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Cardiac function and long-term volume load

Physiological investigations in endurance athletes and in patients operated on for aortic regurgitation

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*To my wife and children,
who load my heart
and make it grow.*

*"Science is much more than a body of knowledge.
It is a way of thinking.
This is central to its success.
Science invites us to let the facts in,
even when they don't conform to our preconceptions."
- Carl Sagan*

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ABSTRACT

Background and aims. The heart is a remarkably adaptable organ, continuously changing its output to match metabolic demands and haemodynamic load. But also in long-term settings, such as in chronic or repeated volume load, there are changes in cardiac dimensions and mass termed cardiac hypertrophy. Depending on the stimulus imposing the volume load this hypertrophy differs in extent and phenotype. We aimed to study cardiac function in two settings with long-term volume load, including patients previously operated for aortic regurgitation and healthy females performing endurance training.

Methods. In *paper I*, 21 patients (age 52 ± 12 years, all male) operated on with aortic valve replacement for aortic regurgitation (AR) underwent a cardiopulmonary exercise test (CPET) and an echocardiographic evaluation in average 49 ± 15 months following surgery. The peak oxygen uptake (peakVO_2) was compared to results from a pre-operative and a six months follow-up, and relations to echocardiographic measures were determined.

In *papers II–IV*, 48 endurance trained female athletes (ATH, age 21 ± 2 years) were compared to 46 untrained females (CON, age 21 ± 2 years) regarding echocardiographic measures of cardiac dimensions, global and regional cardiac function and maximal aerobic capacity ($\text{VO}_{2\text{max}}$) determined with CPET. Relations between $\text{VO}_{2\text{max}}$ and cardiac variables were explored.

Results. In *paper I*, peakVO_2 had decreased from 26 ± 6 to 23 ± 5 mL/kg/min in patients from the first to second, late follow-up. This decrease was larger than expected by their increased age alone, and a majority of patients had a cardiorespiratory fitness below average according to reference values from healthy subjects of the same age, sex and weight.

In *papers II–IV*, we found that ATH ($\text{VO}_{2\text{max}}$ 52 ± 5 mL/kg/min) had larger atrial, ventricular and inferior vena cava dimensions compared to CON ($\text{VO}_{2\text{max}}$ 39 ± 5 mL/kg/min). ATH had increased measures of right ventricular (RV) systolic function (RV atrioventricular plane

displacement indexed by cardiac length 2.5 ± 0.3 vs. 2.3 ± 0.3 , $p=0.001$) and left ventricular (LV) diastolic function (mitral E-wave velocity 0.92 ± 0.17 vs. 0.86 ± 0.11 m/s, $p=0.029$). In addition, systolic synchrony was similar between groups while there were heterogeneous differences in diastolic and systolic function across different myocardial segments. $VO_{2\max}$ was most strongly related to LV end-diastolic volume ($r=0.709$, $p<0.001$).

Conclusions. Decreasing peak VO_2 following surgery for AR, despite a normalisation in cardiac dimension could either be a result of a remaining, slight myocardial dysfunction or post-operative negative influence on cardiac performance by filling disturbances or the prosthetic valve itself, or, a sign of an inadequate post-operative level of physical activity and lack of exercise training. This stresses the importance of post-operative management and methods for increasing aerobic capacity, where exercise testing could be valuable for guiding patients and tailoring exercise protocols.

The eccentric cardiac hypertrophy in ATH, symmetrically distributed across the heart, depicts the physiological hypertrophy in response to volume load in endurance training. Cardiac function was similar, or for some measures slightly improved in ATH compared to CON and LV dimensions, rather than cardiac function, were predictors of $VO_{2\max}$. As the heart of female athletes has been far less studied than that in males, our results add knowledge regarding the female athlete's heart, and our results of differences in segmental cardiac function merits further research.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Hjärtfunktion hos konditionsidrottare och patienter opererade för aortaklaffläckage

Fysiologiska studier av volymbelastningens långtidseffekter

Hjärtat har en fantastisk förmåga att anpassa sig till olika situationer. Detta ses inte minst när man går från vila till hårt arbete, då hjärtminutvolymen ökar mångfaldigt. Men även på lång sikt uppvisar hjärtat förmåga till anpassning, då både hjärtrummen kan bli större och hjärtats väggar tjockare. I denna avhandling studerades hjärtfunktion, hjärtdimensioner och kondition hos individer utsatta för ökad tillströmning av blod (volymbelastning) på grund av dels läckage genom aortaklaffen, dels till följd av flerårig konditionsträning.

Vi fann att konditionen hos patienter opererade på grund av aortaklaffläckage hade sjunkit och var lägre än förväntat utifrån ålder, kön och kroppsvikt fyra år efter operationen, trots att hjärtats dimensioner och funktion hos de flesta patienterna normaliserats. Möjliga förklaringar till detta är antingen att det trots allt fanns en kvarvarande nedsättning i hjärtfunktionen vi inte uppmätt, eller att de blivit mer fysiskt inaktiva efter operationen, trots att de uppmanas att återgå till normal fysisk aktivitetsnivå.

Hos uthållighetstränade kvinnor med god kondition fann vi större hjärtrum och vägg tjocklek än hos otränade kvinnor och nedre hålvenen var signifikant större hos idrottarna. Ingen av de mått på hjärtfunktion vi använde påvisade någon negativ effekt av de förstörade hjärtdimensionerna. Istället fann vi att enskilda segment i hjärtmuskeln uppvisade högre hastigheter under hjärtats kontraktionsfas, eventuellt tydande på en förbättrad funktion. Det var framförallt segment i höger kammars vägg och segment intill denna som uppvisade dessa

förändringar, som tillsammans med en viss ökning av högerkammarens längsaxelfunktion kan innebära att höger och vänster kammare anpassar sig till uthållighetsträning på olika sätt och i olika grad.

Det fanns ett samband mellan konditionsnivå mätt som högsta syreupptag och vänsterkammarens volym och massa, tydande på att hjärtrumsförstoringen var proportionell mot förbättringar i konditionsnivå.

Då kvinnliga idrottare studerats betydligt mer sällan än manliga idrottare kan en del av våra resultat vara av värde för läkare som undersöker kvinnliga idrottare för misstänkt hjärtsjukdom. Vårt fynd av försämrad kondition i efterförloppet av aortaklaffsoperation understryker vikten av att ge förutsättningar för dessa patienter att öka sin fysiska aktivitetsnivå efter operationen, för att påskynda återgång till normal konditionsnivå och undvika ytterligare försämring i kondition.

LIST OF ORIGINAL PAPERS

This thesis is based upon the following four papers, which will be referred to by their Roman numerals:

- I. **Hedman K**, Tamás É, Nylander E. Decreased aerobic capacity 4 years after aortic valve replacement in male patients operated upon for chronic aortic regurgitation.
Clin Physiol Funct Imaging. 2012; 32:167–171.
- II. **Hedman K**, Tamás É, Henriksson J, Bjarnegård N, Brudin L, Nylander E. Female athlete's heart: Systolic and diastolic function related to circulatory dimensions.
Scand J Med Sci Sports. 2015; 25(3): 372–81.
- III. **Hedman K**, Tamás É, Bjarnegård N, Brudin L, Nylander E. Cardiac systolic regional function and synchrony in endurance trained and untrained females.
BMJ Open Sport Exerc Med. 2015; 1:e000033.
- IV. **Hedman K**, Nylander E, Henriksson J, Bjarnegård N, Brudin L, Tamás É. The size and shape of the inferior vena cava in trained and untrained females in relation to maximal oxygen uptake.
In manuscript.

ABBREVIATIONS

σ	wall stress in the LaPlace equation
%COV	coefficient of variation in percent
2D	two-dimensional
A	late atrial Doppler filling velocity over mitral valve
a'	late atrial diastolic peak myocardial velocity
AR	aortic regurgitation
ATH	athletes
AV-O ₂ -diff	arterio-venous oxygen difference
AVR	aortic valve replacement
BMI	body mass index
BP	blood pressure
BSA	body surface area
CO	cardiac output
CON	controls
CPET	cardiopulmonary exercise testing
E	early Doppler filling velocity over mitral valve
e'	early diastolic peak myocardial velocity
E/A	ratio of early-to-late atrial left ventricular filling velocities
E/e'	ratio of early diastolic Doppler filling velocity to peak myocardial velocity
e'/a'	ratio of early-to-late diastolic peak myocardial velocity
ECG	electrocardiogram
EDV	end-diastolic volume
ESV	end-systolic volume
h	wall thickness in the LaPlace equation
HR	heart rate
ICC	intraclass correlation coefficient
IVC	inferior vena cava
LA	left atrium
LAA _s	left atrial area in systole
LAX _{EXP}	maximal inferior vena cava long-axis diameter during expiration
LAX _{INSP}	minimal inferior vena cava long-axis diameter during inspiration
LV	left ventricle or left ventricular
LV _{AVD}	left ventricular atrioventricular plane displacement
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LV-FS	left ventricular fractional shortening
LVID _D	left ventricular internal diameter in diastole
LVID _S	left ventricular internal diameter in systole
LVIL _D	left ventricular internal length in diastole
LVM	left ventricular mass
LV-12-e'	mean e' of six basal and six mid-ventricular LV segments
LV-12-s'	mean s' of six basal and six mid-ventricular LV segments

ABBREVIATIONS

LV-a' _{BASAL}	mean a' of six basal LV segments
LV-e' _{BASAL}	mean e' of six basal LV segments
LV-s' _{BASAL}	mean s' of six basal LV segments
LV-strain _{BASAL}	mean strain of six basal LV segments
Max-LV-delay	maximal delay in T _s between any two LV segments
M-mode	motion-mode echocardiography
P	pressure in the LaPlace equation
peakVO₂	peak oxygen uptake
PWT	posterior wall thickness in diastole
r	chamber radius in the LaPlace equation
RA	right atrium or right atrial
RAA_s	right atrial area in systole
ROI	region of interest
RV	right ventricle or right ventricular
RV _{AVD}	right ventricular atrioventricular plane displacement
RV-a' _{BASAL}	mean a' of basal RV free wall and septum
RV-a' _{LATERAL}	mean a' of basal and mid-ventricular RV free wall
RV-e' _{BASAL}	mean e' of basal RV free wall and septum
RV-e' _{LATERAL}	mean e' of basal and mid-ventricular RV free wall
RV-s' _{BASAL}	mean s' of basal RV free wall and septum
RV-s' _{LATERAL}	mean s' of basal and mid-ventricular RV free wall
RVD1	right ventricular basal diameter in diastole
RV-LV-delay	delay in T _s between right and left ventricular free walls
RVOT-prox	right ventricular outflow tract diameter in diastole
RWT	relative wall thickness
s'	systolic peak myocardial velocity
SAX _{EXP-AREA}	maximal IVC short axis area during expiration
SAX _{EXP-MAJOR}	largest IVC diameter at SAX _{EXP-AREA}
SAX _{EXP-MINOR}	smallest IVC diameter perpendicular to SAX _{EXP-MAJOR} at SAX _{EXP-AREA}
SAX _{INSP-AREA}	minimal IVC short axis area during inspiration
SAX _{INSP-MAJOR}	largest IVC diameter at SAX _{INSP-AREA}
SAX _{INSP-MINOR}	smallest IVC diameter perpendicular to SAX _{INSP-MAJOR} at SAX _{INSP-AREA}
SD	standard deviation
S-L-delay	septal-to-lateral delay in T _s
SV	stroke volume
SWT	septal wall thickness in diastole
TDI	tissue Doppler imaging
T_s	time to s' from beginning of QRS-complex
T_s-SD	standard deviation of T _s in 12 LV segments
VCO₂	carbon dioxide elimination
VO₂	oxygen uptake
VO_{2max}	maximal oxygen uptake
W	Watt

INTRODUCTION

The heart shows a remarkable ability to adapt to different situations and demands. This is apparent in acute settings such as onset of physical activity, where an increased metabolic demand of the skeletal muscles imposes a stimulus for increases in heart rate and stroke volume and thus in cardiac output. But it is also apparent in long-term settings where either constant or repeated elevations in volume or pressure load are imposed upon the heart, and there are cardiac adaptations acting to maintain optimal conditions for heart pumping. One of these long-term adaptations is cardiac hypertrophy.

Physiological cardiac adaptation can be understood as an adequate response to an acute or chronically altered haemodynamic environment, and is advantageous for efficient cardiac pumping under the haemodynamic stimulus imposing the adaptation. However, cardiac adaptation is not always beneficial for cardiac function. In diseases directly affecting the myocardium, inadequate cardiac hypertrophy may occur. Also in diseases chronically imposing a pressure or volume load upon the heart, an initially adequate and favourable cardiac hypertrophy may eventually become insufficient or disproportionate, leading to deterioration in cardiac function.

With the purpose of gaining knowledge about cardiac adaptations in response to long-term volume load, the papers in this thesis include subjects exposed to chronic aortic regurgitation and healthy subjects participating in chronic exercise training; two conditions that present with compensatory cardiac hypertrophy in response to pathological and physiological stimuli, respectively.

BACKGROUND

The heart and physiology of work

Cardiac functional anatomy

The heart consists of a right-sided low-pressure system transporting blood from the central venous system to the lungs, and a left-sided high-pressure system transporting blood from the pulmonary circulation to the systemic arteries (**Figure 1**). The right ventricle (RV) has a thin, highly trabeculated heart wall, while the left ventricle (LV) is much thicker and is not as trabeculated.⁸⁹

Between the atria and ventricles lies the atrioventricular plane, which can be divided into a left and right ventricular portion. These are anchored to a fibrous skeleton called the *anulus fibrosus cordis*, which incorporates the four cardiac valves.⁸⁹

In the normal heart, the atria and ventricles contract rhythmically and with a pre-determined pattern. Following depolarization and

Figure 1. Cardiac anatomy (A) and muscle fibre orientation (B).

(Image in panel B from OpenStax College. Download for free at <http://cnx.org/contents/6394ffc1-5482-4aa6-9233-23ad34848fa0@4>).

contraction of myocytes in the atria, ventricular contraction starts at the apex and continues toward the base of the heart. This rhythmicity and the ability to change cardiac pace is governed by the sino-atrial node situated between the right atrium (RA) and superior vena cava. The apical-to-base pattern of contraction relies on the cardiac conduction system.⁴⁶

The heart performs its pumping by contraction and relaxation of myocytes arranged in myocardial layers with different fibre orientations in the two ventricles (**Figure 1**).^{18, 65} By the contraction of these fibres, the blood is virtually wrung out from the ventricles as the pressure inside the heart chambers increases following myocyte contraction.¹⁷

The left ventricle

Seen from the apex, myocytes in the LV are arranged in an outer left-handed helical orientation, in an inner right-handed helical orientation and in a circumferential orientation between the helical layers.^{18, 65} Contraction of these myocytes induces torsion of the myocardium, with the apex twisting counter-clockwise and the base clockwise, leading to shortening and thickening of the myocardium, which shortens and narrows the LV lumen.^{18, 110} In this manner, blood is ejected from and filled into the LV while the heart maintains an almost constant outer contour during the cardiac cycle.^{23, 88}

The right ventricle

The RV myocardium is principally composed of two distinct layers of myocytes, with an outer circumferentially oriented layer and an inner longitudinal myocardial layer.⁶⁴ The circumferential layers cross over and join with LV fibres in the interventricular septum,⁵⁵ and there is a ventricular interdependence where LV contraction is an important contributor to RV systolic function.¹³⁰

Longitudinal cardiac function

Longitudinal function can be studied and measured as the displacement of the right and left atrioventricular planes (RV_{AVD} and LV_{AVD} respectively) or as the longitudinal myocardial velocities or deformation. The decrease in ventricular cavity dimensions is primarily brought about by a longitudinal shortening and to a lesser extent by radial narrowing (**Figure 2**).²³

The fact that LV_{AVD} has been reported to account for $\sim 60\%$ of the LV stroke volume²⁴ while RV_{AVD} accounts for $\sim 80\%$ of the RV stroke volume,²³ can be interpreted to mean the RV relies more heavily on longitudinal shortening than the LV. This is further supported by the finding of higher longitudinal myocardial velocities in the RV than in the LV.¹⁰¹

Figure 2. Schematic illustration of left ventricular dimension at end-diastole (red, left) and at end-systole (yellow, middle).

Physiology of work and cardiac function

The objective of the heart as a pump is to provide kinetic energy to the blood circulating in our vessels, in order for the blood to act as a transport medium for cells and molecules and to act in thermoregulation. When the heart fails in this objective, the metabolic demands of our cells are not fulfilled, which may eventually lead to cell dysfunction.

Cardiac function is continuously calibrated to match the demands of various tissues in the body via the central and autonomic nervous system, and there is a close relationship between oxygen uptake (VO_2) and cardiac output (CO).¹⁰⁷ According to the principle of Fick,^{41, 137} VO_2 is the product of CO and the difference between arterial and venous oxygen content (AV- O_2 -diff):

$$\text{VO}_2 = \text{CO} \times \text{AV-}\text{O}_2\text{-diff} \quad (\text{The Fick equation})$$

At rest, an oxygen uptake of 0.25–0.35 L/min is normally sufficient to meet metabolic demands, which is accomplished by a CO of four to six litres per minute (L/min) and an AV- O_2 -diff of 40–60 mL/L blood.^{149, 159} Depending primarily on age, sex and fitness, CO can rise four to even eightfold from rest to maximal work intensities, while the AV- O_2 -diff increases two to fourfold.^{7, 107, 159}

Cardiac output, in turn, equals the product of heart rate (HR) and stroke volume (SV). While HR increases linearly from resting conditions to maximal work, SV has been found to increase non-uniformly between individuals.^{125, 150} It has not been established which individual factors determine whether SV plateaus or rises progressively until maximal HR is reached, but the SV response has been suggested to be influenced by sex, age, level of fitness and blood volume.¹⁵⁰

SV is the difference between the end-diastolic and end-systolic volumes of the ventricle (EDV and ESV respectively). The higher SV seen during exercise compared to at rest is primarily brought about

by an increase in EDV^{123, 138, 139} although there have been some reports of a concomitant slight decrease in ESV.^{62, 123, 138} In other words, more blood enters the heart in each cardiac cycle during exercise than at rest, while a similar or slightly smaller amount of blood remains in the ventricle between cardiac cycles.

The acute adaptations in heart function seen during exercise are brought about by several physiological mechanisms. First, according to the Frank-Starling mechanism, when sarcomeres in myocytes are stretched as an effect of increased EDV they generate a larger force of contraction. This increased force results in more blood being ejected by each heartbeat, counterbalancing the increased filling of the heart chamber. This relies in part on a greater tension in the stretched non-contractile components of the sarcomere and in part on augmented calcium utilization.⁴⁶ Second, increased activity in the sympathetic nervous system raises the concentration of circulating catecholamines and also increases HR and cardiac contractility through direct innervation of the sinoatrial node and myocardium.^{46, 126}

Simultaneously with increases in EDV and SV during exercise, the time for diastolic filling and systolic ejection decreases progressively as HR increases. Thus, more blood will enter and leave the heart in a shorter time during exercise than during resting conditions. The diastolic filling time decreases more than the ejection time, which necessitates a rapid filling rate, especially in well-trained subjects exercising with extremely high CO. This was shown in an experiment by Gledhill and colleagues⁵¹ outlined in **Table 1** and it implies an augmented diastolic function in athletes compared to untrained subjects. Whether this difference is apparent and measureable at rest is controversial.^{49, 76, 125}

Table 1. Cardiac functional measurements at different heart rates in seven competitive cyclists and seven untrained men obtained on a cycle ergometer. Modified from Gledhill et al. (1994).⁵¹

		Heart rate (beats/min)		
		90	140	190
VO ₂ (L/min)	Untrained	0.85	2.17	3.56
	Trained	0.87	2.65	4.80
	%-diff	NS	+22%	+35%
CO (L/min)	Untrained	10.8	17.8	24.5
	Trained	12.1	23.2	34.8
	%-diff	NS	+30%	+42%
LVET (ms)	Untrained	212	198	155
	Trained	262	230	185
	%-diff	+24%	+16%	+19%
LVER (L/sec)	Untrained	0.57	0.64	0.83
	Trained	0.51	0.72	0.99
	%-diff	NS	NS	+19%
DFT (ms)	Untrained	342	185	117
	Trained	267	157	99
	%-diff	-22%	-15%	-15%
DFR (L/sec)	Untrained	0.35	0.69	1.10
	Trained	0.50	1.06	1.85
	%-diff	+44%	+54%	+68%

VO₂, oxygen uptake; CO, cardiac output; LVET, left ventricular ejection time; LVER, left ventricular emptying rate; DFT, diastolic filling time; DFR, diastolic filling rate; NS, reported not statistically significant.

Cardiac hypertrophy

The capability of the heart to respond with size and volume changes to various stimuli has long been recognized.^{56, 61} Recently, the molecular signalling pathways underlying this cardiac plasticity have been partly explained.^{40, 63, 78} Increases in cardiac muscle mass are termed cardiac hypertrophy and may be categorized in different ways.

First, based upon the relation between wall thickness and cavity dimensions, there is a *concentric* phenotype with a larger increase in wall thickness than in cavity dimension. This is in contrast to the *eccentric* phenotype, with a proportional increase in wall thickness and cavity dimension (**Figure 3**). The former is generally seen with

Figure 3. Model of left ventricular remodelling in response to pressure and volume load.

pressure loading (increased afterload) while the latter is seen with increased volume loading (increased preload).^{33, 47, 63}

Second, cardiac hypertrophy has also been dichotomized into *extrinsic* (or reactive) hypertrophy, in response to pressure or volume loading, and *intrinsic* (or genetic) hypertrophy seen in patients with inherited myocardial diseases, such as hypertrophic cardiomyopathy.³³

Third, a distinction between *physiological* and *pathological* cardiac hypertrophy is often made, although it is not always clear how to define these conditions.³³ Several pathological conditions can give rise to either an adaptive, functional cardiac hypertrophy or a maladaptive, dysfunctional and possibly deleterious cardiac hypertrophy.

According to the wall stress theory proposed by Grossman,⁵⁶ in pressure loading there is an increase in end-systolic wall stress within the LV. By a parallel addition of new myofibrils within the myocyte, there is a concentric myocardial thickening, which normalizes wall stress according to the law of LaPlace:

$$\sigma = \frac{P \times r}{h} \quad \begin{array}{l} \sigma, \text{ wall stress; } P, \text{ pressure;} \\ r, \text{ chamber radius; } h, \text{ wall thickness.} \end{array}$$

In volume loading there is an increase in end-diastolic wall stress. By the addition of new sarcomeres in series within the myocytes, the LV elongates in order to normalize diastolic wall stress. This will slightly increase end-systolic wall stress, resulting in a subsequent proportional increase in wall thickness named 'eccentric cardiac hypertrophy'.^{56, 57, 63}

These principles apply to the LV as well as to the RV, though in the RV, pressure (P) is lower at rest while the relative wall thickness (r/h) is smaller.⁶⁴

Cardiac hypertrophy in long-term volume load

Endurance exercise training

In 1898, using chest percussion, the Swedish neurologist Henschen found that medal-winning cross-country skiers had larger hearts than less successful competitors.⁶¹ Since then, various imaging techniques have provided evidence for enlarged hearts in endurance athletes, including chest x-ray,¹⁰ echocardiography^{87, 115} and magnetic resonance imaging.¹¹⁶ In addition, the size of peripheral arteries,⁵⁴ the aortic root⁶⁶ and the inferior vena cava^{53, 156} have been found to be larger in endurance trained than in untrained subjects.

The endurance athlete's heart typically shows an eccentric phenotype with increases in both cavity dimension and wall thickness.^{115, 147} In athletes with pronounced LV hypertrophy on echocardiography (i.e. a maximal wall thickness >12 mm or a LV internal dimension >54 mm) there may be a clinical dilemma as cardiomyopathies are the leading cause of sports-related death in this population and often show similar morphological patterns as in the athlete's heart.⁹¹

Cardiac size in athletes has been found to a large extent to be related to body size, but also to age and the type of sport performed.^{91, 112, 113} Female athletes generally show a similar magnitude of increase in cardiac dimensions as their male counterparts compared to untrained subjects, while absolute cardiac dimensions are smaller than in males.¹¹⁴

Cardiac function in endurance athletes

The major advantage of the endurance trained heart during exercise is the ability to deliver a large maximal SV, in order to produce a large CO. The maximal SV in trained subjects is commonly reported to be 30–50% higher than in untrained subjects, in both males and females.^{39, 107, 148}

Already at rest, there is an observable difference in cardiac function, as SV is increased and HR at rest is lower in trained subjects. This could theoretically be a result of improved systolic and/or diastolic function, larger cardiac dimensions or a combination of these factors. Traditional measures of global systolic function at rest (e.g. LV ejection fraction, LVEF) are generally reported to be similar in trained and untrained subjects.^{147, 151} Whether overall LV diastolic function at rest is altered with endurance conditioning is under debate.^{29, 48, 114, 151, 157} It is possible that there are differences in segmental myocardial function between trained and untrained subjects, but that these are not apparent when measures of global cardiac function are used. In general, far fewer studies examine cardiac function in female than in male athletes.¹⁴⁷

Chronic aortic regurgitation

Etiology and diagnosis

Depending on the definition used and what subgroups are included, the overall prevalence of chronic aortic regurgitation (AR) is reported to be in the range of 2–30%, with severe AR occurring in less than 1% of the general population.⁵² The most common etiology for chronic AR in industrialized countries is degenerative disease, which usually presents as a combination of a dilated aortic root and abnormalities in the aortic valve leaflets. In developing countries, rheumatic heart disease with valvular thickening and retraction is the most common etiology.⁶⁷

The AR diagnosis is based upon patient history, physical findings and echocardiographic investigation and the severity of AR is defined from the presence of symptoms, degree of regurgitation, LV dilation and systolic function (**Figure 4**).¹⁰²

Pathophysiology

Chronic AR occurs as a consequence of insufficient aortic valve closure, which permits backward flow from the aorta to the LV during diastole.

This imposes a “double filling” of the LV which must harbour the blood from the left atrium and the regurgitant volume from the aorta. This will increase LV end-diastolic volume, while the compliant LV will maintain LV end-diastolic pressure. End-systolic pressure, however, increases as the LV must produce a larger total SV in each heartbeat to compensate for the regurgitant volume.⁴⁶ Thus, both a volume and a pressure load are imposed upon the LV.^{11,21}

According to the law of LaPlace, wall stress (σ) will increase greatly with increasing end-systolic pressure (P) and increased chamber radius (r), as both are nominators in the LaPlace equation. As a compensatory mechanism, eccentric hypertrophy occurs, which increases wall thickness (h, denominator in the LaPlace equation) and helps to attenuate the increase in chamber radius.⁴⁶ In compensated AR, this is sufficient to maintain a normal wall stress, LVEF and relative wall thickness.

Stage	Definition	Jet width (% of LVOT)	Vena contracta (cm)	Regurgitant volume (mL/beat)	Regurgitant fraction (%)	Hemodynamic consequences		Surgery? (level of evidence)
A	At risk of AR (e.g. bicuspid valve or aortic valve sclerosis)	None or trace				None	Asymptomatic	No
B	Progressive AR Mild Moderate	<25	<0.3	<30	<30	Normal LV systolic function (LVEF ≥50%) Normal LV volume or mild LV dilation		Class IIa If other cardiac surgery (CS)
		25-64	0.3-0.6	30-59	30-49	C ₁ LVEF ≥50% and mild-to-moderate LV dilation (LVID _s ≤50mm) C ₂ LVEF <50% or severe LV dilation (LVID _s >50mm or LVID _{di} >25 mm/m ²)		Class IIa LVEF ≥50% and LVID _s >50mm Class IIb LVEF ≥50% and LVID _{di} >65mm if low surgical risk
C	Asymptomatic severe AR	≥65	>0.6	≥60	≥50	Normal LVEF to severe LV dysfunction Moderate-to-severe LV dilation		Class I LVEF <50% or other CS
D	Symptomatic severe AR	≥65	>0.6	≥60	≥50		Dyspnea or angina	Class I Yes
						Level of evidence Class I: AVR should be performed Class IIa: It is reasonable to perform AVR Class IIb: AVR may be considered		

Figure 4. Definition and classification of chronic aortic regurgitation and indications for surgery adopted from current guidelines.¹⁰²

LVOT, left ventricular outflow tract; AVR, aortic valve replacement; AR, chronic aortic regurgitation; LVEF, left ventricular ejection fraction; LVID_s and LVID_d, left ventricular internal dimension in end-systole and end-diastole, respectively. “i” denotes indexing by body surface area.

However, as the severity of AR increases, a progressive LV dilation and concomitant systolic hypertension due to increased total SV will follow.²¹ In severe, untreated AR LV mass is increased substantially because of marked LV dilation in combination with a modest wall thickening.^{11,21}

As end-systolic pressure (and eventually end-diastolic pressure) continues to rise, compensatory mechanisms are exhausted and wall stress increases. This is paralleled by decreases in LVEF but also in diastolic function as LV compliance falls with LV fibrosis and substantial wall thickening.^{21,75}

Aortic valve replacement

Much effort has been devoted to finding an optimal time for surgery, as aortic valve replacement (AVR) and living with a prosthetic heart valve impose a risk for the patient on one hand, while progressive AR, on the other hand, may induce irreversible cardiac dysfunction which is not fully corrected by an AVR that is too late. A trend toward earlier surgical intervention over the past decades can be seen, and according to current guidelines published in 2014,¹⁰² AVR is indicated when symptoms occur or in asymptomatic severe AR with LV dysfunction (LVEF <50%) or severe LV dilation (see **Figure 4**).

Following AVR, there is a rapid and early decrease in LV dimensions, and most of the decrease in LVID_s has been reported within the first weeks following surgery.^{13, 14} In serial assessment of LV dimensions following AVR for chronic AR, no further decrease in LV dimensions is generally reported beyond six months post-operatively.^{13, 14, 44, 124}

Methodological background

Echocardiography

The first one-dimensional echocardiographic investigation was performed by Edler and Hertz in Lund, Sweden, over 60 years ago.^{35, 77} Since then, the echocardiographic technology has continuously developed and cardiac dimensions can now be measured in one, two and three dimensions.^{77, 81, 85} Moreover, while echocardiography has, for decades, been used for examining overall cardiac function, more recent technological advances have allowed studies of myocardial segmental and regional function with a number of echocardiographic modalities, including tissue Doppler and speckle tracking imaging.⁹⁶

Basic principles

Sound with a frequency above 20 kilohertz is defined as ultrasound and is not hearable by humans. In echocardiography, high frequency ultrasound (1–20 megahertz) is sent from a transducer through the body. When hitting tissues, the ultrasound is reflected (i.e. *echoed*) back toward the transducer, picked up by a receiver and converted into an image by a computer. By adjusting the frequency and amplitude of the ultrasound beam, image quality is optimized by the sonographer according to the properties of the tissue being investigated. In addition, alignment of the beam is crucial for correct image acquisition and interpretation.⁸⁵

Measurements of cardiac dimensions and function can be made during the investigation or later off-line, in images stored digitally.

One- and two-dimensional echocardiography

M-mode echocardiography (M denoting *motion*) measures movement from and toward the transducer in one dimension displayed over time (panel F and G in **Figure 5**). Benefits of the M-mode technique include simultaneous display of several cardiac cycles and superior temporal

resolution compared to other echocardiographic techniques. A drawback is the dependency on accurate beam alignment, especially in non-normally shaped ventricles.^{81, 85}

Two-dimensional (2D) echocardiography, on the contrary, facilitates linear measurements perpendicular to the preferred axis, as a visual display of the cardiac chamber(s) is presented (panel A-C, **Figure 5**).

Figure 5. A selection of one- and two-dimensional (2D) echocardiographic measurements, of which most are applied in the papers included in this thesis. Panels A-C show 2D images of left ventricular three-, two- and four-chamber views respectively. Panels D and E visualize colour flow and pulsed-wave blood Doppler images, respectively. Panels F and G present M-mode images used for determination of cavity dimensions and wall thickness (F) as well as displacement of the septal portion of the atrioventricular plane (G).

The 2D image is constructed as the ultrasound beam sweeps rapidly, generating a sector (or slice) of the scanned tissue.⁸⁵ The 2D technique allows for measurements of areas and calculations of chamber volume. The drawback of the 2D technique is its much smaller temporal resolution, especially with large sectors and measurements deep into the body.^{81, 85}

Blood and tissue Doppler imaging

By using the Doppler principle, which states that the reflected ultrasound will have a different frequency when hitting a target moving toward or away from the transducer, the computer software can present information on the velocity and one-dimensional direction of moving tissues hit by the ultrasound beam.⁸⁵

Red blood cells give rise to echoes with a high frequency and low amplitude, while echoes from cardiac muscles are of low frequency

Figure 6. Colour tissue Doppler image displaying myocardial velocity curves during two cardiac cycles in the basal septum in a four-chamber image. Schematic presentation of peak systolic (s'), early (e') and late (a') diastolic velocity and time to s' (T_s) in the second cardiac cycle.

and high amplitude. By applying different filters, one can either measure movement of blood (pulsed-wave Doppler, continuous-wave Doppler and colour flow Doppler, panels D and E in **Figure 5**) or the myocardium (pulsed tissue Doppler imaging (TDI) or colour TDI).⁸⁵

In colour TDI, a region of interest (ROI) is placed off-line at any place of preference in the myocardium and the average of the myocardial velocities inside the ROI is presented visually (**Figure 6**), allowing manual measurements of velocities (y-axis) and time-intervals (x-axis).^{85, 96}

Although it is a feasible and readily available method for measuring segmental myocardial function, colour TDI is somewhat limited by its angle dependency, as only movements along the ultrasound beam can be measured.⁹⁶

Speckle tracking

Technological advances in echocardiographic software have made it possible to identify unique features inside small portions of the myocardium. By tracking these unique fingerprints (called speckles) frame by frame during the cardiac cycle, it is possible to measure myocardial deformation. The measure is dimensionless, termed 'strain', and is expressed as percentage change from an object's initial dimension.^{50, 96} A positive strain value represents an increase in dimension (stretch) while a negative strain value depicts a decrease in dimension (shortening). The average strain within different myocardial segments is calculated by the echocardiographic software and is presented graphically and numerically (**Figure 7**). Furthermore, the speed at which the deformation occurs is also calculated and is termed 'strain rate'.^{50, 96}

The major advantage of speckle tracking is its angle independency, allowing strain and strain rate to be calculated longitudinally, radially, and circumferentially from a single ultrasound beam.^{50, 96} However, a limitation in the use of speckle tracking is that there is variability in strain measurements from equipment produced by different vendors, dependent on separate algorithms for strain calculations.⁹⁷

Figure 7. Speckle tracking image as presented in EchopAC software, showing longitudinal strain curves in six left ventricular segments. Segmentation outlined in the two-dimensional four-chamber image superimposed on the image to the right.
AVC, aortic valve closure.

Cardiopulmonary exercise testing

By the use of a cardiopulmonary exercise test (CPET), usually on a treadmill or bicycle ergometer, it is possible to evaluate simultaneously cellular, cardiovascular and ventilatory responses to metabolic stress from exercising muscles.¹⁴⁹ The VO_2 and carbon dioxide elimination (VCO_2) can be determined by direct measurements of respiratory gas content and ventilatory flow. This is used in clinical as well as in research settings for prognostic and diagnostic information in cardiac and pulmonary diseases.^{3, 6, 43}

The maximal oxygen uptake ($\text{VO}_{2\text{max}}$, L/min) is an objective measure of the upper limit of an individual's aerobic capacity and is generally defined as the plateau in VO_2 occurring at consecutive near-maximal and maximal workloads.¹⁴⁹ However, in the clinical setting, this plateau is commonly not seen, and the term 'peak VO_2 ' is often used to describe the highest VO_2 reached by a subject, in combination with other signs of maximal effort being reached.³

Maximum oxygen uptake is usually indexed by body mass and presented in mL/kg/min.^{3, 6} This facilitates interindividual comparisons and may be a more relevant measure for the subject being tested, although this method of scaling have been criticized for underestimating performance in obese individuals.^{59, 93}

AIMS OF THE THESIS

The **overall aim** of the current thesis was to investigate the effects of long-term volume load upon the heart, with special focus on cardiac function at rest and how this and cardiac dimensions were related to maximal aerobic capacity.

The **specific aims** were:

- I. To investigate maximal aerobic capacity in subjects with surgically corrected volume load caused by chronic aortic regurgitation.
Paper I.
- II. To investigate cardiovascular dimensions in endurance trained and untrained females.
Papers II & IV.
- III. To investigate right and left ventricular overall systolic and diastolic function in endurance trained and untrained females.
Paper II.
- IV. To investigate segmental and regional longitudinal systolic function in endurance trained and untrained females.
Paper III.
- V. To investigate inter- and intraventricular systolic synchrony in endurance trained and untrained females.
Paper III.
- VI. To investigate the relationship between maximal oxygen uptake and cardiovascular dimensions and function in endurance trained and untrained females.
Papers II & IV.

METHODS

Subjects

Chronic aortic regurgitation patients (*paper I*)

According to the study protocol, all patients scheduled for AVR because of AR between 2002 and 2006 at a tertiary centre in Sweden covering about 1 million inhabitants were eligible for inclusion. Exclusion criteria were active endocarditis, previous heart surgery, aortic stenosis (defined as an aortic valve area $<1.6 \text{ cm}^2$), concomitant heart valve disease or coronary artery disease.

Twenty-nine patients, all male, were enrolled pre-operatively of whom 26 underwent a first follow-up six months post-operatively including CPET,¹⁴² exercise radionuclide ventriculography¹⁴¹ and echocardiography.⁶⁰

Of these 26 patients, 21 were available and consented to participate in a second follow-up CPET. Of the five patients lost to follow-up, one had suffered a stroke, one had been diagnosed with leukaemia, one had died a non-cardiovascular death, one suffered from severe leg pain and one was not reachable.

Healthy trained and untrained females (*papers II–IV*)

According to the study protocol, we enrolled healthy, non-smoking, non-pregnant females younger than 26 years of age. The subjects underwent a CPET after being screened for cardiovascular disease with a questionnaire and a resting electrocardiogram (ECG). Using the Åstrand classification of aerobic fitness,¹⁵⁸ each subject's fitness was categorized as 'low', 'fair', 'average', 'good' or 'high' according to $\text{VO}_{2\text{max}}$ indexed by body weight (mL/kg/min) determined at the CPET.

Trained females

Aiming for a cohort of endurance trained competitive female athletes, 52 females were contacted via athletic sport clubs across Sweden during 2008 and 2009. To be included, athletes should have started dedicated training before the age of 15 and should have been competing for at least five years. Only athletes with a ‘good’ or ‘high’ VO_{2max} (i.e. ≥ 44 mL/kg/min) were included, which excluded six subjects.

Thus 46 athletes (ATH), of whom the majority was at the top level in their sport in Sweden, were included. Six athletes had won medals in world or European championships and 24 had won medals in national or junior national championships. All sports performed by ATH were categorized as having a high amount of a dynamic component,⁹⁴ although with different amounts of static components (**Figure 8**).

Figure 8. Sports performed by athletes and their classification according to the Mitchell classification of sports.⁹⁴ MVC, maximal voluntary contraction; VO_{2max} , maximal oxygen uptake.

Untrained females

Fifty-two female college students not regularly performing endurance or resistance training and of similar age as the trained females were examined for inclusion. Three subjects with a 'high' $\text{VO}_{2\text{max}}$ (i.e. $\geq 49 \text{ mL/kg/min}$) were excluded, in addition to one subject whose CPET had been terminated prematurely.

Thus, 48 controls (CON) were included, of whom 18 categorized themselves as 'normally active' and 33 as 'inactive'.

Echocardiographic measurements (*papers I–IV*)

All echocardiographic investigations were transthoracic and made at rest with the subjects lying in the lateral decubitus position in accordance with current recommendations.^{81, 82, 128} In *paper IV*, additional investigations of the inferior vena cava (IVC) were made in the subcostal window with subjects lying horizontally on their back with only a pillow as head support.

Investigations and off-line measurements of patients in *paper I* were performed by the same experienced investigator. In *papers II–IV*, echocardiographic examinations of the subjects were performed by several experienced echocardiographers while off-line measurements were performed by the same investigator.

Ventricular and atrial dimensions

M-mode echocardiography (panel D, **Figure 5**) was used to measure LV posterior and septal wall thickness in diastole (PWT and SWT respectively) and LV diameter in end-diastole and end-systole (LVID_D and LVID_S respectively), while 2D echocardiography was used to measure LV length in diastole (LVIL_D) in the two- and four-chamber views (panel B and C, **Figure 5**).

The modified Simpson biplane technique was used for computerized calculation of LV end-diastolic and end-systolic volume (LVEDV and LVESV respectively). Left ventricular mass (LVM) and relative wall thickness (RWT) were calculated as:

$$\text{LVM} = 0.8 \times (1.04[(\text{LVID}_D + \text{PWT} + \text{SWT})^3 - \text{LVID}_D^3]) + 0.6).$$

$$\text{RWT} = (2 \times \text{PWT}) / \text{LVID}_D.$$

From a right-oriented 2D four-chamber view, diastolic basal RV diameter (RVD1) and RV proximal outflow tract diameter (RVOT-prox) were determined.¹²⁸ End-systolic left and right atrial areas (LAA_s and RAA_s respectively) were measured in a balanced four-chamber view.

Inferior vena cava dimensions (paper IV)

All images were recorded during quiet respiration, and measurements were determined as maximal dimension during expiration (EXP) and minimal dimension during inspiration (INSP) within the same respiratory cycle.

Figure 9. Schematic illustration of inferior vena cava (IVC) measurements and calculations of inferior vena cava shape and collapsibility.

In the longitudinal long-axis view, IVC diameters were determined perpendicular to the IVC long-axis (LAX_{EXP} and LAX_{INSP}), approximately three centimetres from the RA (**Figure 9**). Short-axis dimensions were determined in images obtained at the same position, after a 90° rotation of the transducer. First, the maximal IVC area during expiration ($SAX_{EXP-AREA}$) was determined. Second, the major-axis IVC diameter was determined as the largest IVC diameter in the maximal area ($SAX_{EXP-MAJOR}$). Third, the minor-axis diameter was defined as the largest IVC diameter perpendicular to the major-axis diameter ($SAX_{EXP-MINOR}$). Finally, the same measurements were applied to the minimal area during inspiration ($SAX_{INSP-AREA}$, $SAX_{INSP-MAJOR}$ and $SAX_{INSP-MINOR}$ respectively).

The IVC shape during expiration and inspiration was calculated as ($SAX_{EXP-MAJOR} / SAX_{EXP-MINOR}$) and ($SAX_{INSP-MAJOR} / SAX_{INSP-MINOR}$), respectively. In addition, the relative decrease in IVC dimension (%) for each measure was calculated as $100 \times (\text{expiratory dimension} - \text{inspiratory dimension}) / \text{expiratory dimension}$.

LV and RV systolic function (papers II–III)

Left ventricular fractional shortening (LV-FS) and LVEF were calculated as measures of global LV function from M-mode and 2D echocardiographic images respectively:

$$\text{LV-FS} = 100 \times (LVID_D - LVID_S) / LVID_D.$$

$$\text{LVEF} = (LVEDV - LVESV) / LVEDV.$$

Systolic displacements of the mitral and tricuspid annular planes (LV_{AVD} and RV_{AVD} respectively) were measured with M-mode echocardiography at four sites for each annular plane and are presented as means. The apical four-chamber view was used for measuring the anterior and posterior parts of the RV_{AVD} , as well as for the lateral and septal parts of RV_{AVD} and LV_{AVD} , while the apical two-chamber view was used for measuring the anterior and posterior parts of LV_{AVD} .

Colour tissue Doppler imaging (papers II–III)

In off-line analysis, colour TDI (**Figure 6**) was utilized to measure peak systolic myocardial velocity (s' , cm/s) and time to s' from the onset of the QRS-complex on a surface ECG (T_s , ms). In standard four-, three- and two-chamber apical views, with a frame rate of 89–184 frames per second, a 6x6 mm round sample volume was placed in six basal and six mid-ventricular segments in the LV (at the septal, anteroseptal, anterior, lateral, posterolateral, and posterior walls) and in the basal and mid-ventricular RV free wall. Measurements were averaged over two or three cardiac cycles, with markers of aortic valve opening and closure superimposed on the TDI images, ensuring measurements from the ejection phase only.

In *paper II*, basal RV s' was determined as the average s' in the RV free wall and septum (termed RV- s'_{BASAL} in this thesis), while basal LV s' was calculated as the average of s' in all six basal LV walls (LV- s'_{BASAL}). In *paper III*, regional systolic LV s' was determined as the arithmetic means of the six basal and six mid-ventricular LV segments respectively, together with overall LV function for all 12 segments (LV-12- s'). In addition, mean RV s' was calculated as the mean of RV basal and mid-ventricular s' (termed RV- s'_{LATERAL} in this thesis). Only measurements from those individuals where all six basal or mid-ventricular LV segments were measurable were included in calculations of regional and overall LV systolic function.

Speckle tracking (paper III)

Speckle tracking echocardiography was used off-line to measure midwall peak systolic longitudinal deformation (strain, %) during the ejection phase (**Figure 7**). The same 12 LV segments and echocardiographic views as for TDI measurements were used in 2D images with a framerate >40 frames per second. The myocardium was automatically outlined with a ROI, which, if necessary, was corrected manually with regard to width and localization to exclude the pericardium. The software automatically analysed the quality of speckle tracking in

each segment and segments with poor tracking were excluded from further measurements.

As for LV s' , regional and overall systolic LV strain were determined by calculating the arithmetic means of the six basal, six mid-ventricular and all 12 LV segments respectively.

Cardiac synchrony (paper III)

Four established systolic dyssynchrony indices were calculated:

1. **S-L-delay**, the largest difference in T_s between basal septal-to-lateral and posterior-to-anterior LV walls.⁴
2. **Max-LV-delay**, the largest difference in T_s between any two out of 12 LV segments.¹⁵⁵
3. **T_s -SD**, the standard deviation of T_s in all 12 LV segments.¹⁵⁴
4. **RV-LV-delay**, the difference in T_s between the basal RV free wall and the LV lateral wall.¹⁵⁴

In addition, T_s was indexed by one RR-interval and was expressed as a percentage of total cardiac cycle length (T_s -%).

Dyssynchrony measurements were compared to cut-off values previously suggested for predicting outcomes following cardiac resynchronization therapy.^{4, 154, 155}

LV and RV diastolic function (paper II)

Pulsed-wave Doppler with a sample volume of 5 mm placed at the tip of the mitral leaflets was utilized in the four-chamber view to measure transmitral blood flow (panel E, **Figure 5**). Early diastolic (E) and late diastolic (A) filling velocities were recorded and their ratio was calculated (E/A). Blood flow velocity was also recorded 5–10 mm into the right pulmonary vein in systole (P_s) and diastole (P_d), and P_s/P_d was determined.

Using TDI, with the same approach and with the same images as for s' , the early diastolic (e') and late diastolic (a') peak velocities were determined in the filling phase. Basal LV e' and LV a' were calculated as the average e' and a' in six basal LV segments (termed LV- e'_{BASAL} and LV- a'_{BASAL} in this thesis), while LV-12- e' was calculated as mean e' in all 12 LV segments. The ratio of LV- e'_{BASAL} and LV- a'_{BASAL} was determined (LV- e'/a'_{BASAL}), as well as E/e' , using an average of septal and lateral e' .⁹⁸

In addition, RV- e'_{BASAL} , RV- a'_{BASAL} , RV- e'_{LATERAL} and RV- a'_{LATERAL} were calculated as the mean of e' and a' in the septum and RV basal free wall and in the RV basal and mid-ventricular wall, respectively. Finally, RV- e'/a'_{BASAL} and RV- e'/a'_{LATERAL} were calculated.

Indexing (papers II–IV)

Body surface area (BSA) was used for indexing cardiac and IVC measurements, adopting the approach of transferring BSA into the same dimension as the variable being scaled.⁹ One-dimensional measures (wall thickness, internal dimensions, IVC diameters) were indexed by $\sqrt{BSA}$, two-dimensional measures (atrial and IVC areas) were indexed by BSA, and three-dimensional measures (LVM, LVEDV) were indexed by $\sqrt[3]{BSA}$.

Right and left ventricular myocardial peak systolic velocities and systolic displacements were indexed by $LVIL_D$, as a measure of cardiac length.⁸

Cardiopulmonary exercise testing (papers I–IV)

In both patients and young healthy subjects a sitting maximal bicycle exercise test using electrically braked cycle ergometers with continuous monitoring of electrocardiograms and ventilatory flow and gas content was performed (see **Table 2** for equipment). In addition, blood pressure and perceived exertion, dyspnea and chest pain¹⁵ were assessed every third minute during the test. Gas and flow analysers were calibrated

prior to each test, and ventilatory data were presented as 15 second averages. The mean of the two highest consecutive values was considered peak VO_2 (*paper I*) or $\text{VO}_{2\text{max}}$ (*papers II–IV*) respectively.

In patients, an individual exercise protocol with a steady-state workload of 30–100 Watts (W) for five to six minutes followed by a continuous increment of 10–20 W per minute was chosen at the pre-operative CPET and used in all three CPETs.

All healthy females underwent an exercise protocol including 100 W steady-state cycling for six minutes, followed by a continuous 10 W increase per minute. Subjects were instructed to pedal at 60 revolutions per minute until exhaustion or until termination by the test leader according to standard criteria for termination. We aimed at VO_2 levelling off and a respiratory exchange ratio (VCO_2/VO_2) >1.1 to ensure a maximal effort from the subjects. No subject perceived chest pain or any adverse event during testing.

Statistical methods

Continuous or interval data were presented as mean $\pm$ one standard deviation (SD) or median with range or 25th or 75th percentiles, depending on the normality of distribution, tested with the Shapiro-Wilk test of normality. For selected, normally distributed variables, range or 95th percentiles were also presented.

Statistical significance was tested two-sidedly, and set to ≤ 0.05 . Within-group difference was tested with a paired t-test, Wilcoxon signed ranks test, sign test or McNemar's test depending on the type and distribution of data. Between-group difference was tested with a Student's t-test, the Mann-Whitney test, Fisher's exact test or the Chi^2 -test depending on the type and distribution of data.

Statistical relationships between variables were explored with bivariate correlation analysis, with calculation of Pearson's correlation

coefficient or Spearman’s rho, depending on the normality of data. Linear univariate and stepwise multivariate regression analyses were further used to determine the art and degree of statistical relationships. In *paper IV*, Bland-Altman plots were constructed for selected variables to explore relations between IVC measurements.

Inter- and intraobserver variability

In *papers II–IV*, the reproducibility in off-line measurements from selected echocardiographic measures was tested in 16 randomly chosen subjects. Intraobserver variability was tested at least two weeks following the first measurements, and interobserver variability was tested against a second experienced investigator. The coefficient of variation (%COV) was calculated as:

%COV = (√(Σd_i²/2n)) / (overall means),

where d_i is the difference between the i:th paired measurement and n is the number of differences.³¹ In addition, the single measure intraclass correlation coefficient (ICC) was calculated for inter- and intraobserver variability in an absolute agreement two-way mixed model.

Table 2. Equipment and software used in the papers.

	Patients (<i>paper I</i>)	Healthy females (<i>papers II–IV</i>)
Bicycle ergometer	E022E, Siemens Elema AB. ¹	eBike basic, GE Medical Systems. ²
Electrocardiographic monitoring	Marquette CASE12, Marquette Medical Systems Inc. ³	Marquette CASE 8000, GE Medical Systems. ³
Gas analysis	MedGraphics CardioO2 & CPX/D Systems, Spiropharma. ⁴	MedGraphics CardioO2 & CPX/D Systems, Spiropharma ⁴ or Jaeger Oxycon Pro, Viasys Healthcare. ⁵
Echocardiograph	Vingmed Vivid 5 or 7, GE Healthcare. ⁶	Vingmed Vivid 7 or E9, GE Healthcare. ⁶
Echocardiographic software	EchoPAC BT11, GE Healthcare. ⁶	EchoPAC BT 11 and BT 13, GE Healthcare. ⁶
Statistical analysis	SPSS version 16, SPSS Inc. ⁷	SPSS version 21 and 22, IBM Software. ⁸

¹, Upplands Väsby, Sweden; ², Freiburg, Germany; ³, Milwaukee, WI, USA; ⁴, Gentofte, Denmark; ⁵, Hoechberg, Germany; ⁶, Horten, Norway; ⁷, Chicago, IL, USA; ⁸, Armonk, NY, USA.

RESULTS

Chronic aortic regurgitation patients (paper I)

Twenty-one patients underwent a second CPET 42 ± 16 months after the first follow-up (range 23–73), corresponding to 49 ± 15 months post-operatively (range 29–78). Sixteen patients had received mechanical aortic valve prosthesis, two received a biological prosthesis and three underwent aortic valve sparing surgery. There was no difference between follow-ups in subjects' self-reported medication use (**Table 3**).

Patients were on average 4% heavier at the second follow-up, which resulted in a slightly increased body mass index and BSA (**Table 4**).

Table 3. Number of patients using various cardiac medications at first and second follow-ups.

	6 months post-op	49 months post-op	P-value
Warfarin	17	17	1.000
Beta blockade	11	12	0.625
ACE-inhibitor	8	9	1.000
Diuretics	3	5	1.000
ASA	1	3	1.000
Calcium-antagonist	0	2	0.500
Digitalis	0	1	1.000
Nitrates	0	1	1.000
Number of cardiac medicines	2 (1–3)	2 (1–3)	0.344

ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid. Total number of cardiac medicines presented as median (25th and 75th percentiles).

Cardiopulmonary exercise testing

Patients presented with lower absolute and weight-indexed peakVO₂ at the second follow-up than six months post-operatively (Table 4), and this decrease was larger than predicted by their increased age (Table 5). All patients but one had a weight-indexed peakVO₂ that was below average at the second follow-up, according to the Åstrand classification.

A tendency could be observed, in that patients with ‘low’ cardio-respiratory fitness pre-operatively and at the first follow-up decreased less in peakVO₂ than patients in other Åstrand categories (Figure 10). The decrease in peakVO₂ from pre-operatively to the 49 months follow-up correlated negatively with pre-operative peakVO₂ ($r=-0.624$, $p=0.003$), and the decrease in peakVO₂ from the first to the second follow-up correlated negatively to peakVO₂ at the first follow-up ($r=-0.479$, $p=0.028$).

Figure 10. Plots showing relation between peak oxygen uptake (peakVO₂) at different cardiopulmonary exercise tests (CPET). Dot colour corresponds to each subject's fitness at first CPET (x-axis) in each plot. Panel A, pre-op (x-axis) vs. 6 months (y-axis); Panel B, 6 months (x-axis) vs. 49 months (y-axis); Panel C, pre-op (x-axis) vs. 49 months (y-axis).

Table 4. Characteristics of patients before and after aortic valve replacement for aortic regurgitation

	Pre-op	6 months post-op	49 months post-op	P-value*
At rest				
Age (years)	49±13	49±13	52±12	-
Weight (kg)	86±14	86±14	89±13	0.029
Body mass index (kg/m ²)	27±3	27±3	28±3	0.032
Body surface are (m ²)	2.06±0.21	2.06±0.21	2.10±0.20	0.027
Heart rate (beats/min)	71±12	72±13	75±24	0.596
Systolic BP (mmHg)	141±26	126±14	127±20	0.977
Diastolic BP (mmHg)	70±14	80±10	81±11	0.827
At maximal workload				
Maximal workload (Watt)	184±48	187±40	187±45	0.890
PeakVO ₂ (L/min)	2.2±0.5	2.2±0.5	2.0±0.5	0.006
PeakVO ₂ (mL/kg/min)	26.2±6.6	26.0±5.8	22.8±5.1	0.001
Oxygen pulse (mL/beat)	14.9±3.1	14.8±3.3	13.5±3.2	0.075
Breaths per minute	30±4	31±6	32±7	0.397
Ventilation (L/min)	75±15	77±14	76±18	0.874
Respiratory exchange ratio	1.16±0.11	1.17±0.08	1.22±0.10	0.029
Heart rate (beats/min)	149±18	150±18	152±26	0.828
Systolic BP (mmHg)	207±31	189±31	177±25	0.036

Data presented as mean±SD. *, p-value for comparison between post-operative tests. BP, blood pressure; PeakVO₂, peak oxygen uptake.

Table 5. Predicted and actual decrease in peak oxygen uptake between first and second follow-ups.

	Predicted decrease*	Actual decrease	P-value
L/min (%)	4.6±2.8	7.9±11.4	0.174
... per year (%)	1.3±0.6	2.7±3.7	0.095
mL/kg/min (%)	4.9±2.7	11.2±11.5	0.020
... per year (%)	1.4±0.5	3.8±4.4	0.018

Data presented as mean±SD. *, predicted value based upon reference values from Fleg et al. (2005).⁴²

Echocardiographic measurements

As presented in *paper I*, the mean absolute LVID_D and LVEDV were similar between the first and second follow-ups. In addition, BSA-indexed LVID_D, LVID_S and LVEDV at the second follow-up were 26±3 mm/m², 18±3 mm/m² and 53±14 mL/m², respectively, and none were statistically different from at the first follow-up (all p>0.10).

While pre-operative weight-indexed peakVO₂ correlated with pre-operative LVESV (and LVEF), absolute pre-operative peakVO₂ did not correlate with any measure of LV dimension (**Table 6**).

Table 6. Statistically significant correlations between left ventricular measures and peak oxygen uptake pre- and post-operatively.

		Left ventricular dimensions		
		Pre-op	6 months post-op	49 months post-op
PeakVO ₂ (L/min)	Pre-op	NS	NS	NS
	6 months post-op	NS	LVIDd r=0.465*	LVIDd r=0.670**
	49 months post-op	NS	NS	NS
PeakVO ₂ (mL/min/kg)	Pre-op	LVESV r=-0.600* LVEF r=0.493*	NS	NS
	6 months post-op	NS	NS	NS
	49 months post-op	LVEF r=0.513*	NS	NS

*, p≤0.05; **, p≤0.01. Correlations tested between peak oxygen uptake (peakVO₂) and left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV), left ventricular internal dimension in diastole (LVID_D) and systole (LVID_S) and left ventricular ejection fraction (LVEF). NS, not statistically significant.

Healthy trained and untrained females (papers II–IV)

Trained females had, in average, been competing for 6 ± 2 years and currently trained 13 ± 5 hours at 9 ± 3 sessions per week. They were taller and heavier than CON, resulting in a 3% larger BSA (**Table 7**). Absolute and weight-indexed $\text{VO}_{2\text{max}}$ was 43% (3.2 ± 0.3 vs. 2.3 ± 0.4 L/min, <0.001) and 33% (52 ± 5 vs. 39 ± 5 mL/kg/min, <0.001) larger in ATH than in CON respectively.

Table 7. Characteristics and ECG-measures of trained and untrained females at rest.

	Trained females	Untrained females	P-value
Age (years)	21 ± 2	21 ± 2	0.743
Weight (kg)	61 ± 6	58 ± 6	0.009
Height (m)	1.68 ± 0.06	1.66 ± 0.05	0.028
Body surface area (m ²)	1.69 ± 0.10	1.63 ± 0.09	0.008
Body mass index (kg/m ²)	22 ± 2	21 ± 2	0.219
Systolic BP (mmHg)	112 ± 11	111 ± 9	0.804
Diastolic BP (mmHg)	65 ± 6	68 ± 8	0.065
Heart rate (beats/min)	54 ± 8	71 ± 10	<0.001
PQ-interval (ms)	154 ± 22	153 ± 24	0.842
QRS-duration (ms)	92 ± 8	88 ± 9	0.019
QTc-interval (ms)	428 ± 26	428 ± 18	0.990
QRS-axis (°)	70 ± 24	66 ± 27	0.377

Data presented as mean $\pm$ SD. BP, blood pressure.

Cardiovascular dimensions

All left and right cardiac dimensions were larger in ATH than in CON, with and without indexing by the proper power of BSA (Table 8). The number of subjects exceeding current reference values for healthy females is presented in Figure 11.

Several IVC dimensions were larger in ATH, including the standard long-axis expiratory diameter ($p<0.001$).

Table 8. Cardiovascular dimensions in trained and untrained females.				
	Trained females	Untrained females	Relative difference	P-value*
SWT (mm)	8.7±1	7.8±1	+13 %	<0.001
PWT (mm)	8.4±1	7.6±1	+11 %	0.001
LVID _D (mm)	51±3	46±3	+11 %	<0.001
LVIL _D (mm)	85±5	79±5	+7 %	<0.001
LVM (g)	156±25	114±24	+37 %	<0.001
LVEDV (mL)	114±19	86±13	+32 %	<0.001
LAA _S (cm ²)	18±3	14±3	+30 %	<0.001
RVOT-prox (mm)	29±3	26±4	+15 %	<0.001
RVD1 (mm)	35±5	31±4	+10 %	0.001
RAA _S (cm ²)	16±3	11±2	+39 %	<0.001
IVC LAX _{EXP} (mm)	24±3	20±3	+17 %	<0.001
IVC LAX _{INSP} (mm)	17±5	15±5	+15 %	0.035
IVC SAX _{EXP-MAJOR} (mm)	31±5	29±5	-	0.054
IVC SAX _{INSP-MAJOR} (mm)	24±5	22±5	+13 %	0.023
IVC SAX _{EXP-MINOR} (mm)	23±4	22±4	-	0.155
IVC SAX _{INSP-MINOR} (mm)	18±5	16±5	-	0.052
IVC SAX _{EXP-AREA} (cm ²)	5.5±1.5	4.7±1.4	+17 %	0.014
IVC SAX _{INSP-AREA} (cm ²)	3.4±1.4	2.7±1.2	+27 %	0.020
Data presented as mean±SD. *, red colour denotes that the measure remained statistically significantly larger in athletes following indexing by the proper dimension of body surface area, as described in 'Methods'. For abbreviations, see 'Methods' and 'Abbreviations'.				

Reference values for females
from Lang et al. (2015)⁸¹

	Normal	Mildly abnormal	Moderately abnormal	Severely abnormal	Untrained females (n)				Trained females (n)			
LVID _D (mm)	38-52	53-56	57-61	>61	47	1	0	0	26	20	1	0
LVID _{Di} (mm/m ²)	23-31	32-34	35-37	>37	44	4	0	0	30	14	1	1
LVID _S (mm)	22-35	36-38	39-41	>41	44	2	2	0	35	8	3	0
LVID _{Si} (mm/m ²)	13-21	22-23	24-26	>26	44	4	0	0	36	10	2	0
LVEDV (mL)	46-106	107-120	121-130	>130	43	5	0	0	16	13	6	11
LVEDV _i (mL/m ²)	29-61	62-70	71-80	>80	40	8	0	0	12	15	13	6
LVESV (mL)	14-42	43-55	56-67	>67	34	14	0	0	14	27	5	0
LVESV _i (mL/m ²)	8-24	25-32	33-40	>40	31	17	0	0	13	25	7	0
SWT (mm)	6-9	10-12	13-15	>15	45	3	0	0	36	10	0	0
PWT (mm)	6-9	10-12	13-15	>15	46	2	0	0	39	7	0	0
LVM (g)	67-162	163-186	187-210	>210	46	2	0	0	31	10	4	1
LVM _i (g/m ²)	43-95	96-108	109-121	>121	45	2	1	0	32	12	6	1
LVEF (%)	54-74	41-53	30-40	<30	37	11	0	0	41	5	0	0

Figure 11. Reference values for left ventricular dimensions according to current guidelines and number of trained and untrained females presenting with abnormal measurements in the current study.

LVID_d and LVID_s, left ventricular internal dimension in diastole and systole, respectively; LVEDV and LVESV, left ventricular end-diastolic and end-systolic volume, respectively; SWT, septal wall thickness; PWT, posterior wall thickness; LVM, left ventricular mass; LVEF, left ventricular ejection fraction. "i" denotes indexing by body surface area.

The RWT was similar between groups (0.33 ± 0.05 in both groups, $p=0.998$) and eccentric hypertrophy was apparent in two CON and 19 ATH (Figure 12).

Inferior vena cava shape

There was no difference between groups in the ratio of SAX major-to-minor dimension (Figure 13). In the whole sample of subjects, IVC shape was similar at $SAX_{EXP-AREA}$ 1.3 (1.2–1.5), and $SAX_{INSP-AREA}$ 1.4 (1.2–1.6), $p=0.054$. At $SAX_{EXP-AREA}$ only one control subject had a ratio >2.0 (2.1), while three CON and one ATH had a ratio >2.0 at $SAX_{INSP-AREA}$ (2.1–2.6).

Figure 12. Relative wall thickness and left ventricular mass index in athletes and controls with cut-off values and remodelling patterns according to current recommendations.⁸¹ LV, left ventricular.

Figure 13. Inferior vena cava shape at minimal (upper panel) and maximal (lower panel) area.

Cardiac function at rest

Overall cardiac function

Systolic function

Measures of overall LV and RV systolic function are presented in **Table 9**. Absolute measures of longitudinal systolic function showed statistically significant correlations with LV length (LV_{AVD} $r=0.379$, $p<0.001$; $LV-s'_{BASAL}$ $r=0.336$, $p=0.001$; RV_{AVD} $r=0.412$, $p<0.001$; $RV-s'_{BASAL}$ $r=0.222$, $p=0.032$). Indexing these measures by LV length altered statistical significance in such a manner that only indexed RV_{AVD} remained higher in ATH (2.5 ± 0.3 vs. 2.3 ± 0.3 , $p=0.001$) and indexed $LV-s'_{BASAL}$ was higher in CON (0.79 ± 0.07 vs. 0.85 ± 0.09 , $p=0.002$).

Diastolic function

Measures of overall LV and RV diastolic function are presented in **Table 9**. E/e' was similar in ATH and CON (7.6±2.0 vs. 7.2±1.2 respectively, p=0.208). While E and LV-e'_{BASAL} were unrelated to heart rate, both A and LV-a'_{BASAL} increased with higher heart rate at rest (**Figure 14**).

Table 9. Cardiac function at rest.				
	Trained females	Untrained females	Relative difference	P-value
Systolic function				
LVEF (%)	59±4	57±4	+3 %	0.039
LV-FS (%)	36±4	34±4	+6 %	0.024
LV _{AVD} (mm)	15±2	14±1	+7 %	0.002
LV-s' _{BASAL} (cm/s)	6.7±0.7	6.8±0.7	-	0.887
LV-strain _{BASAL} (%)	-19±2	-19±2	-	0.072
RV _{AVD} (mm)	21±2	19±2	+15 %	<0.001
RV-s' _{BASAL} (cm/s)	9.0±0.9	8.3±0.9	+8 %	0.001
RV-s' _{LATERAL} (cm/s)	9.7±1.5	8.7±1.5	+10%	0.004
Diastolic function				
E (m/s)	0.92±0.17	0.86±0.11	+8 %	0.029
A (m/s)	0.34±0.09	0.39±0.09	-13 %	0.007
E/A	2.9±0.9	2.3±0.7	+27 %	<0.001
LV-e' _{BASAL} (cm/s)	12.2±1.5	11.8±1.2	-	0.192
LV-a' _{BASAL} (cm/s)	3.2±0.8	3.4±0.9	-	0.183
LV-e'/a' _{BASAL}	4.1±1.2	3.6±0.9	-	0.058
RV-e' _{BASAL} (cm/s)	-12.0±1.6	-11.6±1.6	-	0.321
RV-a' _{BASAL} (cm/s)	-5.3±1.4	-5.1±1.5	-	0.474
RV-e'/a' _{BASAL}	2.4±0.7	2.5±0.9	-	0.554
RV-e' _{LATERAL} (cm/s)	-11.6±2.1	-11.1±2.0	-	0.240
RV-a' _{LATERAL} (cm/s)	-5.3±1.8	-5.0±1.6	-	0.483
RV-e'/a' _{LATERAL}	2.4±0.8	2.4±1.0	-	0.855
Data presented as mean±SD. For abbreviations, see 'Methods' and 'Abbreviations'.

Figure 14. Scatter-dot diagrams showing relations between heart rate and early and late diastolic filling velocity (E- and A-wave, panel A) and peak myocardial velocity in early and late diastole (LV-e' _{BASAL} and LV-a' _{BASAL}, panel B). The red colour represents athletes and the grey colour represents controls.

Systolic synchrony

There was no between-group difference in any of the four dyssynchrony indices presented in **Figure 15**. A majority of subjects exceeded available cut-off values suggested for cardiac resynchronization therapy.^{4, 154, 155}

Figure 15. Histograms showing distribution of dyssynchrony indices in athletes (red) and controls (grey). Dotted lines represent cut-off values for cardiac resynchronization therapy.^{4, 154, 155} Data presented as median (25th and 75th percentiles). No statistically significant differences between groups.

Subgroup analysis

Females categorizing themselves as 'inactive' had lower absolute and weight-indexed $\text{VO}_{2\text{max}}$ than normally active females (both $p < 0.001$, **Table 10**). Endurance athletes performing sports with a low amount of a static component had lower body mass, BSA and lower absolute $\text{VO}_{2\text{max}}$ than ATH performing sports with a high amount of a static component. However, when indexing $\text{VO}_{2\text{max}}$ by body mass, there was no difference in aerobic capacity between groups ($p = 0.556$).

Table 10. Subgroup analysis of selected variables in inactive and normally active females as well as in endurance trained females categorized by different amounts of static components in sports.

	Untrained females			Trained females			
	Inactive (n=30)	Normally active (n=18)	p	Low static (n=20)	Moderate static (n=13)	High static (n=13)	p
Age (years)	21±2	22±2	0.098	21±2	20±2	21±3	0.544
Weight (kg)	56±7	61±4	0.009	57±6	65±5	63±4	0.001
Height (cm)	164±4	168±4	0.012	167±7	170±5	167±4	0.273
BSA (m ²)	1.60±0.10	1.69±0.07	0.002	1.64±0.11	1.74±0.08	1.71±0.07	0.017
$\text{VO}_{2\text{max}}$ (L/min)	2.1±0.3	2.6±0.2	<0.001	3.0±0.3	3.4±0.2	3.4±0.4	0.003
$\text{VO}_{2\text{max}}$ (mL/kg/min)	37±5	43±4	<0.001	53±5	51±5	53±6	0.556
LVM (g)	111±25	119±24	0.255	151±31	154±23	165±15	0.289
LVM_i	55±12	55±10	0.953	72±13	67±11	74±7	0.302
LVEDV (mL)	85±14	88±13	0.507	107±20	120±16	119±17	0.071
LVEDV_i	42±6	40±6	0.290	51±8	53±6	53±8	0.596
E/A	2.2±0.7	2.5±0.7	0.299	3.1±0.7	2.9±1.2	2.7±0.9	0.416
LV_{AVD} (mm)	14±1	15±2	0.069	15±1	15±2	15±2	0.454
RV_{AVD} (mm)	18±2	19±2	0.360	21±2	22±2	22±2	0.082

P-value from Student's t-test and one-way ANOVA for untrained and trained females, respectively. BSA, body surface area; $\text{VO}_{2\text{max}}$, maximal oxygen uptake; LVM and LVEDV, left ventricular mass and end-diastolic volume; "i", indexed by cubed BSA; E/A, ratio of Doppler E- to A-wave; LV_{AVD} and RV_{AVD} , left and right atrioventricular plane displacement, respectively.

Segmental myocardial function

Systolic function

Segmental systolic strain, s' and T_s were different between groups in four, six and four LV segments respectively (**Figure 17**). When accounting for the increased LV length in ATH indexed s' was only higher in ATH in the mid-ventricular septal wall ($p=0.040$). At the lateral and posterolateral walls, indexed s' was higher in CON at both the basal and mid-ventricular levels, as well as at the basal anterior segment (all $p<0.02$).

Diastolic function

Segmental e' was higher in ATH in two mid-ventricular LV segments, but was similar in all basal segments and in the RV (**Figure 16**).

Figure 16. Differences in segmental early peak diastolic velocity between athletes and controls. 4Ch, 2Ch and 3Ch denote four-, two- and three-chamber views respectively.

Figure 17. Differences in segmental systolic strain (Panel A), peak systolic velocity (Panel B) and systolic time-interval (Panel C) between athletes and controls.

4Ch, 2Ch and 3Ch denote four-, two- and three-chamber views respectively.

Relation to maximal aerobic capacity

The strongest correlations between whole-group absolute VO_{2max} and anthropometric, cardiac functional and cardiovascular dimensional variables are presented in **Table 11**.

Table 11. Strongest correlations between absolute maximal oxygen uptake (L/min) and anthropometric, dimensional and overall cardiac function in trained and untrained females.			
	r	p-value	
Body surface area	.535	<0.001	Anthropometrics
Body weight	.521	<0.001	
LVEDV	.709	<0.001	LV dimensions
LVM	.692	<0.001	
RVOT-prox	.489	<0.001	RV dimensions
RVD1	.310	0.002	
LA area	.604	<0.001	Atrial areas
RA area	.641	<0.001	
IVC LAX _{EXP}	.523	<0.001	IVC dimensions
IVC LAX _{INSP}	.274	0.010	
LVEF	.351	0.001	LV systolic function
LV _{AVD}	.320	0.002	
RV _{AVD}	.592	<0.001	RV systolic function
RV-s' _{BASAL}	.393	<0.001	
E/A	.319	0.002	LV diastolic function
LV-12-e'	.299	0.007	

Only the two strongest correlations for each set of variables presented. No measure of RV diastolic function correlated with VO_{2max}. For abbreviations, see 'Methods' and 'Abbreviations'.

DISCUSSION

We set out to examine the effects of long-term volume load upon the heart, with special focus on cardiac function at rest and how this and cardiac dimensions were related to maximal aerobic capacity.

Cardiac hypertrophy in health and disease

Cardiac hypertrophy following volume load is believed to arise from a combination of neurohumoral signalling and biomechanical stress.^{36, 63} However, the cardiac hypertrophy seen in endurance athletes is usually limited to values far from those seen in patients with chronic AR, which the papers in the current thesis support.

In ATH, roughly a third were above current reference values for LVID_D, while only four (8%) CON showed mild increases in LVID_D. This stands in contrast to what has previously been reported for the AR cohort, where pre-operative LVID_D was clearly above current reference values in most patients.^{44, 142}

In ATH, there was a symmetrical bi-atrial enlargement and bi-ventricular eccentric hypertrophy when compared to CON, which depicts the physiological hypertrophy seen in endurance athletes.

The large increases in LV dimensions and mass seen in AR patients have been attributed to the combination of pressure and volume load seen as the regurgitation progresses.^{11, 21} The largest LVM in athletes has also frequently been reported in subjects performing sports with a large amount of both dynamic and static components,^{112, 152} such as rowing, cycling and triathlon.⁹⁴ However, these individuals are usually taller and heavier than most athletes practicing pure dynamic sports, and care must be taken to normalize LV dimensions and mass properly.⁹ We found indexed measures of cardiac function and dimensions as well as VO_{2max} to be similar in ATH performing sports with a low and a

moderate-to-high amount of static training. However, subgroups were small and the current results should be considered indicative rather than conclusive.

There are several differences between the volume load seen in chronic AR and that seen with endurance training beyond concomitant pressure load or not. First, the time during which the heart is exposed to increased volume load is far longer in chronic AR even though elite endurance athletes train 10–20 hours/week.¹³³ Second, the degree of volume load is also different. Endurance athletes commonly increase their SV by 20–40% at maximal work intensities,¹²⁵ while in severe chronic AR the extra volume entering the LV with each beat is more than 60 mL (or a near doubling of SV).¹⁰² Although the eccentric hypertrophy seen in endurance exercise is generally attributed to intermittent increases in volume load during training sessions and competitions, there is also a ~10% blood volume expansion^{27, 38, 131} which, in theory, could induce a slight chronic volume loading. A similar magnitude of increase in LVM and LVEDV to that found in endurance training is seen in normal human pregnancy,¹³² accompanied by an average increase in plasma volume of ~40%.⁴⁵

On a molecular level, there are emerging differences in gene transcription in cardiac hypertrophy following repeated endurance exercise and pathological stimuli, although evidence so far comes from studies of rodents^{16, 40} and more recently of swine.⁷⁸ Although this is an exciting field of research, it remains to be elucidated what inherent characteristic(s) of the stimuli (i.e. volume load) dictate the type and magnitude of the hypertrophy.

Inferior vena cava in volume load

Inferior vena cava dimension

Due to its close anatomical and functional connection to the right side of the heart, echocardiographic examination of the IVC is recommended to be integrated in clinical routine investigations.⁸¹ The size and inspiratory decrease in IVC diameter reflect RA pressure, although this has been questioned in endurance athletes, as there are a few reports on increased IVC diameter in (predominately male) athletes, as summarized in **Table 12**.^{30, 37, 53, 156} Therefore, we wanted to study the IVC dimension in female endurance athletes.

Both absolute and BSA-indexed IVC short-axis area and long-axis diameter were larger in ATH than in CON, while the decrease in IVC dimensions during quiet inspiration was similar between the two groups. As we extended our echocardiographic examination to a cross-sectional view, we were able to show that the IVC long-axis diameter represented its short-axis minor diameter and thus underestimated maximal IVC dimension.

As our study was exploratory rather than experimental, we did not explore the mechanisms underlying a possible IVC dilation with endurance exercise. In theory, a dilation could be attributed to an increased RA pressure with training, or could be a sign of increased vagal signalling with vessel dilation in athletes or an effect of an elevated plasma volume following endurance training.

There are a limited number of studies reporting similar surrogate measures of RA pressure in athletes and controls^{30, 108} and a small study on healthy subjects with varying $\text{VO}_{2\text{max}}$ but similar invasively measured RA pressures.¹³⁶ Thus, we believe there is no evidence to support IVC dilation secondary to increased RA pressures in athletes and that the most plausible explanation for larger IVC dimensions in athletes may be the commonly reported 10% increase in plasma volume.^{27, 131}

Inferior vena cava shape

We found a slightly oval, similarly shaped IVC in ATH and CON. Few subjects had a major-to-minor ratio exceeding 2.0. Thus, endurance training or a large IVC diameter per se does not seem to alter the shape of the IVC, at least not in the group of females considered in this study. To our knowledge, there are no previous comparative data on IVC shape in healthy subjects, although the IVC shape has gained some attention lately in different clinical settings.^{69, 92, 99}

Table 12. Previous studies presenting the inferior vena cava diameter in athletes.

Method	Subjects (n)	IVC size (mm)	P-value
Zeppilli et al. (1995)¹⁵⁶			
M-mode (2D-guided), in subcostal area.	Road and track cycling (15), long-distance running (15), volleyball (15). (No females).	ATH (cyclists): 27.8 (95% CI 27.2–28.4)	<0.05 (based on CI)
LAX, just before outlet of hepatic veins.	20 sedentary male non-smokers.	CON: 20.0 (95% CI 18.7–21.2)	
Goldhammer et al. (1999)⁵³			
2D echocardiography, subxiphoid view.	58 ATH from a variety of eleven sports (11 females).	ATH: 23.4 (SD 4.8)	<0.001
LAX and SAX,* 1–2 cm from RA-junction.	28 control subjects, physically active 3–4 hrs/wk. (8 females).	CON: 11.4 (SD 1.3)	
Erol and Karakelleoglu (2002)³⁷			
2D echocardiography, subxiphoid view.	Running (14), wrestling (10), basketball (5), boxing (4), skiing (3). (No females).	ATH: 18.8 (SD 2.2)	<0.001
Axis not specified, 1 cm from RA-junction.	16 normally active male control subjects.	CON: 15.2 (SD 1.7)	
D’Ascenzi et al. (2013)³⁰			
2D echocardiography, subcostal view.	Soccer (50, male), basketball (26, male), volleyball (24, female).	ATH: 21.5 (SD 4.8)	≤0.001
Axis not specified, 1–2 cm from RA-junction.	78 sedentary subjects (28 female) without cardiovascular disease.	CON: 17.5 (SD 3.2)	

*, which diameter that is presented in paper is not specified by authors.⁵³ IVC, inferior vena cava; 2D, two-dimensional; ATH, athletes; CON, controls; CI, confidence interval; LAX, long-axis; SAX, short-axis; RA, right atrial.

Decline in peakVO₂ following AVR

As a previous study of our group found that maximal aerobic capacity was unchanged and below average in patients with AR six months following AVR,¹⁴² the study presented in *paper I* aimed to investigate maximal aerobic capacity after a longer follow-up time to see whether peakVO₂ normalized more slowly than LV dimensions.

Somewhat surprisingly, peakVO₂ was significantly lower at the second follow-up, and had decreased more than expected by the patients' increased age.⁴² These results are somewhat in contrast to previously published studies.^{71, 144, 146} However, as seen in **Figure 18**, our study differs from previous studies in several respects including pre-operative peakVO₂ (and thus probably the severity of AR), follow-up time, number of patients and heterogeneity regarding valve disease.

One possible explanation for the discrepancy in results could be that our patients were more aerobically fit pre-operatively than those in

Figure 18. Longitudinal change in peak oxygen uptake (peakVO₂) following aortic valve replacement in previous studies^{71, 144, 146} and in *paper I*.
AR, aortic regurgitation; MR, mitral regurgitation.

other studies, and thus had less potential for increases in peakVO₂. Nevertheless, according to both the Åstrand classification of physical fitness published in 1960,¹⁵⁸ and the more recent SHIP-study including 253 males from north-eastern Germany,⁷³ a majority of our patients were indeed unfit at the late follow-up compared to healthy subjects of similar age, weight and sex.

This must be considered clinically relevant, as having low cardio-respiratory fitness is a predictor of all-cause mortality and cardiovascular events,⁷⁴ and longitudinal decreases in cardiorespiratory fitness have been linked to increased risk of cardiovascular death, independent of changes in BMI.⁸³

Either the current results may indicate a decline in cardiac function between the first and second follow-ups or that the patients were more physically inactive after the second follow-up. Although LVEF at rest was somewhat lower at the late follow-up than six months post-operatively, it was previously reported by our group that the same patients showed a slight improvement of the ability to increase LVEF and s' in the basal LV during supine submaximal exercise, from the first to the second follow-up.⁴⁴

Although all patients were encouraged to resume regular physical activity after discharge and were offered participation in cardiac rehabilitation at the referring hospital, we did not measure or enquire into the level of physical activity in patients, leaving us without this part of the puzzle.

While there is solid evidence for beneficial effects of exercise training and of an increased level of physical activity level in patients with coronary artery disease³⁴ and heart failure,¹⁴⁰ there are fewer studies on patients with AR following AVR.^{68, 80, 100, 122, 135, 146} Most available studies are small and contain a mix of valvular pathologies, and the results are somewhat conflicting. However, there is no reason to believe that structured cardiac rehabilitation and exercise training would be

unfavourable or not feasible in this population. One study on patients with coronary artery disease found that there was a relation between fear of movement (*kinesiophobia*) and non-attendance at cardiac rehabilitation, and that the physical activity level was lower in patients with kinesiophobia.²⁰ Our findings support the need for active follow-up and, perhaps, intensified and more structured exercise prescription in these patients to avoid deterioration in aerobic capacity.

Cardiac function in physiological volume load

In our studies upon young, healthy females in *paper II* and *paper III*, we performed a comprehensive echocardiographic examination to assess LV and RV overall and regional myocardial function at rest in systole as well as in diastole. As there are far fewer studies of cardiac function in samples of exclusively female athletes than in their male counterparts, our data are novel in several aspects.

One expected, but still important finding was that cardiac function in ATH, with clear evidence of eccentric remodelling and increased LVM compared to CON, was not impaired in any sense. Although there is abundant evidence that regular physical activity is beneficial,^{83, 84} possible adverse effects upon cardiac function of long-term high-intensity and high-dose endurance exercise have recently been under discussion.^{79, 106}

Systolic function

Overall LV and RV systolic function

There were statistically significant differences between ATH and CON in traditional measures of overall LV systolic function (i.e. LVEF and LV-FS). However, these differences were small and most likely not clinically relevant for the actual LV function. In addition, we found overall as well as basal and mid-ventricular regional strain and peak systolic myocardial velocities to be similar in trained and untrained females. Although LV_{AVD} was greater in ATH, this difference diminished

following indexing by the increased cardiac length in ATH. Thus, we conclude that overall and longitudinal systolic LV function at rest was no different in females exposed to physiological long-term volume load than in untrained females of the same age.

In the RV on the other hand, we found longitudinal systolic function measured as RV_{AVD} , $RV-s'_{BASAL}$ and $RV-s'_{LATERAL}$ to be higher in ATH. When indexing for cardiac length, RV_{AVD} remained 8% higher in ATH than in CON ($p=0.001$), which could imply a difference in RV longitudinal systolic function at rest between groups.

Our results are consistent with previous reports on normal LVEF in male^{118, 147} and female athletes.¹⁵¹ Absolute s' in the basal LV,^{103, 111, 119, 121} LV_{AVD} ¹⁵³ and LV global longitudinal strain¹⁰³ were reported by most authors to be similar in trained and untrained, predominately male subjects. A few studies have reported signs of increased systolic longitudinal function in athletes,^{22, 26, 72} although all these authors have refrained from taking the increased LV length into account, which has been suggested^{8, 76, 111} but rarely applied.¹¹¹

Interestingly, unindexed measures of RV longitudinal function are consistently being reported as higher in trained subjects.^{22, 26, 72, 111} This, together with our finding of larger indexed RV_{AVD} in ATH, may imply that the RV adapts to training with an augmentation in longitudinal function, although the results from studies measuring RV longitudinal strain in athletes are somewhat conflicting.^{5, 143} In normal subjects, the RV has been found to be more dependent on longitudinal shortening than the LV.^{23, 117} This could be a plausible explanation for why measures of RV longitudinal function would be higher in the right, but not the left ventricle of athletes, when compared to untrained subjects.

Segmental LV and RV systolic function

We found higher s' in ATH than in CON in the RV and in LV segments adjacent to the RV. This could either imply that the free RV wall and

septum adapt to endurance training in a similar fashion, possibly augmenting RV longitudinal shortening, or that an adaptation in RV longitudinal function influences septal movement. The septum is an important factor in ventricular interdependence, and both circumferential and longitudinal muscle fibres from the RV free wall traverse into the interventricular septum.⁵⁵

There are no previous studies describing segmental systolic myocardial function in female athletes. Studies reporting s' in a few separate basal LV segments in samples of male or predominately male athletes gave conflicting results.^{5, 90, 105, 119, 134, 145, 157} A few studies reporting segmental strain in the basal LV septal and lateral wall segment found deformation to be either concomitantly similar,¹⁴⁵ concomitantly higher in ATH than in CON,¹³⁴ or higher in CON in the basal septum but not in the basal lateral LV wall.¹⁹ Reports on RV segmental strain are equally conflicting.^{5, 119, 143, 145}

It is possible that differences in athletic populations, characteristics of included control subjects or methodological differences, such as echocardiographic software and settings, explain some of the diversity in results. Nevertheless, it is possible that there are subtle differences in systolic function at rest between trained and untrained subjects, and that these are not always detectable with global measures of systolic function.

Inter- and intraventricular systolic synchrony

We found similar inter- and intraventricular synchrony in trained and untrained females. This concurs with two previous studies using a different measure of synchrony than in the current study.^{25, 32} These results and the fact that ATH had similar synchrony values as previously reported in healthy females,^{95, 129} imply that endurance training in females does not impose systolic mechanical dyssynchrony. This may be clinically relevant for sports cardiologists evaluating female athletes.

Diastolic function

Overall LV and RV diastolic function

Blood flow velocity over the mitral valve was higher in ATH during early diastole (E) and higher in CON in late diastole (A), which rendered higher E/A in ATH. In contrast, myocardial peak velocities in the basal LV ($LV-e'_{\text{BASAL}}$ and $LV-a'_{\text{BASAL}}$), and $LV-e'/a'_{\text{BASAL}}$ were not different between groups. E (but not A) was found to be independent of HR. The lower A velocity, previously reported in female endurance athletes,¹¹⁴ is logical as late diastolic filling, depending on atrial contraction, becomes less important with lower HR and longer diastole in athletes.

Higher E velocity has, to our knowledge, not been reported in female athletes until now, although previously found in mixed samples of male and female athletes^{29, 109, 157} and in male athlete groups.^{5, 70, 104} Altogether, there seems to be an enhancement in cardiac relaxation in endurance athletes, reflected in higher early filling velocity even at rest. In addition, in senior¹ as well as in young athletes,^{86, 136} surrogate measures of LV compliance have been reported to be higher than in sedentary subjects. Furthermore, a recent study indicated a slight increase in LV compliance, accompanied by LV hypertrophy, following one year of intensive endurance training in previously sedentary subjects.² Thus, enhanced LV diastolic function in endurance athletes seems to result from both improved relaxation and higher LV compliance.

As in the LV, there was no difference between ATH and CON in RV diastolic myocardial peak velocities. This conforms to a previous report of similar tricuspid early filling velocity in female long-distance runners and sedentary controls,⁵⁸ and e' in the basal RV has also been found similar in mixed samples of trained compared to untrained subjects.^{30, 143} However, there are reports of increased e' in the basal RV of speedskaters,¹¹⁹ long-distance swimmers^{26, 28} and rowers⁵ compared to controls, or even lower in water polo players than in

controls.¹²⁰ This inconsistency in previous results could probably in part be explained by the diversity in sports performed by included endurance athletes.

Segmental RV and LV diastolic function

In two mid-ventricular LV segments, but in none of the RV segments, e' was 13% higher in ATH than in CON. In both cases, these segments were not the same as those where s' was different between groups. The significance of this finding is unclear, but it could indicate that, similarly to systolic segmental function, there are heterogeneous myocardial adaptations in diastolic function across the myocardium.

Relations to maximal aerobic capacity

Cardiovascular dimensions

In healthy females, there was a relation between the size of the heart at rest and maximal aerobic capacity, and 50% of the variability in VO_{2max} (L/min) could be attributed to inter-individual differences in LVEDV. In healthy females, a large LVEDV at rest implies a large SV at rest, which in turn is related to a large maximal SV, CO and thus VO_{2max} .^{12, 127, 159}

The strongest correlation between VO_{2max} and any IVC dimension was found between IVC LAX_{EXP} and VO_{2max} ($r=0.523$, $p<0.001$), which was a weaker correlation than between VO_{2max} and LVEDV or LVM. This could imply that cardiac dimensions have a more direct effect upon VO_{2max} and that IVC dilation is secondary to other, systemic adaptations occurring in parallel with increases in VO_{2max} and cardiac dimensions.

In AR patients, pre-operative absolute peak VO_2 did not correlate with any pre-operative measure of cardiac size, although pre-operative weight-indexed peak VO_2 correlated negatively with pre-operative LVESV ($r=-0.600$, $p\leq 0.05$). This is probably a sign that when AR severity progresses and the regurgitant volume increases, LVESV will increase while maximal aerobic capacity decreases.

Cardiac function

Although the correlations were strongest between $\text{VO}_{2\text{max}}$ and dimensional variables, there were some weak-to-moderate positive correlations between $\text{VO}_{2\text{max}}$ and measures of cardiac function. Among systolic variables, measures of RV longitudinal function (i.e. RV_{AVD} and $\text{RV-s}'_{\text{BASAL}}$) were more strongly related to $\text{VO}_{2\text{max}}$ than any LV systolic variable. In contrast, while LV diastolic variables (i.e. E/A and LV-12-e') correlated weakly to $\text{VO}_{2\text{max}}$, there was no correlation between $\text{VO}_{2\text{max}}$ and any RV diastolic variable. This may indicate that RV systolic longitudinal function and LV diastolic function at rest are (weak) determinants of $\text{VO}_{2\text{max}}$.

Strengths and limitations

Paper I

A major advantage of this paper was the longitudinal design, which enabled us to follow peak VO_2 over time for up to four years. We also exclusively studied AR patients, which improves our generalizability to this population of patients. In addition, all patients undergoing AVR at our tertiary centre during the study inclusion period participated in the study. As all patients were male, we cannot be sure that these findings would apply for female patients.

In retrospect, it would have been of interest to measure, or at least enquire into, the physical activity level of patients serially, in order to search for an explanation for the decreased aerobic capacity late post-operatively. Ideally, a questionnaire, which has recently been validated, regarding kinesiophobia could have been administered to the patients as well.²⁰ Finally, we categorized the fitness of the patients by using previously published reference values.^{73, 149, 158} Although these are widely used, it would have been a strength to compare fitness serially in a healthy age and sex-matched cohort of subjects from the same geographic region that the patients lived in.

Papers II–IV

We consider our design, including exclusively female athletes and healthy females of similar age, to be a major strength of these studies. As few studies have been performed exclusively upon female endurance athletes, it has been somewhat hard to extrapolate findings from mixed samples of athletes or male athletes to their female counterparts. Furthermore, we have chosen our indexing methods carefully and applied these both to selected functional as well as dimensional variables, to avoid overestimating potential differences between groups.

The cross-sectional design has built-in limitations in determining causality, and thus, we cannot rule out the possibility that the differences between ATH and CON were due to constitutional factors. The present study was designed for echocardiographic measurements at rest only, which leaves us without data on cardiac function during exercise and how this relates to maximal aerobic capacity. Finally, the inter- and intraobserver variability was not negligible for some measurements, although this can be attributed, at least in part, to limitations in the echocardiographic software and algorithms.

CONCLUDING REMARKS

In patients operated on for aortic regurgitation, maximal aerobic capacity did not improve following surgery. This finding stresses the importance of post-operative follow-up and management that includes considering the patient's physical activity level. A post-operative exercise test, ideally a cardiopulmonary exercise test, could be useful for evaluating post-operative aerobic capacity and could guide exercise prescription and need for follow-up.

We found that females with a history of several years of dedicated endurance training presented with symmetric and proportional enlargement of cardiac dimensions and wall thickness. Cardiac function at rest was normal and in some aspects even supranormal in comparison to untrained females. As there are relatively few studies that have exclusively investigated female athletes, our results may contribute to the understanding of the heart in female endurance athletes.

Our finding of differences in segmental myocardial function is interesting and merits further research. In addition, the results regarding similar synchrony in trained and untrained females may be of importance for sports cardiologists evaluating female athletes, as increased dyssynchrony does not seem to be a physiological adaptation to endurance exercise.

FUTURE PERSPECTIVES

Some results of the current studies raise questions that merit further research.

It would be of interest to investigate how structured exercise training and physical activity counselling in patients following AVR would affect their aerobic capacity and well-being, as well as measures of cardiac function.

As differences in cardiac function between trained and untrained females were found even at rest, it would be valuable to see if these differences are more pronounced during exercise. In particular, how segmental myocardial function and diastolic function affect cardiac performance (e.g. stroke volume) during exercise remains to be fully elucidated.

We have not found a definitive causative explanation for the difference in inferior vena cava diameter, as discussed in *paper IV*. Though an increase in plasma volume could cause this dilatation, there are other possible explanations as well. An experimental study could help to answer this physiological question.

Although there has been a plethora of cross-sectional studies comparing athletes with controls, there are still relatively few longitudinal studies. Much is still unknown regarding cardiac adaptations to volume load. For example, what is the minimum requirement in training dose to achieve cardiac hypertrophy, and are there any differences in response to endurance exercises of varying intensity?

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– African proverb

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Papers

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