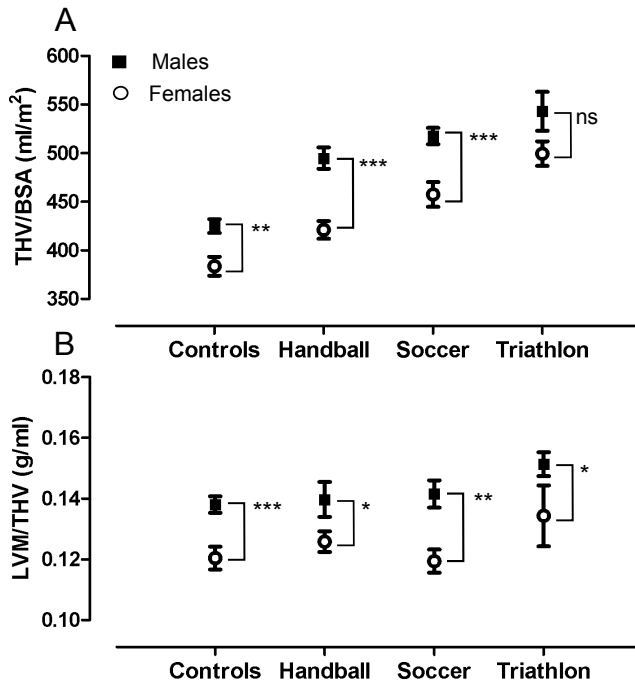


FIGURE 4.3 Comparison of cardiac dimensions between males and females active in the same sport. Panel a shows the total heart volume (THV) normalized for body surface area (BSA). Panel b shows the left ventricular mass (LVM) normalized for THV. Error bars denotes standard error of the mean. All male subject groups had a significantly higher THV/BSA and LVM/THV compared to females, except for THV/BSA in triathletes. This might be explained by the higher training load in female triathletes compared to male triathletes. * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

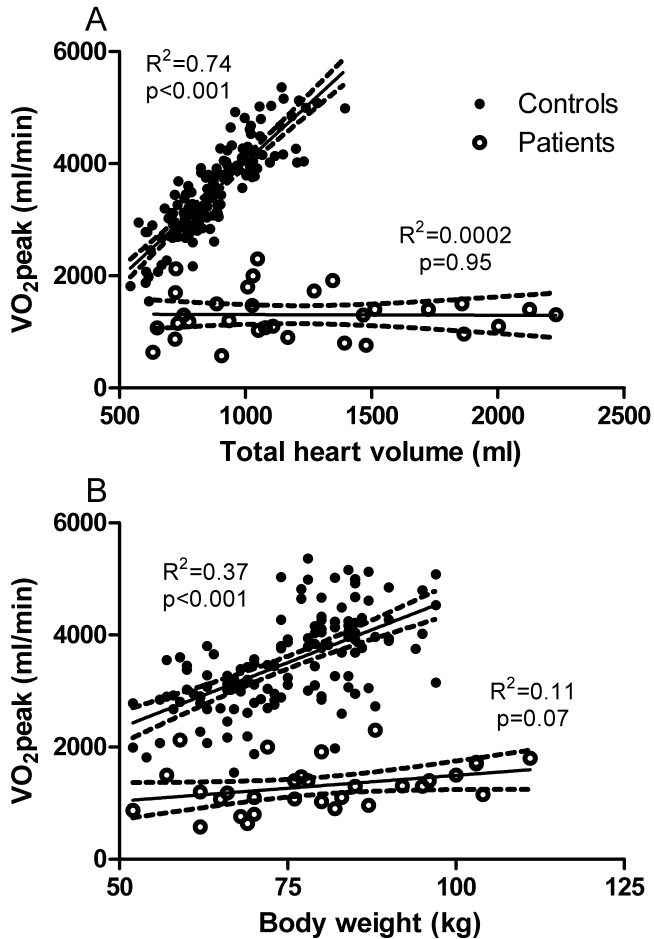


FIGURE 4.4 Peak oxygen uptake in relation to a) total heart volume (THV) and b) body weight. Filled circles denote control subjects, including healthy volunteers and athletes. Open circles denote patients with heart failure. Solid lines represent the regression line and dashed lines the 95% confidence interval. In the control group there was a strong correlation between $\dot{V}O_2\text{peak}$ and THV. Even though there was also a significant correlation between $\dot{V}O_2\text{peak}$ and body weight, there was a considerable variation of $\dot{V}O_2\text{peak}$ for a given body weight.

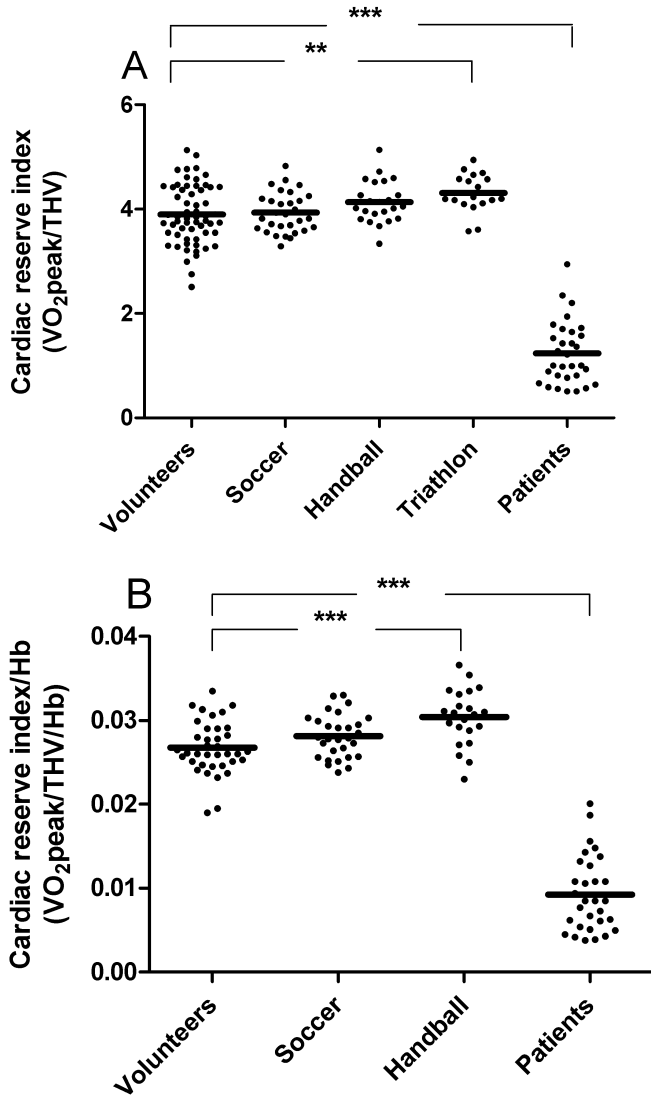


FIGURE 4.5 Cardiac reserve index ($\dot{V}O_{2peak}/THV$) in healthy volunteers, athletes and patients with heart failure. Cardiac reserve index was significantly lower in patients compared to the control group (panel a). The index remained significantly lower after normalizing for hemoglobin levels (panel b). The solid line represents the mean value. $** p < 0.01$ $*** p < 0.001$.

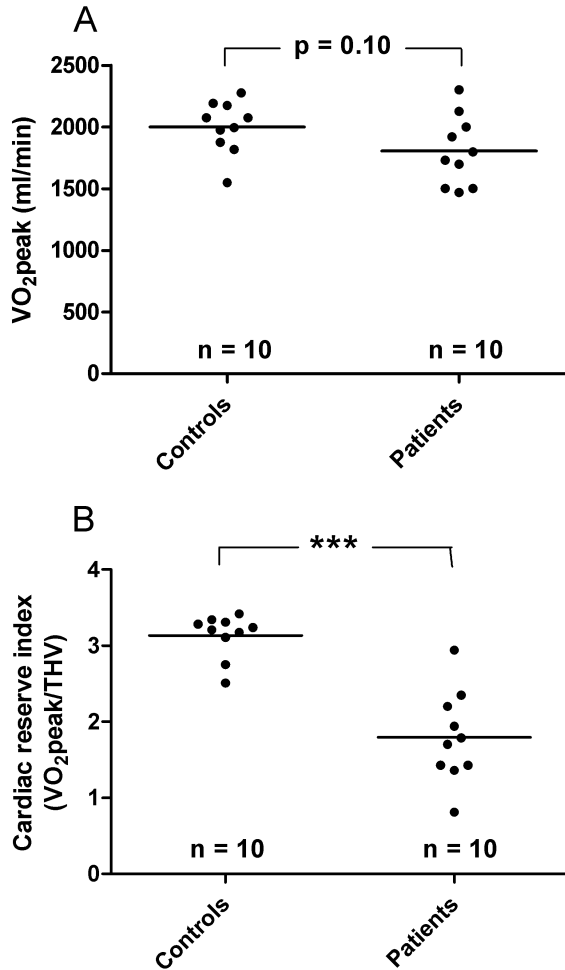


FIGURE 4.6 Panel a shows the peak oxygen uptake ($\dot{V}O_2peak$) for 10 control subjects and 10 patients with heart failure. There was no difference in $\dot{V}O_2peak$ between the groups. Panel b shows the cardiac reserve index for the same controls and patients. Although the $\dot{V}O_2peak$ was similar, there was a statistically significant difference between the groups for the cardiac reserve index. The solid line represents the mean value. $***p < 0.001$.

Although there was a significant difference between the control group and the patients for LVEF% ($p < 0.001$), there was an overlap where 29% of the patients had LVEF% $> 50\%$. However, despite a normal LVEF% in these patients, the cardiac reserve index was significantly lower compared to control subjects ($p < 0.001$). Furthermore, when comparing ten patients and ten controls with no significant differences in $\dot{V}O_{2peak}$, the cardiac reserve index differed significantly between groups (Figure 4.6).

The cardiac reserve index may become useful for diagnosis and follow-up in early-stage heart failure, and perhaps even before the patient exhibit clinical symptoms. Furthermore, the index may potentially be used for patients with a history of endurance training with a sudden change in exercise capacity. These patients may perform well within normal limits when compared to gender- and age-matched normal values. However, in relation to their THV, the working capacity might be decreased as shown by a low cardiac reserve index.

4.3 Respiratory indices in normal subjects and athletes (Paper III)

The effects of exercise on respiratory indices reflecting the metabolism have been of interest for a long time, and a relationship between anaerobic indices and $\dot{V}O_{2max}$ has been established.^{29,35,76,95} However, the inter-relationship between different respiratory indices during an exercise test needs to be studied in order to understand differences between individuals.

In Paper III, two different sequences of the respiratory indices derivative crossing (Dx), point of crossing (Px) and respiratory compensation point (Pq) were identified; $Dx < Px < Pq$ and $Dx < Pq < Px$. Figure 3.6 shows a typical example of the differences in Dx, Px and Pq in a female triathlete and a female control subject. The point Dx always occurred at the lowest $\dot{V}O_2$ whilst Px occur before Pq in untrained subjects and after Pq in well trained subjects. This is also shown in Figure 4.7, where the positive slope of the regression line indicates that a higher Px compared to Pq is related to a high $\dot{V}O_{2max}$. In subjects with the sequence $Dx < Px < Pq$, 28/28 males and 13/13 females had no fat metabolism at Pq. In subjects with $Dx < Pq < Px$, 22/24 males had an average fat metabolism of $0.20 \pm 0.19 \text{ g min}^{-1}$ at Pq and 10/13 females had $0.19 \pm 0.13 \text{ g min}^{-1}$.

The indices Px and Pq are both affected by $\dot{V}CO_2$, and $\dot{V}CO_2$ in turn is affected by 1) the increase in $\dot{V}O_2$, 2) an increase in carbohydrate metabolism in relation to fat metabolism and 3) the buffering of hydrogen ions from lactic acid during anaerobic metabolism. The two different sequences seen in this study are to some extent explained by differences in point 2 and 3 described above. The index Pq reflects the buffering of hydrogen ions from lactic acid by HCO_3^- . As

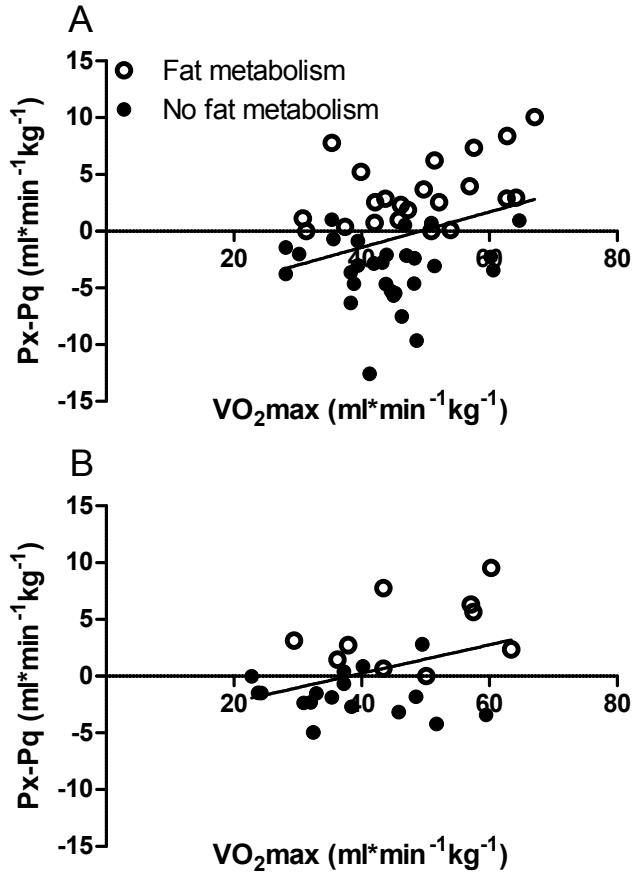


FIGURE 4.7 The differences in the indices P_x and P_q in relation to $\dot{V}O_{2max}$. Panel a shows males and panel b shows females. Subjects below the x-axis have the sequence $D_x < P_x < P_q$, and subjects above the x-axis have the sequence $D_x < P_q < P_x$. Open circles denotes subjects with fat metabolism at P_q and filled circles denotes subjects with no fat metabolism at P_q . The positive slope of the regression line indicates that as $\dot{V}O_{2max}$ increases, the index P_x also increases and occurs at a higher fraction of $\dot{V}O_{2max}$ compared to P_q .

the hydrogen ions are buffered, non-metabolic CO_2 is increased and ventilation increases in order to maintain pH. However, well trained subjects were shown to utilize fat as one of the substrates at Pq, which indicates that anaerobic metabolism of carbohydrates is present at the same time as aerobic fat metabolism at this point. If a subject can utilize fat as a substrate at high work rates, the index Px will occur at a higher fraction of $\dot{V}O_{2max}$, thereby changing the order of Px and Pq. High fat metabolism has previously been shown in well trained subjects.^{45,52}

The respiratory indices as a fraction of $\dot{V}O_{2max}$ were called Dx%, Px% and Pq%. Dx% and Px% was significantly higher in triathletes compared to gender matched control subjects ($p < 0.05$ for both males and females) (Table 4.2). Pq%, however, occurred at approximately 70% of $\dot{V}O_{2max}$ for all test subjects. These results suggests that Px is more affected by fitness status than Pq.

It has been suggested that different protocols affect the respiratory indices,¹⁰⁷ which has to be considered. Therefore, all protocols were chosen to yield an exercise duration of 8-12 min and all test subjects reached RER > 1.15 , as recommended by the American Heart Association.⁴

TABLE 4.2
Derivative crossing (Dx), Point of crossing (Px) and Respiratory compensation point (Pq) expressed as percentages of $\dot{V}O_{2max}$.

	Female controls	Female triathletes	p	Male controls	Male triathletes	p
Dx%	43±10	49±4	0.036	38±11	45±10	0.014
Px%	70±8	79±6	0.031	65±10	71±9	0.043
Pq%	73±8	76±10	0.408	69±9	70±11	0.268

Figure 4.8 shows the minute ventilation, VE, plotted against $\dot{V}CO_2$ for all males and females. The ventilation increased proportional to $\dot{V}CO_2$ for all subjects up to a breakpoint corresponding to Pq, after which the ventilation increased more than $\dot{V}CO_2$. Thus, there were no signs of hyperventilation before Pq, indicating that control subjects and triathletes have the same VE for a given $\dot{V}CO_2$ before Pq. Therefore, the differences in the sequence of the respiratory indices between individuals are likely caused by Px increasing with improved fat metabolism and not by Pq occurring at a lower $\dot{V}O_2$ because of differences in ventilation.

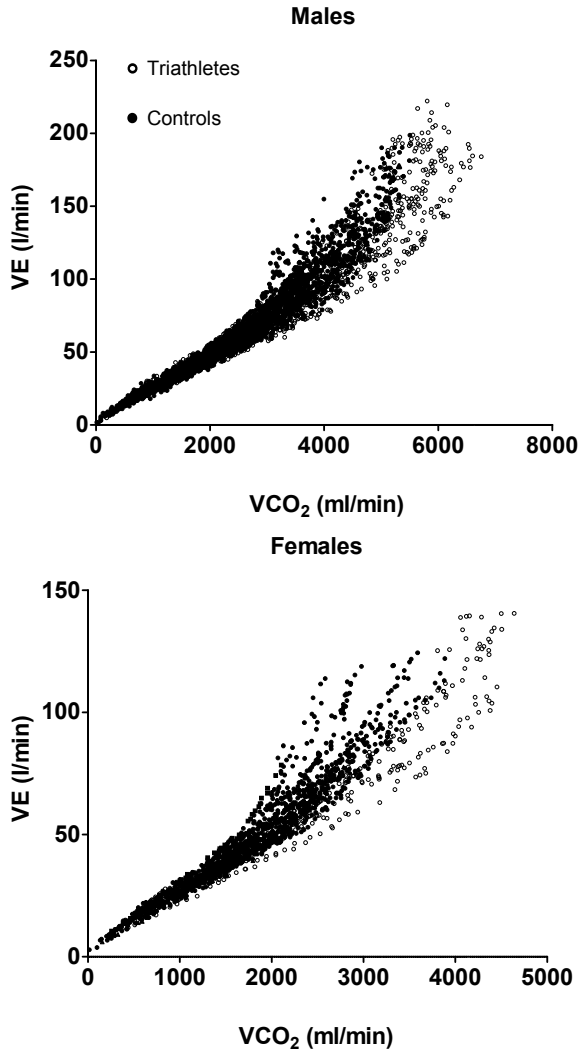


FIGURE 4.8 The relationship between the minute ventilation (VE) and the $\dot{V}CO_2$. The ventilation increased proportional to $\dot{V}CO_2$ for both triathletes and controls up to a breakpoint corresponding to P_q , where the ventilation increased to blow off CO_2 to maintain pH.

4.4 Cardiac pumping in athletes and normal subjects (Paper IV)

Efficiency of cardiac pumping is needed to maintain cardiac output (CO) without unnecessary energy loss. Cardiac pumping can be divided into longitudinal and radial pumping where the longitudinal pumping is caused by the atrioventricular plane moving towards the apex during systole and towards the base during diastole. Radial pumping is defined as the inward movement of the myocardium during systole.

In line with Carlsson et al.,²⁰ the longitudinal contribution determined from AVPD multiplied by the mean short-axis epicardial area was $59 \pm 8\%$ for the LVSV and $78 \pm 10\%$ for the RVSV. Thus, the radial contribution to the LVSV is approximately 40% and to the RVSV approximately 20%. For the TSV, longitudinal contribution was calculated to be $68 \pm 8\%$, and when using the THVV to determine the radial component, $29 \pm 10\%$ was shown to be radial. Thus, the longitudinal pumping is the major contributor to the SV in normal subjects as well as in athletes. Except for the longitudinal contribution to the LVSV in male athletes when compared to male normal subjects, there were no statistically significant differences between groups for the longitudinal and radial contribution to the TSV, LVSV and RVSV (Figure 4.9).

The atrial contraction caused $15 \pm 5\%$ of the LVAVPD and $27 \pm 6\%$ of the RVAVPD, with no statistically significant difference between the groups. These are values at rest for a young (mean age 25 years), healthy population. Atrial contribution is known to become more important for ventricular filling with increasing age.⁷⁴ Studies on the atrial contribution to the AVPD in an older population may therefore show a larger contribution than in the present study.

There were no differences between groups for THVV (%) despite differences in THV. For all groups, the mean THVV was $7.7 \pm 2.8\%$. Furthermore, there were no differences in TSV_{rad}/TSV between groups and no correlation between THV and TSV_{rad}/TSV ($R^2 = 0.03$, $p = ns$). This is in contrast to Gauer³⁸ who showed that larger hearts have a larger THVV and thus, a larger radial contribution to the TSV. A recent study by Slördahl et al.⁹⁶ showed no differences in AVPD at rest in the same subjects before and after 8 weeks of aerobic interval training, although the resting heart rate was significantly reduced. Assuming that the CO at rest was the same, the decrease in HR at a given AVPD must be compensated by either a larger radial contribution or a larger short-axis area. The results of Paper IV have, in contrast to Gauer's animal studies, shown no differences in radial pumping mechanics between groups. However, the results have shown a larger short-axis area in athletes when compared to controls, and in male controls when compared to female controls. This indicates that the increase in

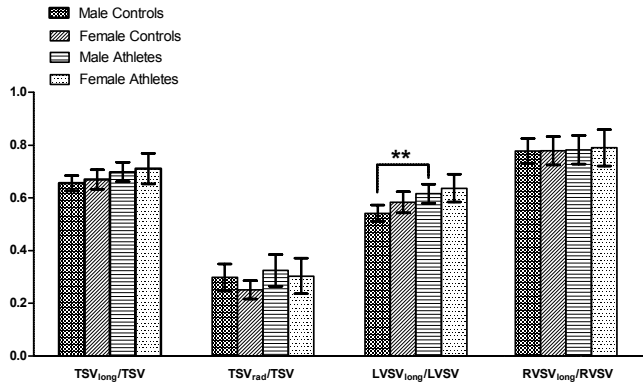


FIGURE 4.9 Total longitudinal and radial contribution normalized for the total stroke volume (TSV_{long}/TSV , TSV_{rad}/TSV), left ventricular longitudinal contribution normalized for left ventricular stroke volume (LVS_{Vlong}/LVS_{V}) and right ventricular longitudinal contribution normalized for right ventricular stroke volume (RVS_{Vlong}/RVS_{V}). There were no statistically significant differences between groups except for longitudinal contribution to the LVS_V where male athletes had a higher LVS_{Vlong}/LVS_{V} compared to male controls.

short-axis area is important for the increase in SV, rather than radial pumping mechanics.

Previous studies using echocardiography have shown correlations between LVAVPD and cardiac volumes and $\dot{V}O_{2peak}$ ($\text{ml min}^{-1} \text{kg}^{-1}$).¹⁷ However, when using CMR, there were poor correlations between LVAVPD and LVS_V and between LVAVPD and LVEDV. There were no correlations between LVAVPD and LVEF% and $\dot{V}O_{2peak}$ (Figure 4.10). Furthermore, there was no correlation between LVAVPD and $\dot{V}O_{2peak}$ (ml min^{-1}) ($R^2 = 0.05$, $p = 0.075$). In the clinical setting, left ventricular EF% is often estimated from LVAVPD. In line with Carlhäll et al.,¹⁷ Paper IV shows that in healthy subjects, there is no statistically significant relationship between the variables. However, when there is a larger range in both LVAVPD and EF%, such as in patients, a relationship can be seen.²

In the methods section of this thesis, the AVPD was theoretically shown to be affected by CO, HR, mean short-axis epicardial area and SV_{rad} . Using equation 3.7, the calculated LVAVPD showed a moderate to good correlation with LVAVPD determined from long-axis CMR images ($R^2 = 0.5$, $p < 0.0001$) (Figure

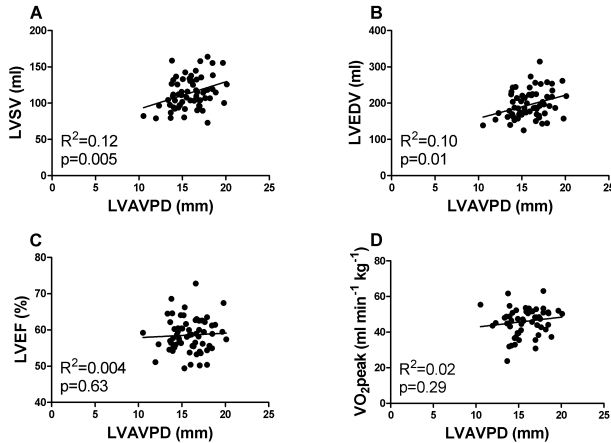


FIGURE 4.10 Panel a: Correlation between the left ventricular atrioventricular plane displacement (LVAVPD) and left ventricular stroke volume (LVSV), Panel b: Correlation between LVAVPD and left ventricular end-diastolic volume (LVEDV), Panel c: Correlation between LVAVPD and left ventricular ejection fraction (LVEF), Panel d: Correlation between LVAVPD and peak oxygen uptake ($\dot{V}O_2peak$). Left ventricular AVPD correlated weakly with LVSV and LVEDV, and no correlation was seen with LVEF and $\dot{V}O_2peak$.

4.11). As previously suggested by Carlhäll et al.¹⁷, there is an interrelationship between the LVAVPD and LVSV as shown by equation 3.2 and 3.4. Furthermore, there is likely also an interrelationship between LVAVPD and LVEDV, as LVEDV is affected by the short-axis area of the ventricle. When the ventricle increases in size as a response to training, it increases in both length and diameter. However, in contrast to Carlhäll,¹⁷ Paper IV showed that the LVAVPD at rest is not related to the measurement of peak exercise capacity. These results are supported by previous studies showing that the LVAVPD increases with 2–7 mm with exercise.^{96,101} Thus when using the AVPD as a measurement of cardiac function, several variables need to be considered.

Limitations

Test subjects did not get an opportunity to get familiarized with the ergometer cycle before the exercise test. This may have affected the results, causing an un-

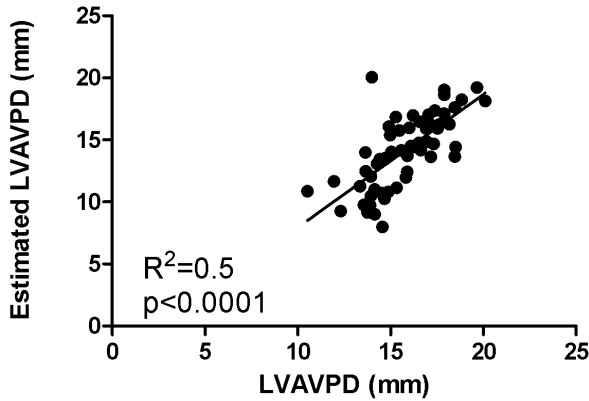


FIGURE 4.11 Correlation between the LVAVPD determined from equation 3.7 in the methods section and the LVAVPD measured in long-axis CMR images. There was a good correlation between the variables indicating that when using the LVAVPD as a measurement of cardiac function, other factors may influence the results.

derestimation of $\dot{V}O_{2max}$. Therefore, the term $\dot{V}O_{2peak}$ is used in this thesis. In Paper II, patients were retrospectively enrolled and the exercise test was performed according to clinical praxis. Patients may not be as motivated as healthy volunteers and $\dot{V}O_{2peak}$ for patients may therefore be underestimated in comparison to normal subjects and athletes. To ensure a maximal effort from all test subjects, it would have been beneficial to also measure lactate levels in blood, in addition to gas analysis.

Hemoglobin levels were not measured in triathletes nor in control subjects who declined blood sampling.

All test subjects were asked not to participate in any vigorous exercise 48 hours prior to the exercise test, to be awake at least two hours before the exercise test, avoid heavy meals one hour before the test and not drink coffee, tea or eat chocolate two hours before the test. However, the food intake the previous day and the same day was not standardized which may have influenced the results of the respiratory indices in Paper III. Furthermore, the values from the exercise test used to determine fat metabolism were not taken during steady state, which can affect the results.

Chapter 5

Major Conclusions

The major conclusion of each paper was:

- I. The total heart volume (THV) is a strong, independent predictor of maximal work capacity for both males and females. Long term endurance training is associated with a physiologically enlarged heart with a balance between the left and right ventricular dimensions in males and females.
- II. The novel cardiac reserve index $\dot{V}O_{2peak}/THV$ can be used to distinguish patients with known heart failure from healthy volunteers and athletes, even in patients with preserved systolic LV function and after normalizing for hemoglobin levels.
- III. There are two different sequences of the respiratory indices D_x , P_x and P_q occurring in subjects of varying levels of training and working capacity. The individual differences in the order of occurrence of P_x and P_q during an incremental exercise test are most likely caused by different abilities to utilize fat as a substrate at high workloads.
- IV. Except for LV longitudinal pumping in males, there are no statistically significant differences between groups in longitudinal and radial contribution to the SV at rest. Furthermore, there are no differences in THVV or atrial contribution to AVPD between groups. The similar results in cardiac pumping for males and females of varying fitness indicate that the higher stroke volume seen in athletes is likely due to larger cardiac volumes and not to differences in pumping mechanics.

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Acknowledgments

There are many people I would like to thank. Without your help, this thesis would not have been written.

First, I would like to thank my main supervisor **Håkan Arheden**, for believing in me, teaching me leadership and patience, and for allowing me to pursue my goals even at times when I could not define what they were. To my co-supervisor **Björn Wohlfart**, for inspiring conversations on physiology and on life, and for being a great teacher. My co-supervisor **Torsten Buhre**, for asking me the right questions that made me decide to pursue a PhD, and for pep-talks at times when they were very much needed. My co-supervisor **Henrik Engblom**, for always having time to answer my questions and for teaching me scientific writing and statistics.

Two persons have been just as important as my supervisors and I am forever thankful to you. Professor emeritus **Björn Jonson**, for all your help, and for being a great inspiration. **Erik Hedström**, for friendship and for being at the right place at the right time, guiding me to the Cardiac MR-group and then leaving me there to grow.

To my colleagues in the Cardiac MR-group: Our wonderful technicians **Ann-Helen Arvidsson**, **Christel Carlander**, **Johanna Carlson** and **Lotta Åkesson**. This would not have been possible without you. To **Henrik Mosén**, for sharing my interest in athletes and for all the laughs while trying not to talk to our test-subjects on the ergometer cycle. **Bo Hedén**, for all your help with the athletes and for inspiring me to take up music again. **Marcus Carlsson**, for your patience when explaining cardiac pumping and for sharing chocolate desserts with me at TGIs. **Karin Markeroth Bloch**, for friendship, for giving me private lessons on MR physics and for dancing the hula with me on Hawaii. **Einar Heiberg**, for developing Segment, my favourite software. **Martin Ugander**, for teaching me the basics of CMR scanning. **Olle Pahlm**, for being a role model and for providing the opportunity to collaborate with NASA. **Mikael Kanski**, for friendship and for constantly supplying me with new music. **Helen Soneson** for friendship and for convincing me to do a come-back on the soccer field. **Jane Sjögren** for friendship and for inspiring me to develop my sewing skills. **Johannes Töger**, for friendship and for great company on our road trip around Hawaii. **Joey Ubachs**, **David Strauss** and **Ulrika Pahlm-Webb**, for friendship in the 4 ch and during our conferences. To **Jonas Jögi**, **Fredrik Hedeer** and **Magnus Hansson**, for always adding an interesting aspect to discussions.

To our invaluable secretary, **Märta Granbohm**, for helping me with all the formalities the university system has invented. **Kerstin Brauer**, for your help with small things over

the years, and especially for helping me with figure 1.1 of this thesis.

To my friends and mentors **Örjan Sundewall** and **Pär Herbertsson**, for allowing me to hang out at the Orthopaedic department whenever I felt the need to be a Physiotherapist again, and for helping me to include injured athletes for my future studies.

To my parents and their respective partners, **Margaretha Steding** and **Anders Klemedson**, **Bo Steding** and **Barbro Eriksson**, for believing in me.

And finally, to **Christian Ehrenborg**, for your love and for helping me remember what really matters in life.

The studies in this thesis were supported by grants from the Swedish Research Council, the Swedish National Centre for Research in Sports, the Swedish Heart and Lung Foundation, the Medical Faculty at Lund University, Sweden and the Region of Scania, Sweden.

Papers I–IV