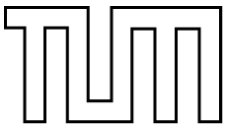

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Isolated aortic regurgitation and submaximal steady-state exercise: Changes of aortic regurgitation fraction, left ventricular end-diastolic and end-systolic volume

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Abbreviations

ACE	Angiotensin-converting enzyme
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
AS	Aortic stenosis
AVR	Aortic valve replacement
Bo	B zero, main magnetic field
B1	Radiofrequency field
BP sys	Systolic blood pressure
BP dias	Diastolic blood pressure
BSA	Body surface area
CI	Cardiac Index
CMR	Cardiovascular magnetic resonance
CPET	Cardiopulmonary exercise testing
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram
EF	Ejection fraction
EDV	End-diastolic volume
EDVI	End-diastolic volume index
ESC	European Society of Cardiology
ESD	End-systolic diameter
ESV	End-systolic volume
ESVI	End-systolic volume index
fCI	Forward cardiac index
fSV	Forward stroke volume
GE	Gradient echo
HR	Heart rate
LV	Left ventricle
LVOT	Left ventricular outflow tract
min	Minute
M	Net magnetization
Mo	Net magnetization at equilibrium
MRI	Magnetic resonance imaging

nCI	Net cardiac index
NIH	National Institute of Health
nSV	Net stroke volume
NYHA	New York Heart Association
p	Pressure
RF	Regurgitation fraction
rf	Radiofrequency
RV	Regurgitation volume
SE	Spin echo
SSFP	Steady-sate free precession
SV	Stroke volume
SVI	Stroke volume index
S1	First heart sound
S2	Second heart sound
S3	Third heart sound
S4	Fourth heart sound
VEC	Velocity-encoded cine
VO_2	O_2 uptake
VO_2max	Maximal possible O_2 uptake
2D	Two-dimensional

Abstract

OBJECTIVE Aortic regurgitant volume, left-ventricular volume and left-ventricular function reaction upon steady-state submaximal exercise by cardiovascular magnetic resonance were evaluated in isolated aortic regurgitation.

BACKROUND Patients with chronic aortic regurgitation (AR) often remain asymptomatic for a long period of time and show good preservation of exercise tolerance. Tachycardia with a consequent shortening of diastolic filling period has been suggested as the underlying mechanism.

METHODS Cardiovascular magnetic resonance (CMR) with data acquisition at rest and during steady-state submaximal exercise was performed in 12 healthy controls and 12 asymptomatic patients with isolated chronic AR. Forward and backward stroke volumes (SV) as well as end-diastolic (EDVI) and end-systolic volume indexed to BSA (ESVI) were measured directly from CMR images, remaining flow and volume parameters were subsequently calculated.

RESULTS Regurgitation fraction (RF) in patients ranged from 9 to 64% at rest. EDVI (p=0.017) and ESVI (p=0.002) at rest were markedly elevated and net cardiac index (CI) slightly lower (p=0.045) in the patient group. During exercise, heart rate (HR) in healthy volunteers (p=0.008) and patients (p=0.008) increased comparably, and diastolic filling period shortened during submaximal exercise in healthy volunteers (p=0.005) and patients (p=0.002). In patients, regurgitation volume (RV) (p=0.002), regurgitation volume per minute (p=0.023) as well as regurgitation fraction (p=0.002) decreased significantly and uniformly during exercise. EDVI (p=0.004) and ESVI (p=0.009) decreased and ejection fraction (EF) improved slightly (p=0.009) under exercise in patients. A linear correlation (R^2= 0.53, p=0.003) was found between the level of RF under rest and the change in percent points of RF from rest to exercise. Concordantly, a strong linear correlation (R^2= 0.64, p=0.001) was also seen between the level of RF under rest and percent change in net SV from rest to exercise.

CONCLUSION Evaluation of aortic regurgitant volume, left-ventricular volume and left-ventricular function by CMR under continuous steady state submaximal exercise is possible without waiving image quality. The observed hemodynamic response to exercise in healthy volunteers and patients fitted well with previously gathered data and current concepts of cardiac physiology.

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1 Introduction

1.1 Preface

In 1832 Irish physician Dominic Corrigan first described chronic aortic regurgitation (AR) in medical literature. He referred to it as “Permanent Patency of the Mouth of the Aorta or Inadequacy of the Aortic Valves” (Corrigan 1832, p.225). Today’s understanding and knowledge of the general pathomechanisms, symptoms and signs of the disease go back to his work and have remained unchanged in great parts. Corrigan’s suggested treatment, however, was merely symptomatic and a cure seemed out of reach at that time (Corrigan 1832, pp.238-244). If left untreated, symptomatic patients had a poor prognosis with a mortality of approximately 25% (Dujardin et al. 1999, p.1853). A successful treatment became conceivable when American surgeon Charles Hufnagel implanted the first artificial valve in 1952 (Hufnagel et al. 1989). Since then substantial progress in valve architecture and material has been made (Gott et al. 2003; Tamames Escobar 2006), making aortic valve replacement (AVR) a common, routine treatment for chronic AR (Nishimura et al. 2014, p. e86).

The optimal timing of AVR, however, remains a topic of great controversy (Bonow 2013, p.693). The intention is to operate late enough in the natural history of the disease to justify the risks of intervention, but early enough to prevent irreversible left ventricular (LV) dysfunction and progressive congestive heart failure (Bonow 2013, p.699). However, until today, there is no method of determining the optimal time point for each individual patient and clinicians struggle to balance the course of natural history and the short- and long-term risks of AVR. Numerous studies of the past decades verified that the development of severe symptoms, categorized as class III or IV in New York Heart Association (NYHA) classification (America Heart Association 1994, p.664) is associated with a poor prognosis (Dujardin et al. 1999, p.1853) and should be a strong indication for AVR (Bonow et al. 1991, p.1627; Tornos et al. 1995, p.334; Borer et al. 1998, p.528; Vahanian et al. 2012, p.12; Bonow 2013, pp.697-698; Nishimura et al. 2014, p.e86). However, rather than waiting until patients are severely symptomatic, which was the clinical paradigm 50 years ago, current guidelines emphasize earlier intervention before the onset of symptoms, LV dysfunction, and other adverse endpoints, such as pulmonary hypertension and atrial fibrillation (Bonow 2013, p.694). AVR is therefore recommended before a considerable decrease in LV function and

severe enlargement of the left ventricle have developed, even in asymptomatic or mildly symptomatic patients. (Vahanian et al. 2012, p.12; Nishimura et al. 2014, p. e86)

In most patients successful AVR is associated with favorable results linked to normalization of left-ventricular ejection fraction (EF) and size (Senechal et al. 2011, p.1009). However, some patients with severe AR do not regain full LV-function after surgery and have most probably been operated on too late (Hirshfeld et al. 1974, pp.1193-1195; Bonow et al. 1980, p.1287; Donaldson et al. 1982, p.594; Bonow et al. 1985, p.1254; Bonow et al. 1988, p.1118; Klodas et al. 1996, p.673; Villari et al. 2009, p.2390; Buddhe et al. 2012, p. 335).

Therefore, inquiring patients about the development of symptoms is not sufficient and quantitative evaluation of the disease is essential. Thus, scientific attention has benn repeatedly paid to the finding of suitable parameters to predict impending ventricular dysfunction and postoperative outcomes. It is generally agreed upon, that the optimal timing is when the left ventricle is still compensating for the volume overload without irreversible dysfunction, but despite extensive scientific efforts no parameter has yet been agreed upon to mark this time point. (Enriquez-Sarano et al. 2004, p.1544-1545; Bonow et al. 2006, p.e114). Also, so far, no suitable parameter has been identified to detect patient subgroups that are at high risk of irreversible LV dysfunction.

Currently, either the presence of severe symptoms, categorized as NYHA III or IV (America Heart Association 1994, p.664), LV end-systolic diameters (ESD) larger than 50mm or LV-EF below 50% are indications for valve surgery (level of evidence: B) (Nishimura et al. 2014, p. e86). However, in asymptomatic AR with normal EF and ESD the timing of AVR remains a topic of great debate (Bonow 2013, p. 693). As asymptomatic AR usually aggravates very slowly with a protracted time course toward symptom onset or LV dysfunction, and sometimes remains without any need for intervention, it can be very difficult to justify preemptive AVR. Especially in children, as early AVR increases the possibility for later operation due to their growth in height (Buddhe et al. 2012, p.331). On the other hand however, more than one fourth of patients with AR who die or develop LV-dysfunction do so before the onset of warning symptoms (Bonow et al. 2006, p.e114). Therefore, individual decisions rather than standardized protocols continue to be the order of the day.

1.2 Problem statement

One examination method frequently considered for diagnostics and clinical studies is cardiopulmonary exercise testing (CPET). In previous American guidelines exercise testing was recommended for assessment of functional capacity and symptomatic sta-

tus in patients with AR and a history of equivocal symptoms (Bonow et al. 2008, p.553). Present guidelines do not include this recommendation, but exercise testing in AR remains frequently used in clinical research. Decrease of LV-EF during exercise has been suggested as a marker of impending ventricular dysfunction, as the exercise EF and the change in EF from rest to exercise have been shown to be often abnormal, even in asymptomatic patients (Bonow et al. 1991, p.1629; Tornos et al. 1995, p.337; Borer et al. 1998, p.529; Bonow 2013, p.698). They have, however, not been verified to have any independent prognostic value as long as LV function at rest and severity of volume overload estimated by echocardiography are already known (Bonow et al. 2008, p. e553).

While LV-function under exercise has been frequently examined in recent clinical studies using echocardiography, data about the response of regurgitation fraction (RF), which cannot be quantified by echocardiography, to physical exercise are scarce. Theoretical considerations suggest a reduction of RF under exercise, as the diastolic filling period shortens with tachycardia. Few experimental studies in the 1970s have confirmed this hypothesis under maximal exercise levels, but examination methods were imprecise and partially highly invasive (Judge et al. 1971; Firth et al. 1982; Steingart et al. 1983; Iskandrian et al. 1984; Massie et al. 1985). Cardiovascular magnetic resonance (CMR) allows for direct quantitative assessment of RF and ventricular volumes under exercise (Mohiaddin et al. 1997, p.662; Powell et al. 2000a, p.55; Powell et al. 2000b, p. 106; Cawley et al. 2009, p.475; Myerson 2012, p. 10), but data have not been presented so far. In patients with other cardiac diseases physical exercise has been performed during magnetic resonance in several previous studies, mostly using specially designed bicycle ergometers or steppers. These types of exercise techniques however, have not gained large acceptance, as they are costly, sensitive for motion artifacts, require suspension of exercise in cardiac gated sequences, and have physical limitations for tall patients in the magnet bore. (Niezen et al. 1998, p.199; Holverda et al. 2009, p.271; Steeden et al. 2010, p.287) Thus, scientific data regarding the amount of regurgitation under exercise remain scarce.

The aim of this study is to investigate the change of aortic regurgitant volume, LV-volume and LV function under exercise in patients with asymptomatic AR without concomitant lesions. Therefor, a simple and adequate form of conducting physical exercise during CMR studies was established and verified. A submaximal exercise level was chosen instead of maximal exercise test, because it is known that most hemodynamic changes during exercise are already present at submaximal exercise levels (Astrand et al. 1964, p. 271; Higginbotham et al. 1986, p. 287; Wilson et al. 1988, p. 607) and do not need maximal exercise. Additionally, CMR requires a certain amount of time for

acquisition, which is easier to obtain during a stable phase of submaximal exercise than during a short period of maximal exercise.

1.3 Fundamentals

1.3.1 Anatomy and physiology of the aortic valve

The normal human heart has four valves. They regulate the inflow and outflow of the heart's ventricles. A distinction is made between the aortic and pulmonary valve, which are referred to as semilunar valves, and the mitral and tricuspid valves, which are called atrioventricular valves. The aortic, pulmonary and tricuspid vales are tricuspid, saying that they consist of three cusps or leaflets. The mitral valve has two leaflets. All cardiac valves are surrounded by a fibrous tissue, forming partial or complete valvular rings or annuli. These rings join the fibrous skeleton of the heart to anchor and support the valvular structures. The aortic valve (valvula semilunaris aortae) lies in the aortic root, the structure connecting the LV with the ascending aorta.

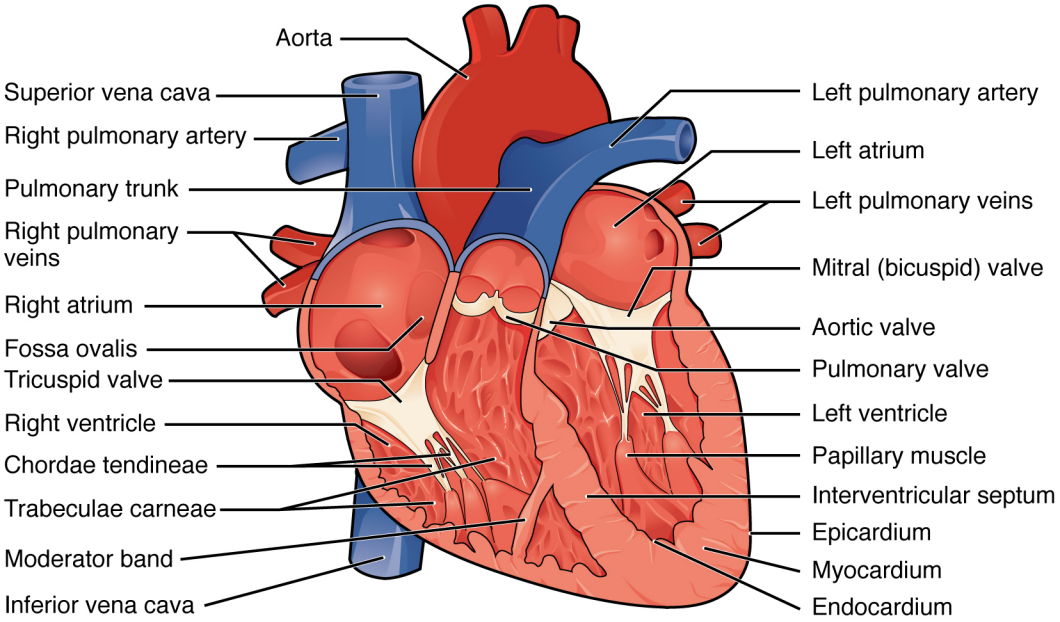

Figure 1: Internal anatomy of the human heart (OpenStaxCollege 2013, p. 20)

When looking at the valvular level it forms the centerpiece of the heart with all other valves surrounding it. It functions as a one-way valve to prevent regurgitation of blood from the aorta during diastole back into the LV and to allow the appropriate flow of blood from the LV into the aorta during systole. As said before, the aortic valve consists

of three cusps. The margin of each cusp has a central thickening, forming a fibrous nodule of dense connective tissue (nodulus valvulae semilunaris). To each of the nodules sides is a fine non-fibrous rim called lunula (lunula valvulae semilunaris). Once the pressure in the left ventricle drops below the level in the ascending aorta, the cusps fill with blood and their margins meet in the center of the orifice, with the nodules and lunulae ensuring a tight seal. (Schünke et al. 2010, pp.106-108)

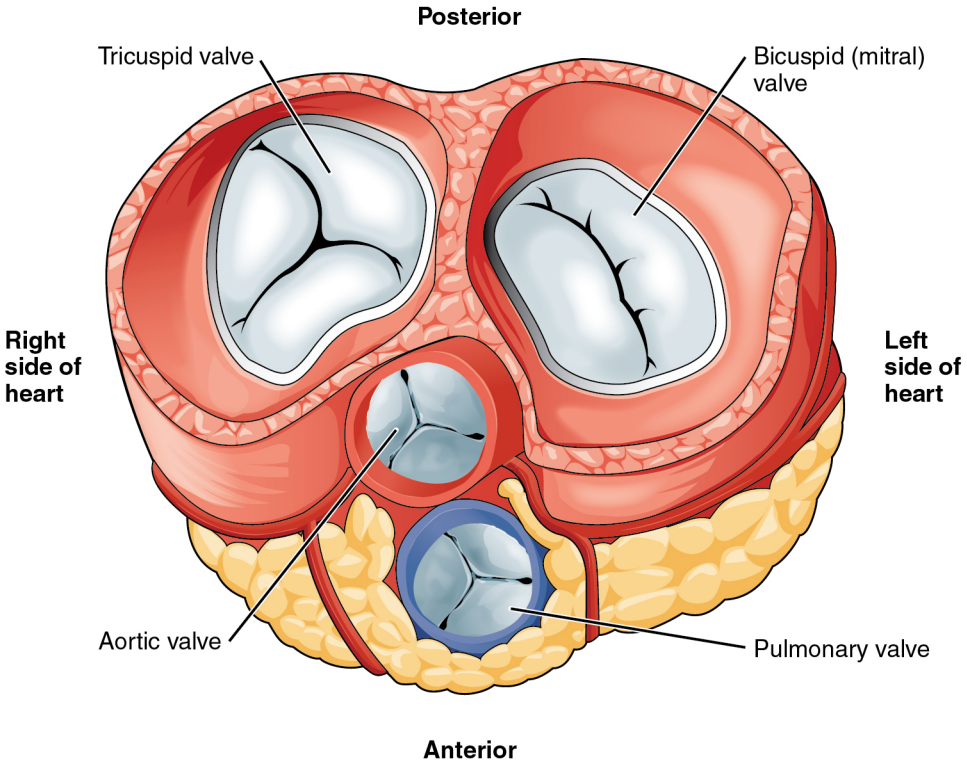

Figure 2: Anatomy of heart valves (OpenStaxCollege 2013, p.14)

1.3.2 Etiology of chronic aortic regurgitation

When the leaflets of the aortic valve do not provide a tight closure during diastole, blood regurgitates from the aorta into the LV. This regurgitation can occur as an acute event, which will not be discussed in this thesis, or chronic, i.e. progressing slowly over time. Chronic AR can either be due to a primary valvular disease (two thirds of all cases) or aortic root dilation (one third of all cases). Both forms can be caused by congenital or acquired conditions. (Flesch 2011, p.441) Isolated congenital AR due to valvular diseases is relatively uncommon in the pediatric population, but can be seen, particularly in patients with a congenital bicuspid aortic valve (Donofrio et al. 1992, p.366). In

this case, two of the normally three leaflets fuse during development, resulting in an aortic valve with only two leaflets (Braverman et al. 2005, p.473). However, chronic AR is more often seen in conjunction with abnormal aortic valves that feature both, insufficiency and stenosis (Hahn et al. 1992, p.283). AR also occurs in association with other congenital cardiovascular malformations, such as aortic stenosis (AS) (Morrow et al. 1958, p.1102), coarctation of the aorta (Baylis et al. 1956, p.481), or ventricular septal defects (Halloran et al. 1965, p.283). Congenital root dilation is seen in children with Marfan's syndrome, but this is more common in young adults with Marfan's syndrome in association with progressive aortic root dilation (Bruno et al. 1984, p.223; Aburawi et al. 2007, p.378).

Acquired valvular diseases that can lead to chronic AR are rheumatic heart disease, infectious endocarditis, degenerative calcification, or intervention for AS such as surgical or balloon valvuloplasty. Acquired causes for root dilation are systemic hypertension, syphilitic aortitis, trauma, or a dissecting aneurysm (Agabegi et al. 2008, pp.38-39; Allen et al. 2008, p.73).

The most common cause of AR in developing countries is rheumatic disease. In Western Europe and North America rheumatic disease is rare, and congenital or degenerative diseases are more frequently the origin of AR (Enriquez-Sarano, Tajik 2004, p.1539).

1.3.3 Pathophysiology and hemodynamic considerations of chronic aortic regurgitation

All forms of chronic AR lead to similar hemodynamic abnormalities. The leaflets are unable to seal off the orifice of the valve sufficiently to prevent regurgitation during diastole. This is either due to abnormalities of the leaflets themselves, or due to a dilated aortic root, the latter resulting in a relatively larger orifice diameter than leaflet diameter (Gouley et al. 1943, p.36). A portion of each heartbeat's stroke volume leaks back into the LV producing an increase in end-systolic volume, and after venous return, consequently an increase in end-diastolic volume (Flesch 2011, p.441). The early response to this volume overload can be described by the Frank-Starling mechanism (Flesch 2011, p.441). The regurgitant volume leading to a higher end-diastolic volume raises the preload, the initial stretching of the cardiac myocytes prior to contraction. Myocytes stretching increases sarcomere length, which causes a rise in force generation, and a larger stroke volume (SV) compensating for the regurgitation. Consequently, resting LV output, defined as SV multiplied by heart rate (HR), is increased (Daut 2010, pp.543-544).

If the AR persists, the volume overload leads to a series of deeper compensatory changes, including dilation and eccentric hypertrophy of the LV. The dilation occurs through addition of sarcomeres in series, forming longer myocytes (Grossman et al. 1975, p.62). As a result, the LV is larger, more compliant, and has a greater capacity to accommodate a large volume without an increase in filling pressure. However, following the law of Laplace, dilation of the ventricle also leads to an increase in afterload (Flesch 2011, p.441).

Afterload can be thought of as the "load" against which the heart contracts to eject blood. It is closely related to the ventricular wall stress (σ), which increases with ventricular radius (r) and ventricular pressure (P), and decreases with wall thickness (h).

$$\sigma \propto \frac{P \cdot r}{h} \qquad (1)$$

A larger radius due to dilation therefore raises afterload. This increased afterload is believed to lead to a decrease in ejection velocity, and consequently a lower stroke volume. If the AR is still compensated, the high preload leads to a compensatory increase of force generation through the Frank-Starling mechanism preserving net stroke volume, even in the case of dilation. In addition, the LV myocardium hypertrophies, lowering afterload by increasing the wall thickness (h). (Ross 1976, p.871)

In a large subset of patients, this delicate interaction between afterload excess, preload reserve and hypertrophy cannot be balanced indefinitely. Preload reserve may be exhausted, or the compensatory hypertrophy is inadequate, so that further dilation and afterload increase cannot be compensated by the Frank-Starling mechanism and eventually the EF starts to diminish, first to low normal and then subnormal levels (Ricci 1982, p.833; Bonow et al. 2008, p.e549). Up to this point in the natural history, even if there is progressive dilation and hypertrophy of the LV, patients may be asymptomatic. But with ejection performance dropping, patients unusually start to develop symptoms (Flesch 2011, p.442).

1.3.4 History and physical examination

Patients with chronic AR are often asymptomatic for many decades, as the transition to LV dysfunction represents a continuum with a very delayed onset of symptoms (Bonow et al. 2008, p.e549). The most common clinical complaint is shortness of breath on exertion, but also at rest (Maurer 2006, p.994). Patients may also suffer from symptoms related to the increased mass of the enlarged LV. These include a sense of pounding or an uncomfortable awareness of the heartbeat, atypical chest pain induced by a mechanical interaction between the heart and the chest wall, and palpations due

to tachycardia or premature beats. (Gaasch 2012) Symptoms of angina pectoris are uncommon and seen less frequently than with aortic stenosis (Flesch 2011, p.442; Gaasch 2012).

The physical findings of chronic aortic regurgitation can be divided into two categories; abnormal heart sounds and murmurs detected during cardiac auscultation, and palpable or observable findings caused by increased pulse pressure.

Heart sounds and murmurs are detected by auscultation with a stethoscope placed on the chest. The first heart sound (S1) marks the beginning of systole, and arises from the closure of the atrioventricular valves. The second heart sound (S2) is caused by the closure of the semilunar valves and marks the end of systole. Usually the pulmonary valve closes slightly after the aortic valve which can, especially during inspiration lead to a splitting S2. A third heart sound (S3) occurring shortly after the second as a sign of rapid ventricular filling can be detected in children, in adults however it is considered pathological. A fourth heart sound (S4), which can sometimes be detected slightly before S1 is always considered pathological and is a sign of increased ventricular diastolic stiffness (Mohrman et al. 2003, p.53). Heart murmurs are additional sounds during a heart beat caused by turbulent blood flow in or near the heart. Most murmurs are considered innocent, but they might also be a sign of an underlying heart disease. A distinction is made between systolic and diastolic murmurs according to the heart phase in which they arise. Systolic murmurs occur between S1 and S2, diastolic murmurs occur between S2 and S1. Murmurs are also described by their sound's shape. It is commonly distinguished between a crescendo shape indicating an increasing intensity and decrescendo shape, indicating an decreasing intensity of the sound. (Bickley 2003, pp. 243-293)

The classic murmur of AR is a decrescendo diastolic murmur produced by the backflow of blood from the aorta into the LV that can be heard best at the left third and fourth intercostal space. It is usually soft but can be accentuated with the patient leaning forward (Flesch 2011, p.442). In cases of moderate and severe AR, a systolic flow murmur after S1 may be audible at the second right intercostal space. It is produced by the flow of increased stroke volume across the aortic valve. In addition, a lower-pitched, rumbling late-diastolic murmur may be heard over the apex, which is called Austin-Flint murmur (Bickley 2003, p. 292). Chronic AR is also associated with changes in heart sounds. Inadequate closure of the aortic valve may lead to a very soft or absent S2 heart sound. A S3 heart sound may be heard with development of LV dysfunction. (Flesch 2011, p.442) Chronic AR typically results in a widened pulse pressure and a bounding pulse (Maurer 2006, p.994). The pulse pressure, which is the difference be-

tween systolic and diastolic blood pressure, rises as the large forward stroke volume increases systolic pressure and the regurgitant flow reduces diastolic pressure (Stimpel 2001, p.201; Horstkotte 2006, p.299). This quick rise and fall can be observed in a rapidly swelling and collapsing radial pulse, especially during wrist elevation. This sign is called Corrigan's sign (pulsus celer et altus). There are many other eponymous signs associated with a bounding pulse. However, the specificity and sensitivity of these signs is low and they should only be used as supportive evidence (Babu et al. 2003, pp.737-738).

1.3.5 Diagnosis

A number of additional tests can help identify patients with chronic AR and add essential details to classify the severity of the disease.

1.3.5.1 Electrocardiography

Electrocardiography may be normal in early chronic AR. In later stages, it may show QRS complex left-axis deviation, supporting LV volume overload and problems with the conduction system, such as left bundle-branch block. However, results in electrocardiography correlate weakly with severity of AR and the extent of hypertrophy. (Flesch 2011, p.442)

1.3.5.2 Chest radiography

Chest radiography provides images of the chest in posteroanterior and lateral views, and permits evaluation of size and shape of the heart and great vessels. In chronic AR, the image of a large heart may suggest LV volume overload and hypertrophy. Also, dilation of the ascending aorta may be visible. However, just as electrocardiography results, chest radiography correlate poorly with severity of AR (Flesch 2011, p.442).

1.3.5.3 Echocardiography

Echocardiography is the key examination technique for detection and grading of chronic AR severity as well as for serial follow-up (Maurer 2006, p.995). A trans-thoracic echocardiogram is usually sufficient, but a trans-esophageal echocardiogram can be used if the quality of the trans-thoracic echocardiogram is inadequate. Two-dimensional Doppler allows for detailed morphological assessment of the aortic valve, its valvular ring, root, and the ascending aorta. It may help determine the cause of AR and feasibility of valve repair. It also permits evaluation of LV size during end-diastole and end-systole as well as LV function in terms of fractional shortening and ejection fraction. Color Doppler is a highly sensitive and specific tool to detect AR as it provides

clear visualization of the regurgitant jet. (Enriquez-Sarano, Tajik 2004, p.1540; Bartel et al. 2007, p.152-155) Continuous and pulse wave Doppler can offer further hemodynamic details for grading of AR severity (Maurer 2006, p.995). In conclusion, color Doppler echocardiography is a very sensitive and specific tool to identify AR and provides a basis for serial testing. However, quantitative measurement of regurgitation flow, LV dimensions and LV function by echocardiography has notable constraints.

1.3.5.4 Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) complements echocardiography, as acoustic windows and body size do not limit image acquisition and blood flow can be quantitated. Contrary to cardiac catheterization and CT-scans, CMR does not use ionizing radiation and is thereby non invasive. (Stern 2008, p.110)

In patients with chronic AR, CMR allows for assessment of valve morphology, quantification of regurgitant flow, LV size and LV function. Multiple studies have shown that measurement of ventricular dimensions and function by CMR are highly accurate and reproducible (Pattynama et al. 1995; van der Geest et al. 1997; Bellenger et al. 2000a; Bellenger et al. 2000b; Fratz et al. 2009) as is the quantification of blood flow (Dulce et al. 1992; Mohiaddin et al. 1997; Powell, Geva 2000a; Powell et al. 2000b; Kilner et al. 2007; Cawley, Maki, Otto 2009; Myerson 2012). Further details on CMR basics will be given in section 1.3.8 below.

1.3.6 Classification of severity of aortic regurgitation

The guidelines of the American College of Cardiology / American Heart Association classify the severity of regurgitation into four stages, A to D. Stages A to C include asymptomatic patients with increasing severity of AR. Stage D is defined by severe AR and the presence of symptoms. Stage A comprises patients simply at risk of AR, such as patients with a history of rheumatic fever or known bicuspid aortic valve. Stage B includes patients with progressive AR, this stage is subdivided into mild and moderate AR according to valve hemodynamics. Patients in stage C suffer from severe AR defined by valve hemodynamics and patients in class D additionally suffer from symptoms such as dyspnea or angina. Qualitative parameters are provided by Doppler and color echocardiography whereas quantitative data can be generated by MRI or cardiac catheterization. Detailed classifications according to valve hemodynamics ranging from mild and moderate (stage B) to severe (stages C and D) adapted from the 2014 guidelines of the American College of Cardiology / American Heart Association are listed in Table 1 (Nishimura et al. 2014, p. 2453).

Indicator	Mild	Moderate	Severe
Qualitative			
Color Doppler jet width	< 25% of LVOT	25%–64% of LVOT	> 65% of LVOT
Doppler vena contracta width (cm)	< 0.3	0.3-0.6	> 0.6
Quantitative			
Regurgitant volume (ml/beat)	< 30	30-59	≥ 60
Regurgitant fraction (%)	< 30	30-49	≥ 50
Regurgitant orfice area (cm^2)	< 0.10	0.10-0.29	≥ 0.30
Additional essential criteria			
Left ventricular size			Increased

Table 1: Classification of the severity of aortic regurgitation adapted from 2014 guidelines of the American College of Cardiology / American Heart Association; LVOT: left ventricular outflow tract

1.3.7 Therapy

Asymptomatic patients with severe chronic AR and normal LV function have a good prognosis. There is a low likelihood of progression to symptoms, LV dysfunction, or sudden death. Once symptoms come apparent, mortality rates rise significantly. In a clinical study following patients with severe AR, those patients in NYHA class III or IV had a mortality rate of 24,6% per year. But also patients in NYHA class II had an increased mortality rate of 6,3% per year (Dujardin et al. 1999, p.1854). In this case, AVR is the treatment of choice to diminish symptoms, prevent death and the development of heart failure (Tornos et al. 2006, p.1014). In experienced centers aortic valve repair represents an alternative to valve replacement, especially in cases of bicuspid aortic valves (Davierwala et al. 2003; Minakata et al. 2004, p.650; Vahanian et al. 2012, p.10).

1.3.7.1 Indications for surgery

Nowadays, AR can be corrected successfully by AVR. The appropriate timing of surgery, however, is disputed, because, amongst other reasons, a relatively high inci-

dence of patients with remaining post-operative LV dysfunction is reported (Klodas et al. 1996, p.674; Villari et al. 2009, p.2390; Buddhe et al. 2012, p.331). According to the 2014 of the American College of Cardiology / American Heart Association AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function and for asymptomatic patients with severe AR and LV dysfunction, defined by EF of 50% or less. Surgery is also indicated for asymptomatic patients with severe AR and normal LV function, but LV dilation defined by end-systolic dimensions (ESD) greater than 50mm measured in echocardiography. Increased ESD is not only associated with increased risk of death, symptoms and LV dysfunction (Bonow et al. 1991, p.1633), but also with poorer outcomes after AVR (Dujardin et al. 1999', p.1856). AVR may also be considered for patients with end-diastolic dimensions (EDD) greater than 65mm as increased EDD might also be associated with higher mortality, however less than ESD (Bonow et al. 1991, p. 1632; Klodas et al. 1996, p.675). The guidelines of the European Society of Cardiology on Valvular Heart Disease set the threshold at ESD of 50mm and EDD of 70mm respectively (Vahanian et al. 2012, p.11). After AVR, close follow-up is necessary to assess prosthetic valve function and LV function early postoperatively and in the long term (Bonow et al. 2008, p.e558). Figure 3 depicts the decision diagram for AVR adapted from current guidelines (Nishimura et al. 2014, p.2454).

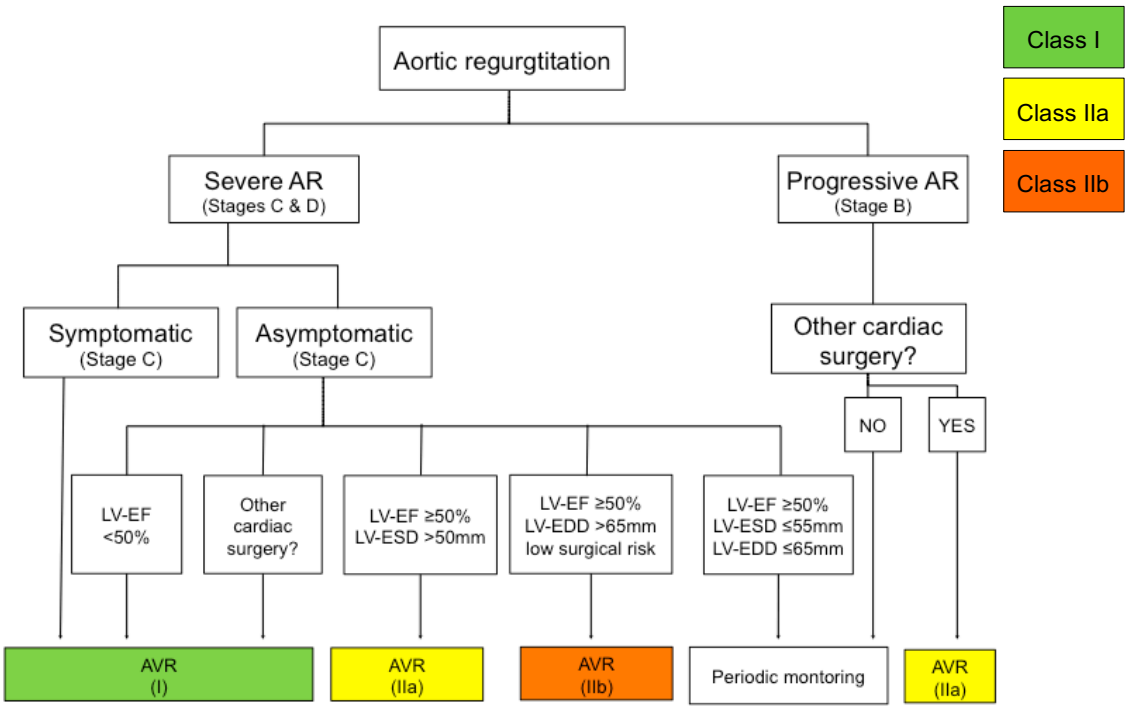

Figure 3 Indications for AVR for chronic AR adapted from present guidelines

1.3.7.2 Medical therapy

Vasodilators, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) are indicated in patients with severe AR who have symptoms or LV dysfunction and surgery is contraindicated. This medical therapy is also reasonable as a short-term therapy to improve the hemodynamic condition before AVR in the presence of severe heart failure symptoms and severe LV dysfunction. Vasodilators may be considered as a long-term treatment for asymptomatic patients with severe AR and LV dilation but no LV dysfunction. (Vahanian et al. 2012, p.12; Nishimura et al. 2014, p.e85) A pilot study has shown that ACE inhibitors were effective in reducing LV dimensions and hypertrophy, but further studies have been considered necessary to prove that this therapy improves the natural history and delays AVR (Mori et al. 2000, p.273-274).

1.3.8 Cardiovascular magnetic resonance

Magnetic resonance imaging (MRI) is an imaging technology based on the concept of nuclear magnetic resonance. It has evolved from a tomographic imaging technique, producing only cross-sectional images to a volume imaging technique. Its origins go back to the 18th century mathematician and engineer Jean Baptiste Joseph Fourier. He developed a mathematical transformation method, which, among many other applications, is used to transform the frequency-encoded signals of an MRI into an image (Geva 2006, p.573). In 1946 the scientists Felix Bloch and Edward Purcell, without knowledge of each other's work, first described the magnetic resonance phenomenon. They found that magnetic nuclei absorb and re-emit energy in the electromagnetic spectrum when placed into a magnetic field. They were both awarded the Nobel Price in Physics in 1952. (Geva 2006, p.575)

In 1974 Paul C. Lautenbur and Peter Mansfield independently of each other described the use of magnetic field gradients to acquire spatial information in nuclear magnetic resonance experiments. One year later Richard Ernst used the Fourier transformation to reconstruct two-dimensional (2D) images, a technique that is used until today. (Geva 2006, p.576) Specific MRI imaging of the heart and the great vessels was first preformed in the 1980s and has undergone considerable development since then (Geva 2006, pp.577-578).

MRI systems comprise a set of main magnets, a radiofrequency transmitter coil, gradient coils, and a receiver unit. The static magnetic field emitted by the main coils, and the radiofrequency field together generate magnetic resonance signals that can be spatially localized by the aid of the gradient coils. (Ridgway 2010, p.71) The specific

principals involved are complex and beyond the scope of this thesis, so that only an overview of the basic physical elements shall be given.

The human body is primarily made out of water and fat, which consist of many hydrogen molecules. The hydrogen's nuclei, single protons, posses an intrinsic property called spin that gives rise to a small magnetic field. When a person is placed into a strong linear magnetic field (Bo), as the one generated by the main magnetic coil, these protons tend to align themselves toward or against Bo and hereby form a net magnetization (M) that, at equilibrium (Mo), is aligned with Bo. The protons hereby precess at a specific frequency which directly correlates to the strength of the magnetic field by the Lamour equation. To create an MR signal from this net magnetization a radiofrequency signal (rf), often referred to as B1, is applied as a short pulse. When this rf pulse is switched on, the protons are knocked out of alignment and the net magnetization moves away from its alignment with the Bo field. The degree of rotation is referred to as the flip angel and the specific pulse frequency is called resonant frequency. After the B1 is switched off, the protons reestablish the previous equilibrium, a process referred to as relaxing. During relaxation, the protons emit an rf signal, which can be measured by the receiver unit. The time required by the protons to regain equilibrium state is characterized by a specific relaxation time that differs amongst tissues leading to different signal intensities that are used to construct the image. The MRI signals can also be spatially localized in three dimensions by three additional magnetic fields generated by gradient coils. These magnetic fields have different strengths in varying locations, for instance increasing from the feet to the head of the patient. They hereby modify the strength of the main magnetic field along cross sections of the patent's body as well as the precession frequency of protons which is correlated to the strength of the magnetic field. The above described rf pulse only knocks protons out of alignment which precess with the same frequency as the rf signal. By varying the strength of the magnetic field and thereby the precession frequency of the protons along the patient's body one can determine the location of a slice by selecting a certain rf pule frequency. The in return emitted rf signals are analyzed and transformed into voxels of different shades of grey using the mathematical Fourier transformation (Schild 1990; Ridgway 2010, p.71).

Cardiovascular magnetic resonance (CMR) is derived from the same principals as MRI, but with optimization for use in the cardiovascular system including ECG gating and fast imaging techniques. There are two main types of sequences used in CMR: gradient echo (GE) and spin echo (SE) sequences. In SE sequences blood appears black and in GE sequences it appears white. Thus, they are also referred to as black blood imaging and bright blood imaging. SE sequences are more useful for anatomical imag-

ing, while GE sequences are better suited for functional imaging. A variation of the GE sequence, the fast imaging steady-sate free precession (SSFP) sequence is very important in CMR nowadays. This sequence visualizes myocardial wall dysfunctions and abnormal flow patterns very well with a technique called Cine Imaging. As its name suggests, cine images are short movie clips that show the heart motion and blood flow patterns throughout the cardiac cycle. They are obtained by acquiring data for a single slice at multiple time points of the cardiac cycle. Retrospective ECG gating acquires data continuously and records its temporal position relative to the R-wave. After acquisition the data is sorted into cardiac phases retrospectively. (Stern 2008, pp.110-111; Ridgway 2010, p.71)

Quantification of blood flow is performed by phase contrast measurement MRI. It is based on a flow depended phase shift. In addition to the usually reconstructed magnitude image a phase image, or velocity map is created. In the later, each voxel's signal intensity (gray value) refers to its average velocity. In order to obtain a flow pattern throughout the cardiac cycle, an ECG-gated cine GE sequence is employed. Flow at each time point of the cardiac cycle (ml) is obtained by multiplying average flow velocity (cm/s) by the area of the vessel (cm^2). A flow curve can be plotted against time and the area under this curve is equivalent to stroke volume. (Weber et al. 2006, p.609-610)

1.4 Objective

The aim of this study was to further evaluate the applicability and reliability of the CMR exercise apparatus developed by this research laboratory. CMR is known to be an accurate non-invasive method for evaluation of aortic regurgitation at rest, but data on exercise testing in AR using CMR are not available. Also, quantitative data on regurgitation during exercise is very scarce. It was therefore the aim of this study to investigate the change of aortic regurgitant volume, LV-volume and LV function under steady-state submaximal exercise in asymptomatic patients with isolated AR, and compare the generated data to previous exercise studies. A submaximal exercise level was selected because it is known that most hemodynamic changes during exercise are already present at submaximal exercise levels and do not need maximal exercise (Higginbotham et al. 1986, p.287; Wilson et al. 1988, p. 607). Additionally, all previous studies examining AR under exercise have applied maximal exercise levels, so that data about AR under mild exercise are not available to date.

2 Material and methods

The implementation of this study can be summarized as a five-step process. The first step comprised the formulation of inclusion and exclusion criteria for the study group. Next, patient files were studied and potential study patients identified. When a patient was suitable, he or she was examined by CMR on a voluntary basis. In the third step CMR data were post-processed to gain the parameters relevant to the study. At last, the data obtained were analyzed statistically. For control purposes a group of healthy volunteers was also recruited and examined under the same conditions.

2.1 Study groups

The purpose of this study was to examine changes in hemodynamic parameters in patients with chronic AR under steady-state submaximal exercise. To differentiate between normal hemodynamic adjustments and those related to AR, a study group of patients with chronic AR and a control group of healthy volunteers had to be recruited and examined in CMR.

2.1.1 Inclusion and exclusion criteria of study groups

Inclusion criterion for the group of AR patients was the presence of chronic AR of any degree by echocardiography. Exclusion criteria were age under 10 years, presence of any other cardiac or vascular disease, and the intake of any cardiac medication such as beta-blockers or ACE inhibitors. These conditions exclude most patients with AR and leave a highly selected subgroup of the overall AR population seen at Deutsches Herzzentrum München. As patients with AR have an increased net flow through the aortic valve, patients with maximum flow velocities (Vmax) up to 4,0m/s were not excluded from the study. For mathematical explanation see Appendix B. Further exclusion criteria were claustrophobia, mental impairment, arrhythmia, and ferromagnetic implants. Table 2 summarizes the exclusion criteria.

Apart from the requirement to be healthy from a cardiovascular point of view, the same exclusion criteria were applied to the control group.

Exclusion criteria
Age <10 years
Vmax > 4,0 m/s
Other cardiac disease
Intake of cardiovascular medicine
Claustrophobia
Arrhythmia
Mental impairment
Ferromagnetic implants

Table 2: Exclusion criteria

2.1.1.1 Recruitment

The majority of patients seen in the Department of Pediatric Cardiology and Congenital Cardiac Disease at Deutsches Herzzentrum München do not necessarily live in Munich. The associated long journey did not seem reasonable for an exclusive study examination, which is why the patient recruitment was done in cooperation with the outpatient department. In doing so, the exercise CMR examination could be scheduled together with an already arranged clinic and regular CMR appointment. This cooperation involved studying the records of all anticipated outpatients one week in advance to filter out a potential study patient. Then, the selected patient was reviewed with the attending physician to clarify questions and confirm study suitability. On the day of the appointment one of the CMR physicians examined the patient, introduced the study and ask for voluntary participation. All anticipated patients and if necessary a parent agreed to volunteer and gave their written informed consent. They were then examined by CMR at rest, as it had already been scheduled, and in additions as part of the study under steady-state submaximal exercise.

2.2 Acquisition of data sets

All CMR scans were performed using a standard 1.5 Tesla CMR-scanner (MAGNETOM Avanto®, version software B17, Siemens Healthcare, Erlangen, Germany) and a standard cardiac 12-channel coil. LV end-diastolic and end-systolic volumes as well as flow measurements in the ascending aorta were registered at rest and during submax-

imal exercise. Heart rate was determined from the ECG monitor. Systolic, diastolic and mean blood pressures were measured on the right arm during rest and steady state exercise. Three measurements were performed and the mean value calculated at rest and exercise respectively. Blood pressure was taken by oscillometry using a MR compatible device (Invivo Precess™, Series 3160).

2.2.1 Submaximal steady-state exercise during CMR

It is known that most hemodynamic changes during exercise are already present at light exercise levels and do not require maximal work load (Higginbotham et al. 1986, p. 287; Wilson et al. 1988, p. 607; Schairer et al. 1992, p. 932; Kraemer et al. 2006, p. 160; Plowman et al. 2014, p.353). It is also well recognized that at the onset of light to moderate exercise, there is an initial increase in cardiac output to a plateau at steady state cardiac output. This plateau has been shown to be reached within two minutes of work-out (Plowman, Smith 2014, p.353). The mode of exercise in our study had to be simple to implement, tolerable for most patients and show little interference with image acquisition. To this end, we designed and built an exercise apparatus to easily enable steady-state light exercise over longer periods of time during CMR scanning (patent utility no. 202013006749.7), see Figure 4: Exercise apparatus for steady-state submaximal exercise testing The apparatus is intrinsically auto-normative, as the workload depends only on the length and weight of the subject's legs. For this purpose a pulley was fixed to an aluminum frame, which again was mounted on the MR table. A rope with loops for the patient's legs was pulled through the pulley. After CMR measurements at rest, the scanning table was moved out of the magnet to allow the subject's feet to be fixed to the ends of the rope. Two crossing straps immobilized the hip.

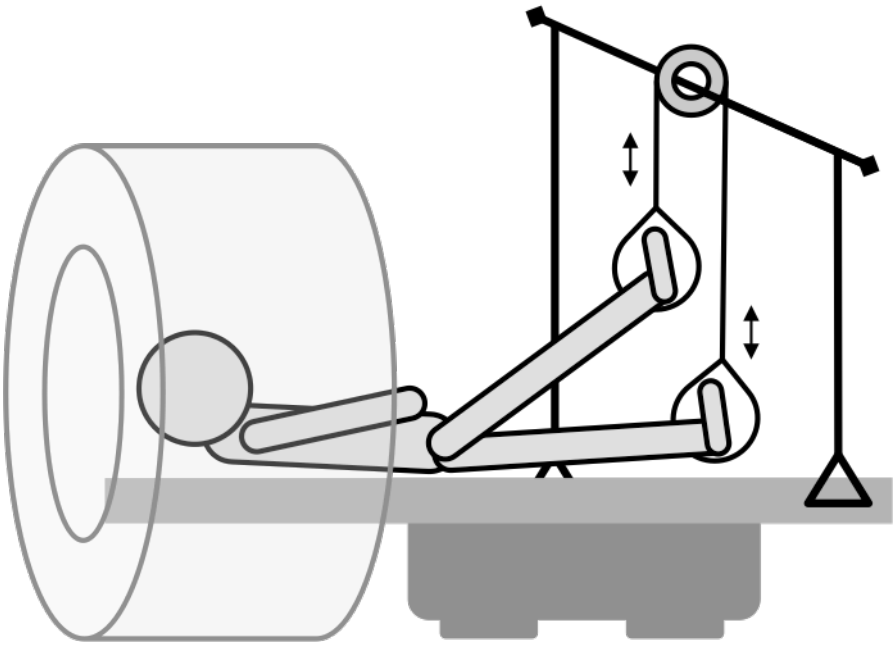

Figure 4: Exercise apparatus for steady-state submaximal exercise testing

Steady-state submaximal exercise was achieved by 144 strokes per minute of the extended legs. Stroke frequency was directed by an electronic metronome, connected to the patient`s headphone in the magnet. Exercise at this frequency had, in a previous study of this laboratory, been identified to lead to 24% of maximal O_2 consumption (VO_2Max) (Stern et al. 2014, p.314).

To study steady-state physiology, exercise was continuously performed for five minutes prior to image acquisition and then maintained. To reduce hemodynamic effects of leg elevation during exercise CMR measurements, the subject's legs were already passively elevated by pads throughout rest measurements.

2.2.2 Volumetric measurements

End-diastolic and end-systolic LV volumes were measured from CMR LV short-axis cuts at rest and during submaximal exercise, as they are described in literature (Fratz et al. 2009, p.1765). Patients were imaged in supine position at breath holding in expiration, using retrospective ECG gating. The sessions were initiated with steady state free precession localizing views in the three orthogonal planes to determine the position of the ventricles, followed by a 2-chamber localizer, 4-chamber localizer, short-axis localizer, and a 4-chamber multiphase slice.

SSFP images were acquired from the 4-chamber multiphase slice by planning a stack of short-axis slices parallel to the mitral valve and perpendicular to the interventricular septum, covering the entire heart. Short-axis multiphase steady state SSFP images were acquired with a slice thickness of 8 mm, 25 phases per heart cycle in a matrix size 192 x 192 pixels. A gap of 8 mm between the slices was used to keep forward breath hold time short under exercise.

Typical CMR short axis images under rest and exercise are shown in Figure 5.

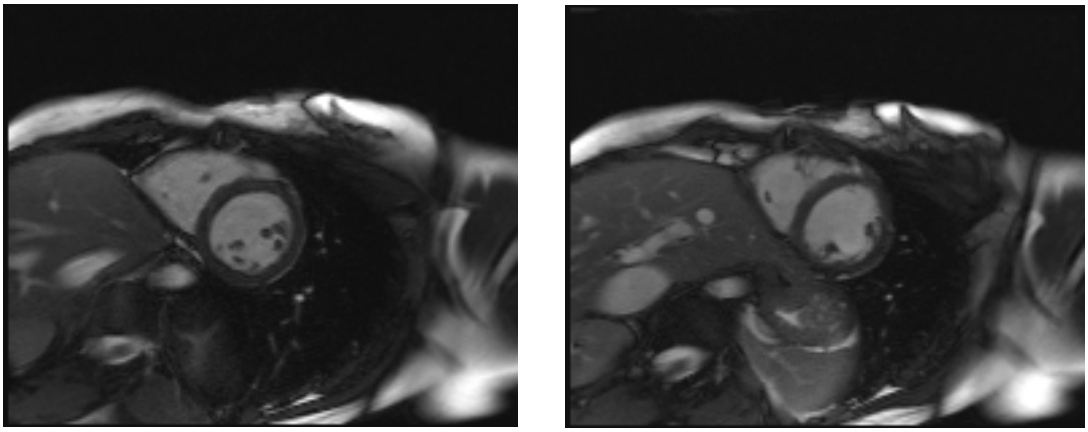

Figure 5: CMR short axis images under rest (left) and exercise (right)

2.2.3 Flow measurements

For flow measurements, a standard free breathing, phase sensitive gradient echo sequence was used, as described in literature (Fratz et al. 2002, p.1511; Fratz et al. 2008, p.1132). Parameters of image acquisition are summarized in Table 3.

Parameters of data acquisition		
Velocity encoding (VENC)	250 – 400	cm/s
Slice thickness	5	mm
Repetition time	36,7	ms
Echo time	3,1	ms
Flip angle	30	deg.
Receiver bandwidth	31,25	kHz
Field of view	260 – 330	mm
Matrix	256 x 256	pixel

Table 3: Parameters of image acquisition for flow measurements

The imaging plane was set strictly perpendicular to the course of the ascending aorta. Aortic flow was measured approximately 2cm above the sinutubular junction. This measure keeps the measuring plane above the level of the aortic valve even under reinforced motion during exercise. The velocity encoding was set between 250 and 400 cm/s depending on the presence or absence of concomitant aortic stenosis. The ECG was closely monitored during data acquisition. The acquisition was aborted if more than four beats per acquisition were not correctly detected. Scans were repeated until satisfactory triggering during the entire acquisition was achieved. Typical CMR images of the aorta under rest and exercise are shown in Figure 6.

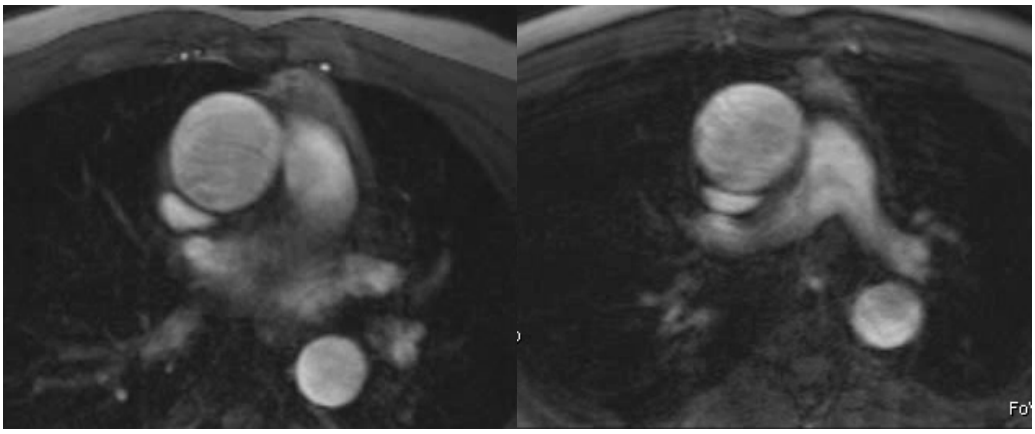

Figure 6: CMR images of aorta at rest (left) and under exercise (right)

2.3 Post-processing of data sets

After data acquisition the raw sets of images were post-processed using standard analysis software (ARGUS, Syngo Multi Modality Workplace, Version VE23B, Siemens Healthcare, Erlangen, Germany).

2.3.1 Volumetric measurements

End-diastolic and end-systolic LV volumes were calculated from the short-axis data sets. LV end-systole and end-diastole were detected manually. The phase with the smallest ventricle volume, judged by eye, was assigned end-systole and the phase with the largest ventricle volume end-diastole. The endocardial contours of the LV were then traced by hand. The papillary muscles and trabecula were considered part of the myocardium and were excluded from the volume. The contours were traced using information from the 4-chamber multiphased cine view. Contour tracing was aided by reviewing the multiple phase scans in the movie mode. The stroke volume and ejection fraction were derived from end-diastolic and end-systolic volumes, calculated by equa-

tion (2) and (4). For statistical analysis all volume data were indexed to body surface area (BSA). Stroke volumes derived from volumetric measurements will be abbreviated as SV (vol) and SVI (vol). Stroke volumes measured directly through flow measurements will be abbreviated by SV.

$$SV\ (vol)(\mathrm{ml}) = EDV - ESV \qquad (2)$$

$$SVI\ (vol)\ (\mathrm{ml}) = (EDV - ESV)/BSA \qquad (3)$$

$$EF(\%) = \frac{SV\ (vol)}{EDV} \cdot 100 \qquad (4)$$

2.3.2 Flow measurements

Forward SV, net SV and regurgitant volume through the ascending aorta were calculated using the same standard analysis software by tracing the contours of the aorta in all 30 phases. Forward SV shall be defined as total flow through the aortic valve including the regurgitation volume. Net flow is defined as the effective flow through the valve, i.e. excluding the regurgitant volume. The regurgitant fraction was calculated by equation (5). Net and forward cardiac output were calculated, multiplying heart rate by the respective SV (6). Cardiac index (CI) is cardiac output indexed to BSA.

$$RF(\%) = \frac{regurgitant\ volume}{forward\ SV} \cdot 100 \qquad (5)$$

$$forward\ CI(\mathrm{l/min/m2}) = (forward\ SV * HR)/BSA \qquad (6)$$

$$net\ CI(\mathrm{l/min/m2}) = (net\ SV * HR)/BSA \qquad (7)$$

In addition, post processing of flow data allows approximation of systolic and diastolic times. As regurgitation takes only place during diastole, diastolic times of all study participants were estimated at rest and under submaximal exercise using the individual time vs. flow graphs of the aortic valve. Figure 7: Typical flow graphs over the cardiac

cycle in one subject at rest (left) and under submaximal exercise (right)shows two exemplary flow charts at rest and under exercise. Diastole was approximated by

$$diastole\ (ms) = \ full\ cardiac\ cycle\ (ms) - systole\ (ms) \qquad (8).$$

Systole was estimated according to visual judgment. It was defined as the time between initiation of data acquisition, triggered by ECG to be the beginning of systole up to the zero point of each flow curve.

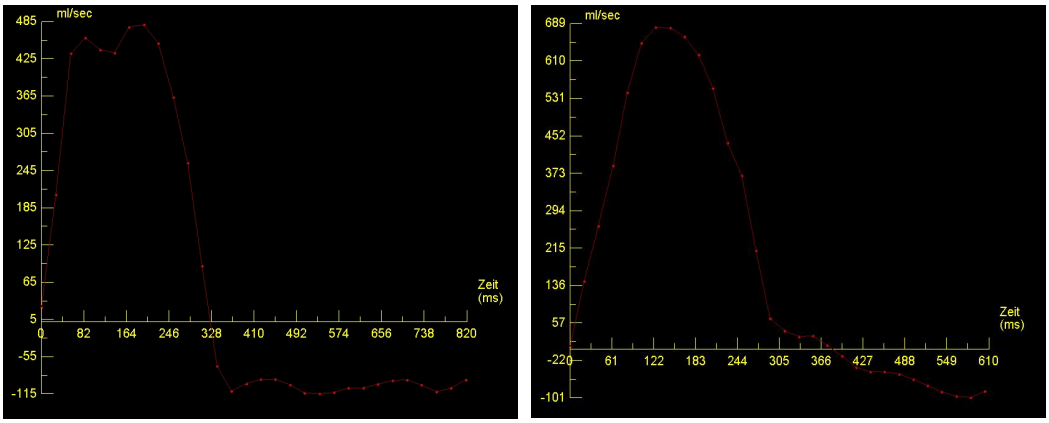

Figure 7: Typical flow graphs over the cardiac cycle in one subject at rest (left) and under submaximal exercise (right)

2.4 Statistical analysis

For descriptive statistics median values and range were used instead of mean and standard deviation, as normal data distribution could not be confirmed. The Kolmogoroff-Smirnov test for normal distribution did not reject the hypothesis of normal distribution. However, the sample size of twelve is very small and normality tests are known to be less powerful in small samples. Therefore, a second approach was tested. Miles and Shevlin (2000, p.74) state that if the value of skew and kurtosis is greater than twice the standard error, the distribution differs significantly from normal distribution. Following this robust rapid test, it was concluded that normal distribution is not probable for most parameters taken during CMR examination. In skewed populations median and range are more representative and were used accordingly (Feinstein 2004, pp.31-35). Consequently, non-parametric tests were used for the following statistical analysis.

Hemodynamic values under rest and during steady state submaximal exercise in each group were compared by Wilcoxon´s rank test for paired variables.

Comparisons between the groups of healthy volunteers and patients with AR were performed using Mann-Whitney U test. Correlation between aortic regurgitant fraction at

rest and percent increase of cardiac output was tested by least square linear regression analysis.

Differences in parameters were accepted as statistically significant, when the probability of error for zero hypothesis was less than 5%.

All statistical analyses were performed by SPPS version 22 for Mac OS (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Study groups

3.1.1 Healthy volunteers

A group of twelve healthy volunteers was recruited and examined from 06/2009 to 04/2010. The group comprises three females and nine males (n=12). They participated on a voluntary basis. The group's median age at study was 25 (range 20-39) years. Their median body weight was 72 (range 53-95) kg and their median body height 179 (range 165-188) cm. None of the volunteers had a history of cardiovascular or pulmonary disease. All healthy volunteers were examined by CMR at rest and during steady-state submaximal exercise. Appendix A shows the baseline characteristics of the healthy volunteers.

3.1.2 Patients with chronic aortic regurgitation

The patient group was recruited and examined from 03/2010 to 08/2011 and includes two female and ten male patients (n=12) with chronic AR. The median age at study was 22 (range 10-40) years, the median body weight was 64 (range 29-83) kg and the median body height 170 (range 92-199) cm. These were similar to the controls' parameters. All patients were previously examined by echocardiography according to guidelines. Hereby, one patient was diagnosed with mild to moderate, two with moderate, another two with moderate to severe, and seven with severe chronic AR. The regurgitation fractions measured in CMR ranged from 9% to 64% with a median of 35%. All patients were in NYHA functional class I, which is defined as follows: "Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpation, dyspnea or angina pain (America Heart Association 1994, p.664)". In eight patients a bicuspid aortic valve had been determined as the cause of the regurgitation. Two patients underwent valvuloplasty for aortic stenosis and subsequently developed progressive AR, which is not an uncommon consequence (Balmer et al. 2004). In the case of the remaining two patients no clear cause of AR was determined. Table 4 summarizes volunteers' and patients' baseline characteristics. For individual data see Appendix A.

	Healthy volunteers (n=12)	AR patients (n=12)	
Variable	Median (range)	Median (range)	p value
Age (years)	25 (20-39)	22 (10-40)	*0.378*
Body weight (kg)	72 (53-95)	64 (29-83)	*0.198*
Body height (cm)	179 (165-188)	171 (92-199)	*0.089*
BSA (m^2)	1.9 (1.6-2.2)	1.7 (1.0-2.0)	*0.053*

Table 4: Volunteers' and patient's baseline characteristics

3.2 Hemodynamic findings

3.2.1 Hemodynamics at rest

There were no significant differences in heart rate, systolic (BPsys) or diastolic (BPdia) blood pressure at rest between patients an control subjects.

LV-EDVI (p=0.017) and LV-ESVI (p=0.002) were significantly larger in the patient group, compared to healthy volunteers, as was SVI (vol). LV-EF in AR patients was not different from controls.

Forward SV did not differ between groups, but net SV (p=0.010) was significantly lower in the patient group. Forward CI was larger in patient group (p=0.028). Net CI, however, was significantly smaller in patients (p=0.045). Table 5 summarizes these findings.

	Healthy volunteers (n=12)	AR patients (n=12)	
Variable	Median (range)	Median (range)	p value
HR (1/min)	64 (57-91)	72 (57-87)	*0.178*
BPsys (mmHg)	110 (102-126)	111 (97-134)	*0.887*
BPdia (mmHg)	60 (51-81)	53 (42-65)	*0.078*
EDVI (ml/m^2)	74 (59-99)	118 (52-193)	***0.017***
ESVI (ml/m^2)	20 (15-34)	38 (18-66)	***0.002***
EF (%)	73 (61-80)	68 (58-73)	*0.078*
SVI (vol) (ml)	57 (42-65)	84 (34-133)	***0.039***
Forward SV (ml)	96 (83-138)	112 (51-239)	*0.755*
Net SV (ml)	96 (82-135)	68 (44-138)	***0.010***
Forward CI (l/min/m_2)	3.7 (2.9-5.0)	4.9 (3.2-7.5)	***0.028***
Net CI (l/min/m^2)	3.7 (2.9-5.0)	3.0 (1.8-6.0)	***0.045***

Table 5: Differences in flow and volumetric measurements between volunteers and patients at rest

3.2.2 Hemodynamics under steady state submaximal exercise

All subjects, control group and patients completed the CMR rest and submaximal exercise protocol without limitations. All patients tolerated the exercise level well and did not complain of dyspnea, exhaustion or leg fatigue.

Heart rate and blood pressure values did not differ between groups under submaximal exercise.

Except for LV-EDVI (p=0.045) and LV-ESVI (p=0.033) which were still significantly larger in the patient group, all remaining parameters did not differ significantly between groups. Table 6 summarizes these findings.

	Healthy volunteers (n=12)	AR patients (n=12)	
Variable	Median (range)	Median (range)	p value
HR (1/min)	90 (71-115)	90 (76-135)	*0.478*
BPsys (mmHg)	126 (104-143)	121 (99-160)	*0.347*
BPdia (mmHg)	73 (43-94)	64 (56-90)	*0.316*
EDVI (ml/m^2)	74 (53-100)	102 (54-173)	***0.045***
ESVI (ml/m^2)	19 (13-32)	27 (14-51)	***0.033***
EF (%)	72 (62-80)	71 (65-83)	*0.755*
SVI (vol) (ml)	53 (27-69)	78 (38-144)	*0.068*
Forward SV (ml)	103 (86-128)	103 (49-256)	*0.843*
Net SV (ml)	103 (85-128)	84 (44-171)	*0.178*
Forward CI (l/min/m^2)	4.7 (3.7-6.6)	6.3 (3.0 -9.7)	*0.052*
Net CI (l/min/m^2)	4.7 (3.7-6.6)	4.8 (2.6-7.6)	*0.713*

Table 6: Differences in flow and volumetric measurements between healthy volunteers and patients during exercise

3.2.3 Hemodynamic response to exercise

3.2.3.1 Vital parameters

In healthy volunteers heart rate increased from median 64 (range 57-91) to 90 (range 71-119) beats per minute (p=0.008). Systolic blood pressure increased from median 110 (range 102-26) to 126 (range 104-143) mmHg (p=0.002). Diastolic blood pressure increased from median 60 (range 51-81) to 73 (range 43-94) mmHg (p=0.008).

In patients heart rate rose from median 72 (range 57-87) to 90 (76-135) beats per minute (p=0.002). Systolic blood pressure increased from median 111 (range 97-134) to 121 (range 99-160) mmHg (p=0.026), and diastolic blood pressure from median 53 (range 42-65) to 64 (range 56-90) mmHg (p=0.005). Table 7: Vital parameters in healthy volunteers and AR patients at rest and under submaximal exercise

summarizes these data. Appendix C includes the individual values of HR, BPsys and BPdia at rest and under submaximal exercise for all study subjects.

Figure 8, Figure 9, and Figure 10 show HR, BPsys and BPdia under rest and during submaximal exercise in controls and patients as boxplots. P-values for changes rest versus exercise are given.

	Healthy volunteers (n=12)			AR patients (n=12)		
	Rest	Submaximal exercise		Rest	Submaximal exercise	
Variable	Median (range)	Median (range)	p value	Median (range)	Median (range)	p value
HR (1/min)	64 (57-91)	90 (71-115)	***0.002***	72 (57-87)	90 (76-135)	***0.002***
BPsys (mmHg)	110 (102-126)	126 (104-143)	***0.002***	111 (97-134)	121 (99-160)	***0.026***
BPdia (mmHg	60 (51-81)	73 (43-94)	***0.008***	53 (42-65)	64 (56-90)	***0.005***

Table 7: Vital parameters in healthy volunteers and AR patients at rest and under sub-maximal exercise

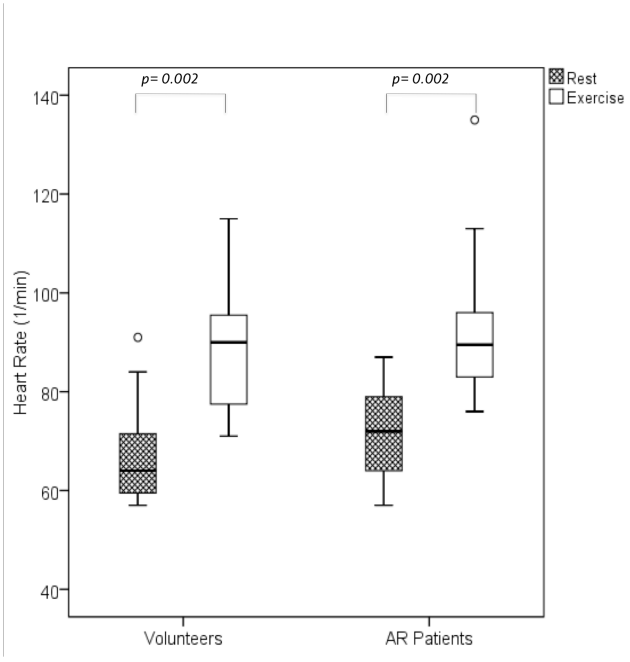

Figure 8: Heart rate in healthy volunteers and AR patients under rest and submaximal exercise

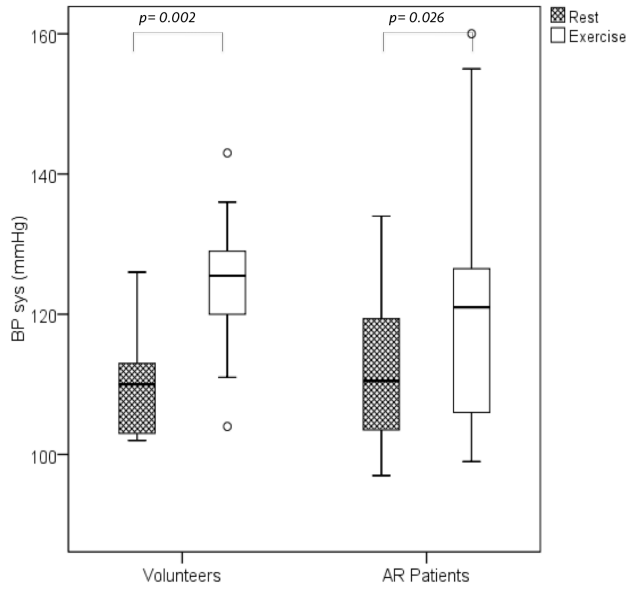

Figure 9: Systolic blood pressure in healthy volunteers and AR patients under rest and submaximal exercise

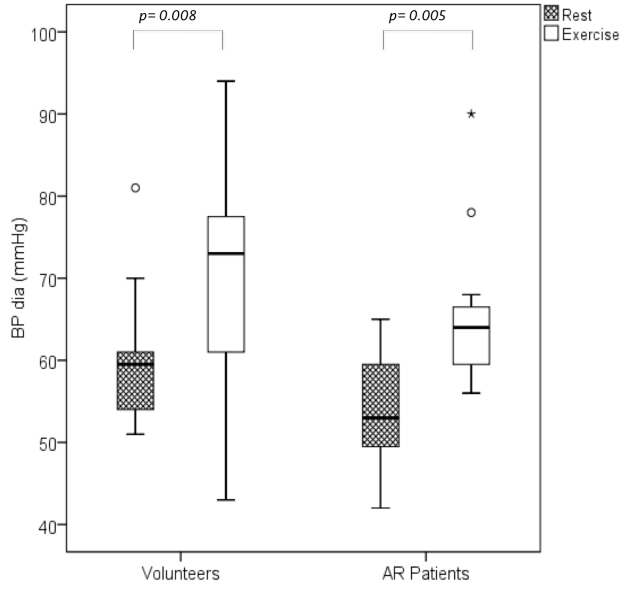

Figure 10: Diastolic blood pressure in healthy volunteers and AR patients under rest and submaximal exercise

3.2.3.2 Volumetric measurements

LV-EDVI and LV-ESVI as calculated from the short axis measurements did not change significantly under steady-state submaximal exercise in healthy volunteers. Concordantly LV-EF and SVI (vol) did not change significantly either.

In patients LV-EDVI and LV-ESVI decreased from median 118 (range 52-193) to 102 (range 54-173) (p=0.004) and from median 38 (range 18-66) to 28 (range 14-51) ml/m^2 (p=0.009), respectively. LV ejection fraction improved slightly, but significantly (p=0.021) from median 68 (range 58-73) % to 71 (range 65-83) %. SVI (vol) did not change significantly under exercise. Table 8 summarizes the data from the short-axis measurements. Appendix E includes the individual values for LV-EDVI, LV-ESVI, LV-EF and SVI at rest and under submaximal exercise for all study subjects.

Figure 11, Figure 12, and Figure 13 show LV-EDVI, LV-ESVI and EF under rest and during submaximal exercise in healthy volunteers and patients with AR. P-values for changes rest versus exercise are given.

	Healthy volunteers (n=12)			AR patients (n=12)		
	Rest	Submaximal exercise		Rest	Submaximal exercise	
Variable	Median (range)	Median (range)	p value	Median (range)	Median (range)	p value
EDVI (ml/m^2)	74 (59-99)	74 (53-100)	0.169	118 (52-193)	102 (54-173)	***0.004***
ESVI (ml/m^2)	20 (15-34)	19 (13-32)	0.125	38 (18-66)	27 (14-51)	***0.009***
EF (%)	73 (61-80)	72 (62-80)	0.271	68 (58-73)	71 (65-83)	***0.021***
SVI(vol) (ml/m^2)	57 (42-65)	53 (27-69)	0.609	84 (34-133)	78 (38-144)	*0.181*

Table 8: Volumetric measurements under rest and submaximal exercise

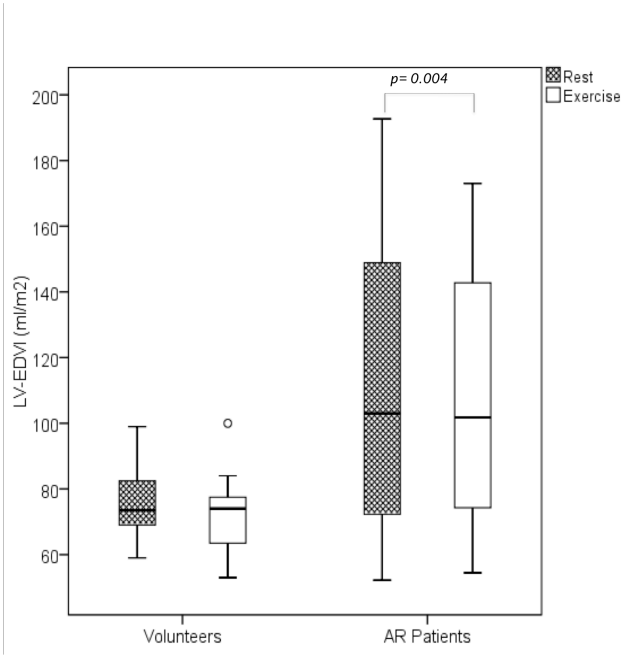

Figure 11: LV-EDVI in healthy volunteers and AR patients under rest and submaximal exercise

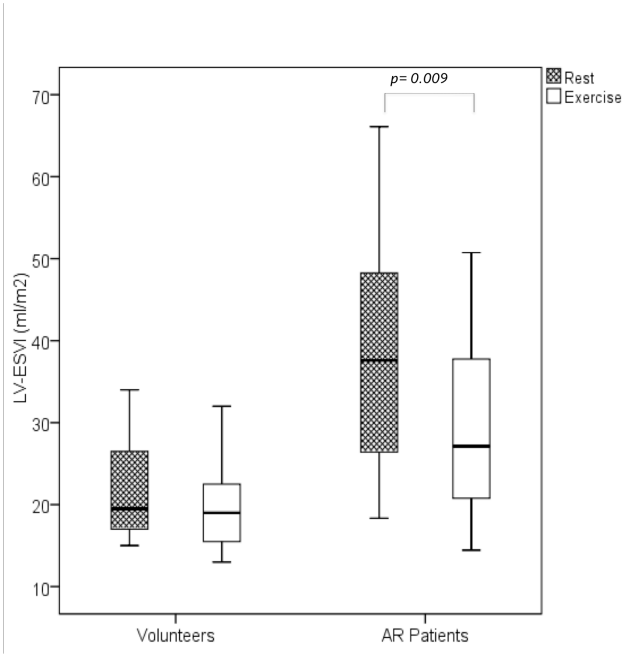

Figure 12: LV-ESVI in healthy volunteers and AR patients under rest and submaximal exercise

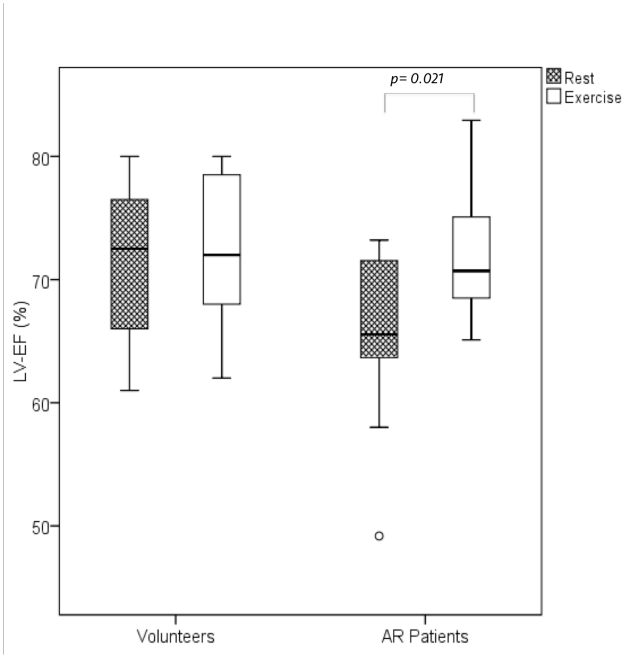

Figure 13: LV-EF in healthy volunteers and AR patients under rest and submaximal exercise

3.2.3.3 Flow measurements

Forward and net SV derived from the velocity flow measurements in the ascending aorta were identical in healthy volunteers due to the absence of regurgitant flow. Their values did not change significantly under exercise. Forward and net cardiac index were also the same. Their values increased significantly from median 3.7 (range 2.9-5.0) to 4.7 (range 3.7-6.6) l/min/m^2 under steady-state submaximal exercise (p=0.002).

In patients net stroke volume was significantly lower than forward stroke volume under rest (p=0.002) as well as during submaximal exercise (p=0.002); so was net CI compared to forward CI under rest (p=0.002) and during submaximal exercise (p=0.002). Forward stroke volumes did not change significantly under exercise. Regurgitation fraction decreased significantly in all twelve patients from median 35 (range 9-64) to 16 (range 7-42) % (p=0.002). Median regurgitant volume per minute also decreased from 2.4 (Range 0.5-6.4) to 1.7 (range 0.5-6.5) l (p=0.023).

As a result net SV clearly increased under exercise from 68 (range 44-138) to 84 (range 44-171) ml, but not significantly. Net and forward cardiac index increased significantly from 3.0 (range 1.8-6.0) l/min/m^2 to 4.8 (range 2.6-7.6) l/min/m^2 (p=0.003) and from 4.9 (range 3.2-7.5) l/min/m^2 to 6.3 (range 3.0-9.7) l/min/m^2) respectively (p=0.004).

Table 9: Flow measurements under rest and submaximal exercise summarizes the data from the flow measurements in the ascending aorta. Appendix F includes the

individual values for forward SV (fSV), net SV (nSV), regurgitant fraction and forward (fCI) and net CI (nCI) at rest and under submaximal exercise for all study subjects

Figure 14, Figure 15, Figure 16, and Figure 17 show Forward SV and net SV under rest and during submaximal exercise in healthy volunteers and patients with AR as boxplots. P-values for changes rest versus exercise are given.

	Healthy volunteers (n=12)			AR patients (n=12)		
	Rest	Submaximal exercise		Rest	Submaximal exercise	
Variable	Median (range)	Median (range)	p value	Median (range)	Median (range)	p value
fSV (ml)	103 (86-128)	96 (83-138)	*0.288*	112 (51-239)	103 (49-256)	*0.388*
nSV (ml)	103 (85-128)	96 (82-135)	*0.139*	68 (44-138)	84 (44-171)	*0.130*
RF (%)	NA	NA	*NA*	35 (9-64)	16 (7-42)	***0.002***
RV (l/min)				2.4 (0.5-6.4)	1.7 (0.5-6.5)	***0.023***
fCI (l/min/m^2)	3.7 (2.9-5.0)	4.7 (3.7-6.6)	***0.002***	4.9 (3.2-7.5)	6.3 (3.0 -9.7)	***0.004***
nCI (l/min/m^2)	3.7 (2.9-5.0)	4.7 (3.7-6.6)	***0.002***	3.0 (1.8-6.0)	4.8 (2.6-7.6)	***0.003***

Table 9: Flow measurements under rest and submaximal exercise

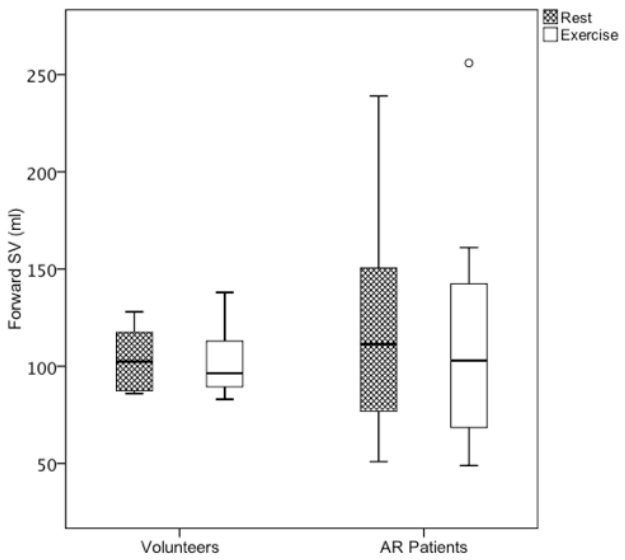

Figure 14: Forward SV in healthy volunteers and AR patients under rest and exercise

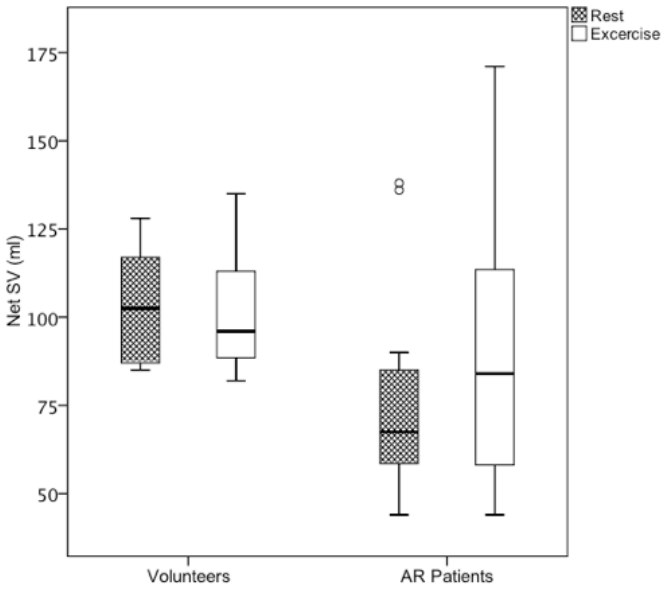

Figure 15: Net SV in healthy volunteers and AR patients under rest and exercise

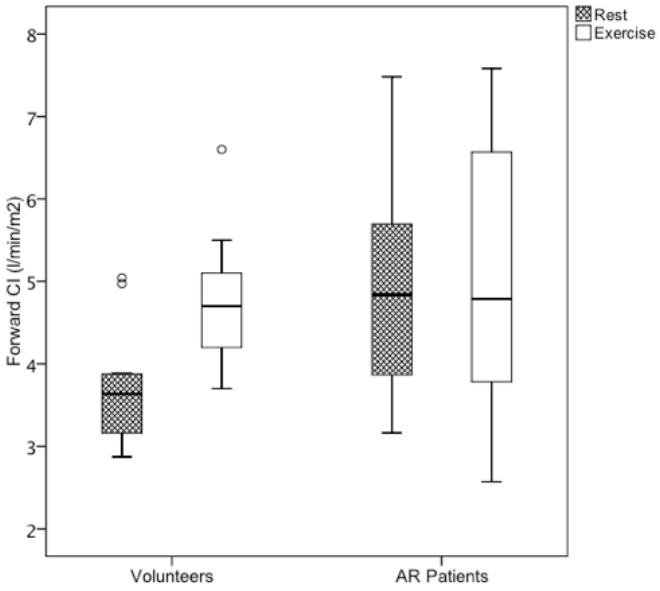

Figure 16: Forward CI in healthy volunteers and AR patients under rest and exercise

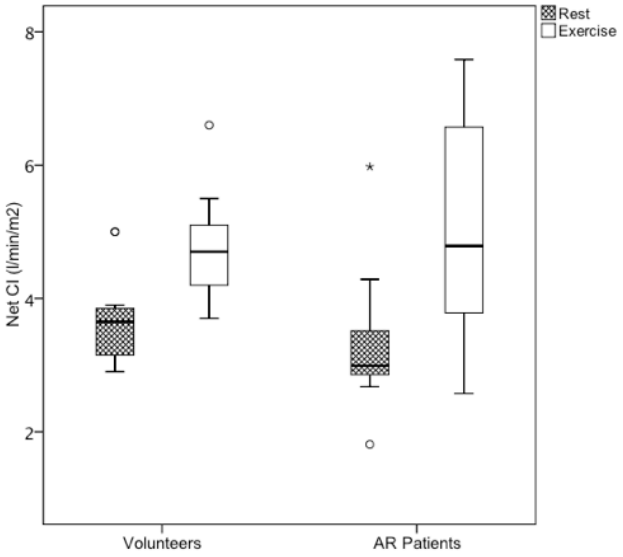

Figure 17: Net CI in healthy volunteers and AR patients under rest and exercise

3.2.3.4 Diastolic filling period

Exercise induced tachycardia led to a significant shortening of diastolic filling time from 519 (range 360-710) ms to 345 (range 190-540) (p=0.005) ms in healthy volunteers and from 510 (330-700) ms to 340 (220-460) ms (p=0.002) in patients.

3.2.3.5 Regurgitation fraction at rest as independent variable

Relative percent changes of all hemodynamic parameters from rest to submaximal exercise did not differ significantly between the group of healthy volunteers and patients with AR. The only exception was the change in percent aortic regurgitation, which was, however, per definition not present in the healthy volunteer group. See Appendix G for respective boxplots. Individual variations in hemodynamic responses, however, are better appreciated when expressed as percent changes. These results are shown in Table 10: Patients' individual changes in hemodynamic responses, expressed as percent changes. NSV= net SV, FSV=forward SV, NCI net CI, FCI=forward CI A linear correlation (R^2= 0.53, p=0.003) was found between the level of RF under rest and the change in percent point of RF from rest to exercise, see Figure 18. Concordantly, a strong linear correlation (R^2= 0.65, p=0.001) was also seen between the level of RF under rest and percent change in net SV from rest to exercise, see figure 19. Patients with more severe AR under rest had significantly higher increase in net SV during submaximal exercise. A similar correlation was found between RF at rest and change in net CI (R^2= 0.64, p=0.001), which by definition is closely related to net SV, see Figure 19 and Figure 20.

Patient No.	ΔHR (%)	ΔEDVI (%))	ΔESVI (%)	ΔEF (%)	ΔnSV (%)	ΔfSV (%)	ΔnCI (%)	ΔfCI (%)	ΔRF (%)
1	46	-19	-23	3	52	-6	121	36	-35
2	30	-4	-39	13	-10	-11	16	15	-4
3	22	-3	-2	0	24	7	51	29	-21
4	3	-3	-11	15	0	-4	3	-1	-26
5	27	-9	-18	5	35	2	69	29	-49
6	34	-18	-32	56	80	16	141	55	-75
7	23	-25	-34	7	-7	-9	15	12	-23
8	80	-22	-43	19	-8	-20	66	45	-49
9	22	4	-21	13	-21	-23	-4	-6	-13
10	27	-2	21	-9	14	1	45	28	-24
11	17	-8	-18	5	9	-1	27	15	-20
12	41	-2	-6	2	55	3	118	46	-70

Table 10: Patients' individual changes in hemodynamic responses, expressed as percent changes. NSV= net SV, FSV=forward SV, NCI net CI, FCI=forward CI

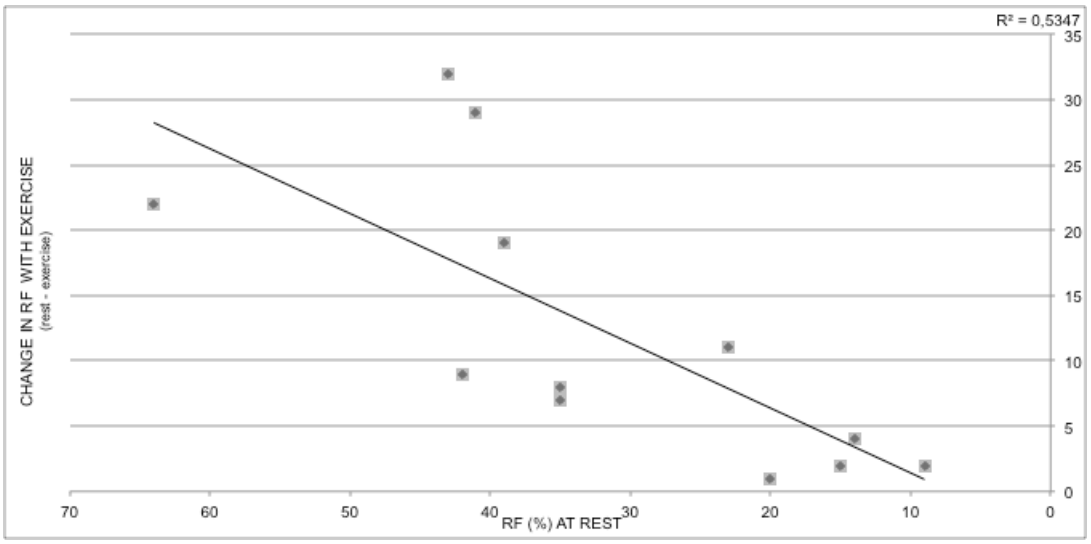

Figure 18: Correlation between the level of RF under rest and the change in percent point of RF from rest to exercise

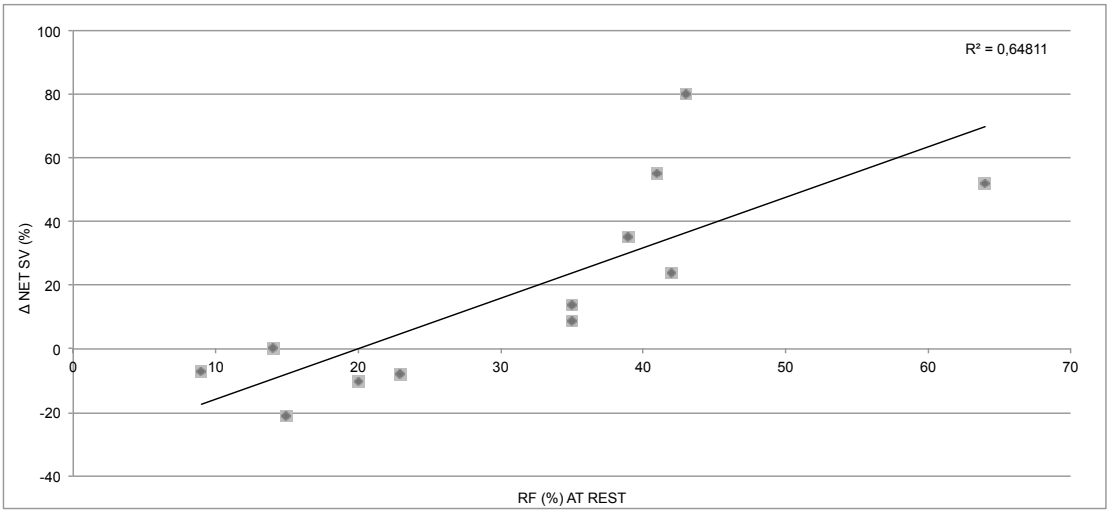

Figure 19: Correlation between the level of RF under rest and the change in percent point of net SV from rest to exercise

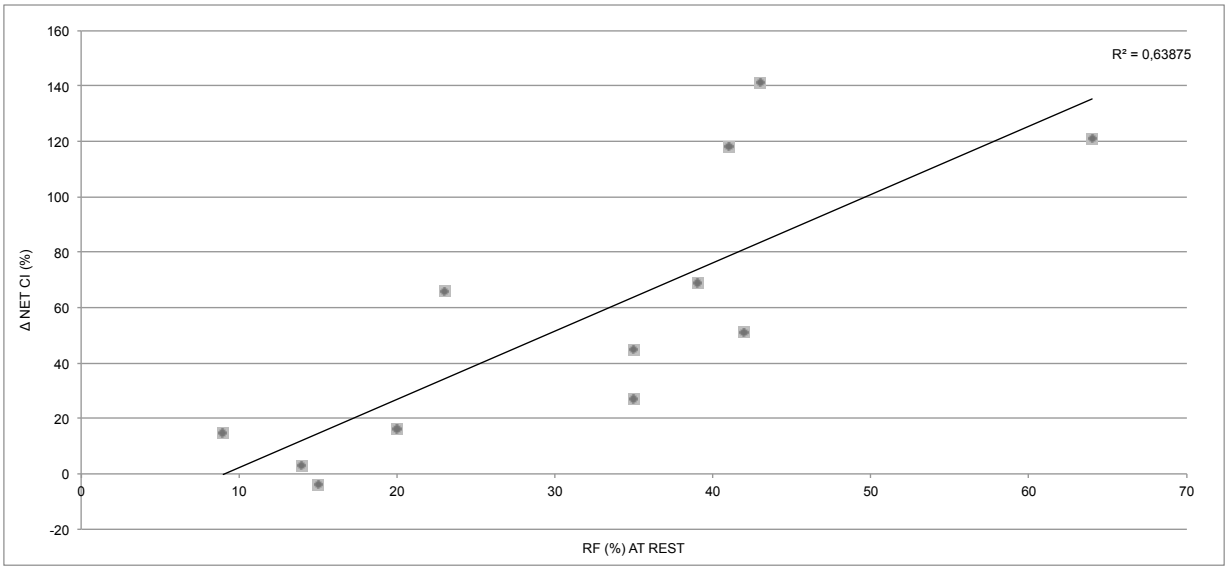

Figure 20: Correlation between the level of RF under rest and the change in percent point of net CI from rest to exercise

4 Discussion

4.1 Hemodynamic response to steady-state submaximal exercise

Exercise requires an expenditure of energy above resting values. This necessary energy is mostly provided through the use of oxygen. In order to meet the higher demand of oxygen, more blood has to be delivered to the active muscle tissue (Plowman, Smith 2014, p. 353). This response to exercise can be measured as an increase in cardiac output, or CI, when indexed to BSA. As equation 6 and 7 above have demonstrated, cardiac output is the product of stroke volume and heart rate. While athletes can increase cardiac output through an increase in heart rate and SV, healthy, but untrained adults increase cardiac output mainly through an increase in heart rate alone, which rises proportionally with the level of exercise. Increased cardiac output then, in return, raises arterial blood pressure. The mechanism responsible for the regulation of cardiac output in healthy adults are shown in Figure 21.

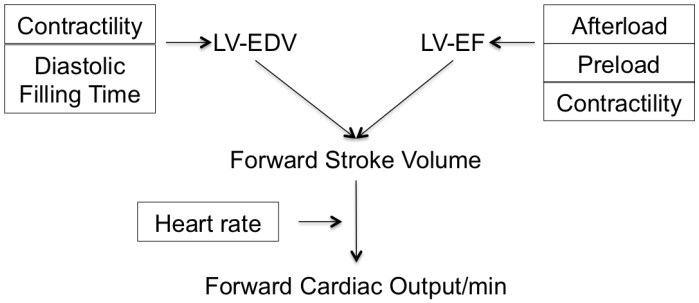

Figure 21: Regulation of cardiac output under exercise in healthy adults

This study's group of healthy controls performed as this theory would lead to expect. Volumetric parameters remained mostly unchanged under exercise, as did median stroke volume. Heart rate increased as response to the exercise and cardiac output, in their case net and forward CI being identical, increased significantly. Systolic and diastolic blood pressure also increased slightly.

To interpret the hemodynamic response to exercise in AR patients, it is valuable to take a look at their resting parameters first. Their baseline characteristics, such as age and body measurements did not differ from the controls'. Median heart rate was slightly, but not significantly higher in patients compared to healthy volunteers (72/min versus 64/min). This could possibly be tied to nervousness in that group, as members of the control group were already well acquainted with the CMR procedure. It could also be interpreted as a inherent compensation mechanism to reduce regurgitation. Diastolic blood pressure was slightly, but also not significantly lower in patients (53mmHg versus 60mmHg), possibly a result of the aortic backflow during diastole. Volumetric measurements at rest showed significantly higher values for end-diastolic and end-systolic LV volumes than controls, confirming the volume overload accompanying chronic AR. Median as well as all individual values of ejection fraction were within normal range in patients. Flow measurements presented the most interesting findings at rest. While net SV ($p=0.010$) and net CI ($p=0.0.045$) were larger in controls, forward SV ($p=0.755$) and forward CI ($p=0.028$) were larger in patients. These findings correlate well with the previously outlined pathophysiology of chronic AR. Net SV and CI are compromised due to the regurgitant volume. The elevated forward SV and CI values can be explained by the Frank-Starling mechanism (Flesch 2011, p.441). The regurgitant volume leads in to a higher end-diastolic LV Volume, i.e preload, resulting in a rise in contractility, and in succession, a larger forward stroke volume. Consequently, forward SV and CI are increased.

Under exercise patients' vital parameters did not differ from the controls', they increased comparably. Besides this, the reduction of regurgitant flow under exercise ($p=0.002$) was the most consistent finding among patients. Median regurgitation fraction decreased from 35% to 16%. All further registered hemodynamic changes in the patient group can be related to this reduction in RF.

Net CI increased significantly under exercise. This can, in part, be tied to tachycardia, but in contrast to the control group, not alone. As regurgitations goes down, net SV, being the difference between forward and regurgitant SV, consequently increases, Therefore, when studied as a group, AR patients increased their cardiac output, not only through tachycardia, but also by an increase in net SV.

However, while this can be concluded for patients as a group, individual parameters varied considerably among them. For example, in patient 10, the increase in net CI was primarily due to tachycardia and to a lesser extent to the increase in net SV. In patient 1, the increase in heart rate and net SV contributed almost equally to the increase of net CI. In patient 8 the increase in net CI was due only to tachycardia, since in this patient net SV actually decreased under exercise.

Median end-diastolic and end-systolic volumes decreased significantly under exercise in patients. This, too, can be tied to the reduced aortic backflow, as there is less volume remaining in the left ventricle. The mechanisms responsible for the regulation of cardiac output in patients with AR are represented in Figure 22, adapted from (Iskandrian et al. 1984, p.580)

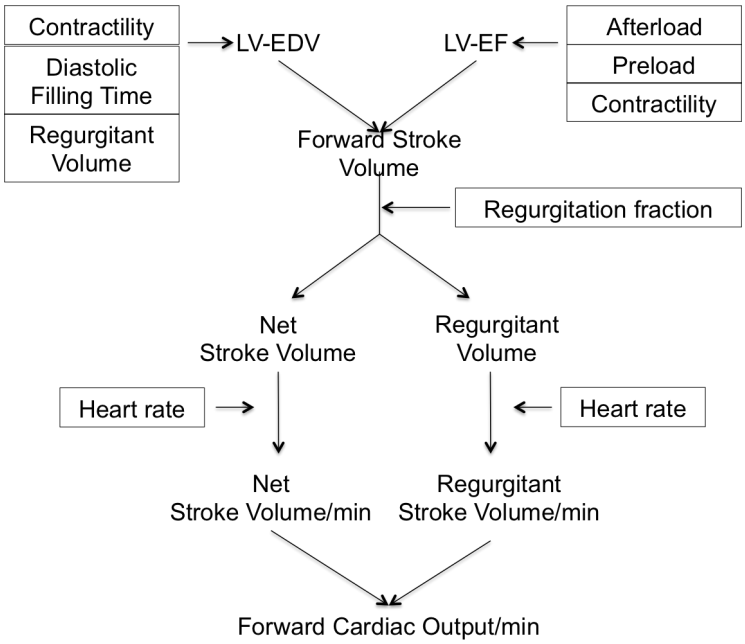

Figure 22: Regulation of cardiac output under exercise in patients with chronic AR

4.2 The effect of tachycardia on regurgitant fraction

Patients with aortic regurgitation often remain asymptomatic for a long period of time and show good preservation of exercise tolerance. As illustrated in the above section, the reduction of regurgitation faction plays a vital role in their hemodynamic adaptation to exercise. Tachycardia with a consequent shortening of diastolic filling period under exercise has repeatedly been suggested as the underlying mechanism behind this. Almost two centuries ago, in 1832, Dominic Corrigan made the following observation: *"The danger of the disease [aortic regurgitation] is in proportion to the quantity of blood that regurgitates and the quantity that regurgitates will be large in proportion to the degree of inadequacy of the valves and to the length of pause between the contractions of the ventricle during which the blood can be pouring back. If the action of the heart be rendered very slow, the pause after each contraction will be long, and consequently the regurgitation of blood must be considerable. Frequent action of the heart, on the con-*

trary, makes the pause after each contraction short; and in proportion as the pauses are shortened, the regurgitation must be lessened. (Corrigan 1832, p. 238)“

In the early 1970s Judge et al. tried to confirm Corrigan’s hypothesis using rapid atrial pacing to shorten diastolic filling time in eight patients with chronic AR. Regurgitant flow was estimated using quantitative angiocardiography. A decrease in regurgitant flow per heart beat was registered in five patients under tachycardia (Judge et al. 1971, p. 363). Firth et al. also studied the effects of atrial pacing in 12 patients with chronic AR. The regurgitation volume was calculated as the difference between gated radionuclide ventriculographic forward stroke volume and simultaneously measured thermodilution net stroke volume. Incremental increase in heart rate resulted in progressive decrease in regurgitation per heart beat in all patients. Regurgitant volume per minute, however, did not decrease. (Firth et al. 1982, p. 1864). Levinson et al. were the first to measure regurgitant fraction under actual physical exercise (Levinson et al. 1970). Two National Institute of Health (NIH) catheters were put in place, one just distal to the aortic valve, the other into the left-ventricular apex. Regurgitant flows were then measured by upstream and downstream dye dilution with continuous infusions of indocyanine green during maximum supine exercise and at rest. A uniform rise of regurgitation fraction from exercise to rest was shown in all ten patients.

Up to this point, all approaches to estimate aortic regurgitant volume had involved cardiac catheterization. Examinations were time-consuming, imprecise and most importantly, highly invasive. Around the same time, several research laboratories began examining left ventricular function under exercise using radionuclide ventriculography (Borer et al. 1978; Dehmer et al. 1981; Iskandrian et al. 1983). Steingart et al. were the first to also examine regurgitant flow using this approach (Steingart et al. 1983). Regurgitant index was estimated by calculating the ratio of right and left ventricular stroke counts. 20 Patients with isolated AR were examined a rest an under maximum supine bicycle exercise. The regurgitant index decreased during exercises in all 20 patients. Later, Iskandiran et al., Gerson et al., and Kawanishi et al. performed similar studies. Although changes of volumetric measurements varied between them, all studies showed a uniform decrease of regurgitant flow under exercise (Gerson et al. 1984; Iskandrian et al. 1984; Kawanishi et al. 1986). With technological advancement, echocardiography gradually replaced radionuclide ventriculography as routine diagnostic modality in AR. It, however, does not allow quantification of regurgitation, and until this study, aortic regurgitation volume of fraction had no longer been studied under exercise.

The main finding of this study, a uniform decrease of regurgitation volume under exer-

cise aligns well with the mentioned exercise studies of the 1970s and 1980s. Another finding of this study correlates well with previous results. In our study population, the resting regurgitation had a strong linear correlation with its percent point decrease under exercise (Figure 18: Correlation between the level of RF under rest and the change in percent point of RF from rest to exercise). Also, a strong linear correlation between regurgitation fraction at rest and change in net stroke volume as well as change in net cardiac index under exercise could be seen. Steingart et al. and Gerson et al came to comparable conclusions. Both saw a significant correlation between the level of decrease in regurgitation and its original value (Steingart et al. 1983; Gerson et al. 1984). Gerson et al. gave a possible explanation for this phenomenon. Because most aortic regurgitant flow occurs early in diastole, a shorter diastole has most hemodynamic effect on severe, longer lasting aortic insufficiency. The individual flow-time graphs generated in this study confirm this theory. Figure 23: Aortic flow over the cardiac cycle in patient 6 depicts resting and exercise aortic flow graphs of patient 6. Systole stays almost unchanged under exercise. Diastole, however, is considerably shorter, thus giving aortic backflow less time to take place. In this particular case, only about one third of the original backflow takes place under exercise before the next heart beat begins. Regurgitation decreased from 49ml to 14ml under exercise in this particular patient. Also, regurgitation volume/min decreased from 3.5l to 1.3 liters in this patient. Median regurgitation volume/min in patients decreased significantly from 2.4 (range 0.5-6.4) l to 1.7 (range 0.5 to 6.5) l, deviating from Firth et al.'s finding of no change in regurgitation volume/min under atrial pacing. A reason for the deviating results under atrial pacing might lie in the increase in venous return induced by physical exercise, however patient populations are too small to jump to conclusions.

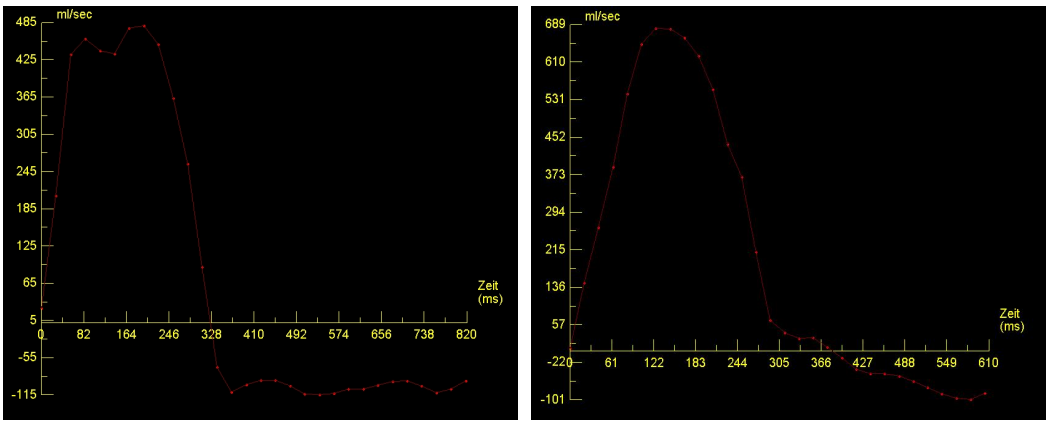

Figure 23: Aortic flow over the cardiac cycle in patient 6

Regurgitation has been assumed to decrease under exercise due to the induced tachycardia for almost two centuries. A few studies in the 1970s and 1980s, using cardiac

catheterization or radionuclide ventriculography, have confirmed Corrigan's hypothesis. The aim of this study was to evaluate aortic regurgitation under exercise using CMR as a new image modality for this question. The results regarding regurgitant volume under exercise are in good agreement with earlier findings. It is important to note, that all mentioned studies described the hemodynamic response to maximal exercise. This study has shown, that the described effects of exercise already occur at a very mild level of exhaustion, as it is present during most activities of daily living.

4.3 Left ventricular response to exercise in aortic regurgitation

Timing of aortic valve replacement and the search for reliable parameters to predict postoperative outcome have been a central theme in AR research for the past decades. This study is not intended to determine factors of postoperative mortality. However, in the quest for valuable predictive parameters exercise testing has become a frequently advocated approach. Radionuclide ventriculographic (Borer et al. 1978; Borer et al. 1979; Wilson et al. 1988; Borer et al. 1998; Tamás et al. 2009) and more recent echocardiographic exercise studies (Wahi et al. 2000; Forsberg et al. 2013; Kusunose et al. 2014) provide data about left ventricular function under exercise in chronic AR. A consensus about reliable exercise parameters as predictors of postoperative LV dysfunction has not yet been found and data is not always consistent. The existing data shall be used to briefly assess this study's results on LV volume and LV function under exercise.

In the patient group, median end-diastolic and end-systolic volumes decreased significantly. Ejection fraction, defined by their difference, increased slightly, but significantly. A reduction in end-diastolic volume under exercise can be seen in the vast majority of available exercise studies and there is wide agreement about its origin. With regurgitation reduced during exercise there is less volume remaining in the left ventricle at the end of diastole. Results on end-systolic volumes and ejection fraction, however, vary among studies, as do opinions about their implications. Decrease of LV-EF during exercise has been suggested as a marker of impending ventricular dysfunction, as the exercise EF and the change in EF from rest to exercise are often abnormal, even in asymptomatic patients (Bonow et al. 1991, p.1629; Tornos et al. 1995, p.337; Borer et al. 1998, p.529; Bonow 2013, p.698). They have, however, not been verified to have any independent prognostic value as long as LV function at rest and severity of volume overload estimated by echocardiography are already known (Bonow et al. 2008, p. e553). In this study, ejection fraction increased with exercise in 11 of 12 patients. In the

same 11 patients ESVI decreased comparably to EDVI. Such a decrease of end-systolic volume under exercise has been discussed to be evidence of good contractile reserve. In the presence of myocardial damage, a reduction in preload, that is end-diastolic volume, could lead to a deterioration of LV function, ejection fraction would then decrease and end-systolic volume remain unchanged or even increase. However, data supporting this hypothesis have been gathered using maximal exercise and are therefore not comparable to results in this study.

4.4 Clinical implications

Timing of aortic valve replacement remains a topic of great discussion among experts. Currently unquestioned indications for surgery include the development of symptoms and beginning of LV-dysfunction, represented by an impairment of ejection fraction (Nishimura et al. 2014, p. e86). In patients with AR and a history of equivocal symptoms exercise stress testing used to be recommended for assessment of functional capacity and symptomatic response. Therefore, when using stress testing as selection criterion it has to be recognized, that development of symptoms under exercise is expected. However, as shown in our study, AR decreases during exercise. Even more, patients with higher degree of RF across the aortic valve showed a more pronounced increase in cardiac output, compared to patients with less aortic regurgitation. This means, that the increase in cardiac output during submaximal exercise was more pronounced in more diseased patients. A possible answer to this paradox might lie in the patient selection of this study. In order to investigate hemodynamic changes of chronic AR, patients with other cardiovascular diseases, including relevant aortic stenosis were excluded from the study. However, commonly AR patients show signs of concomitant aortic valve stenosis. Therefore, development of symptoms under exercise is most probably not related to the level of insufficiency but the severity of concomitant stenosis. Possibly taking this into account, present guidelines do not recommend exercise stress testing in AR anymore.

In addition to its clinical use in testing for symptoms, exercise stress testing, mostly used in combination with echocardiography, is repeatedly used in research settings. Echocardiography, however, cannot quantify regurgitation, and is difficult to apply until after exercise is completed, thereby slightly changing registered hemodynamic data. This study served as a pilot study to evaluate the applicability of the developed CMR exercise apparatus. CMR is known to be an accurate non-invasive method for evaluation of AR and LV-function at rest. This study has shown that evaluation of those parameters under continuous steady state submaximal exercise is possible without waiv-

ing image quality. The observed hemodynamic response to exercise in healthy volunteers and patients fitted well with previously gathered data and current concepts of cardiac physiology.

As timing of AVR remains an unanswered question, exercise testing in CMR might be able to reveal further insight in the hemodynamic specifics of chronic AR. As the described exercise apparatus has been shown to be reliable and applicable, a prospective study with a larger patient population and post-operative follow up might proof to be of value.

4.5 Limitations

This study had the aim to evaluate hemodynamic changes to exercise in patients with aortic regurgitation. The applied exclusion criteria were chosen to improve the quality of the study and to avoid other sources for abnormal hemodynamic changes under exercise other than isolated aortic regurgitation. The study population is therefore not representative for the overall population of AR patients results should only with caution be applied in patients with concomitant valve disease or coronary artery disease.

Although appropriate non-parametric statistical tests with respect to the small group size were used, the number of patients available limited the ability to perform multivariate and subgroup analyses, results should be interpreted accordingly.

The hemodynamic adjustments to leg exercise in a supine position are manifold and complex. The results and theoretical deliberations of this study cannot and do not claim to capture these entirely.

5 Summary

Cardiovascular magnetic resonance with data acquisition a rest and during steady-state submaximal exercise was performed in 12 healthy controls and 12 asymptomatic patients with isolated chronic AR. Net and regurgitant stroke volumes as well as end-diastolic and end-systolic volume index were measured directly from CMR images, remaining flow and volume parameters were subsequently calculated. Resting regurgitation fraction in patients ranged from 9 to 64%. EDVI (p=0.017) and ESVI (p=0.002) at rest were markedly elevated and net CI slightly lower (p=0.045) in the patient group. During exercise, heart rate in healthy volunteers (p=0.008) and patients (p=0.008) increased comparably, and diastolic filling period shortened during submaximal exercise in both groups. In patients, regurgitation volume (p=0.002), regurgitation volume per minute (p=0.023) as well as regurgitation fraction (p=0.002) decreased significantly and uniformly during exercise. EDVI (p=0.004) and ESVI (p=0.009) decreased and ejection fraction (EF) improved slightly (p=0.009) under exercise in patients. A linear correlation (R^2= 0.53, p=0.003) was found between the level of RF under rest and the change in percent point of RF from rest to exercise. Concordantly, a strong linear correlation (R^2= 0.64, p=0.001) was also seen between the level of RF under rest and percent change in net SV from rest to exercise.

Patients with chronic aortic regurgitation often remain asymptomatic for a long period of time and show good preservation of exercise tolerance. Tachycardia with a consequent shortening of diastolic filling has been suggested as the underlying mechanism. This study confirms this hypothesis. Patients increased their cardiac output during exercise not only by elevation of heart rate, but also through a reduction in regurgitation and a consequent increase in net stroke volume. Exercise testing in CMR is possible without waiving image quality and offers great potential that has not yet been realized in in routine clinical practice and research settings.

6 Zusammenfassung

Bei 12 gesunde Probanden und 12 asymptomatischen Patienten mit isolierter Aortenklappeninsuffizienz wurde eine kardiovaskuläre Magnetresonanzuntersuchung mit Datenerhebung in Ruhe und unter steady-state submaximaler Belastung durchgeführt.

Das Netto-Schlagvolumen und Regurgitationsvolumen sowie das end-diastolische und end-systolische Volumen wurden direkt aus den CMR-Bildern bestimmt, die restlichen Fluss- und Volumenmessungen wurden anschließend abgeleitet.

In Ruhe lag die Regurgitationsfraktion der Patienten zwischen 9 und 64%. EDVI (p=0.017) und ESVI (p=0.002) der Patientengruppe waren in Ruhe deutlich höher und der Netto-Herzindex leicht geringer (p=0.045) als in der Kontrollgruppe.

Unter submaximaler Belastung stieg die Herzfrequenz der gesunden Probanden (p=0.008) und Patienten (p=0.008) vergleichbar an. Die diastolische Füllungsperiode verkürzte sich in beiden Gruppen.

In der Patientengruppe reduzierte sich das absolute Regurgitationsvolumen (p=0.002), das Regurgitationsvolumen pro Minute (p=0.023) sowie die Regurgitationsfraktion (p=0.002) signifikant und uniform unter Belastung. EDVI (p=0.004) und ESVI (p=0.009) sanken ebenfalls und die EF verbesserte sich leicht (p=0.009). Es ließ sich eine lineare Korrelation (R^2= 0.53, p=0.003) zwischen dem Ruhelevel der RF und der prozentualen Reduktion der RF unter Belastung nachweisen. Übereinstimmend lag auch eine starke Korrelation (R^2= 0.64, p=0.001) zwischen dem Ruhelevel der RF und der prozentualen Anstiegs des Netto-Schlagvolumens vor.

Patienten mit chronischer Aortenklappeninsuffizienz sind häufig lange Zeit asymptomatisch und weisen eine gute Belastbarkeit auf. Tachykardie mit der damit zusammenhängenden Verkürzung der Diastole wurde bereits früh als der für die gute Belastbarkeit verantwortliche Mechanismus vermutet. Die Studie belegt diese Hypothese. Die Patienten erhöhten ihren Herzindex unter Belastung nicht allein durch einen Anstieg der Herzfrequenz, sondern auch durch eine Reduktion der Regurgitation und daraus folgend mit einem Anstieg des Netto-Schlagvolumens.

Belastungsuntersuchungen in der Kardiovaskulären Magnetresonanz sind ohne Einschränkung der Bildqualität möglich und bieten ein großes, noch nicht genutztes Potential in Klinik und Forschung.

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Appendix A

Volunteer No.	Sex	Age at study	Body weight (kg)	Body height (cm)
1	M	39	72	178
2	M	35	95	180
3	F	25	53	170
4	M	23	70	188
5	M	26	75	185
6	F	24	54	165
7	M	22	75	182
8	F	25	65	172
9	M	20	85	186
10	M	26	80	188
11	M	27	71	171
12	M	22	65	169

Table 11: Volunteer’s baseline characteristics

Patient No.	Sex	Age at study	Body weight (kg)	Body height (cm)	AR° in echo	AR in CMR (%)	Vmax (m/s)
1	M	40	77	178	II-III	64	-
2	M	29	83	192	III	20	-
3	M	21	81	180	III	42	3,8
4	M	10	43	140	I-II	14	-
5	M	27	63	172	III	39	-
6	M	18	58	179	III	43	3,4
7	M	23	64	168	II	9	-
8	M	29	75	199	II-III	23	-
9	F	19	69	169	II	15	2,2
10	F	31	55	177	III	35	3,0
11	M	11	29	136	III	35	-
12	M	11	38	152	III	42	3.3

Table 12: Patients's baseline characteristics

Appendix B

The echocardiographic quantification of stenosis severity is done in terms of pressure gradients, which are calculated with the modified Bernoulli equation (equation (8)). The original Bernoulli equation is a complex formula that relates the pressure drop or gradient across an obstruction to many factors (equation (1)). For practical use in echocardiography the formula has been simplified. Equation (7) shows the first modification. The term Δp is the difference in pressure between a point before the obstruction (p_1) and within (p_2). The term ϱ represents the specific density of the fluid, and v_1 and v_2 are the flow velocities before and within an obstruction. Equation (8) shows the final formula that is usually used to calculate pressure gradients in cardiology. The term ϱ has been substituted with the specific density of blood, and the flow velocity before the obstruction, that is before the valve, is assumed to be negligible low and has been omitted. (Flachskampf 2011, pp.28-30)

$$p_1 - p_2 = \frac{1}{2}\varrho(v_1^2 - v_2^2) + \varrho \int_1^2 \frac{d \cdot v(s,t)}{d \cdot t} d \cdot s + R(v) \qquad (7)$$

$$\Delta p = \frac{1}{2}\varrho(v_1^2 - v_2^2) \qquad (8)$$

$$\Delta p = 4 \cdot v_2^2 \qquad (9)$$

As described earlier, the forward LV SV in patients with AR is increased to compensate for the regurgitation. A larger volume flow leads to a higher flow velocity, as derived in equation (9) and (10).

$$m = \varrho \cdot \mathrm{V} \qquad (10)$$

$$\frac{dm}{dt} = \varrho \cdot \frac{dV}{dt} = \varrho \cdot A \cdot \frac{dx}{dt} = \varrho \cdot A \cdot v \qquad (11)$$

Due to the increased volume flow, not only v_2 but also v_1 is very high, but since the latter is neglected in the calculation of, the pressure gradient appears falsely high (Flachskampf 2011, p.355).

Appendix C

	Rest			Submaximal Exercise		
Volunteer No	HR (1/min)	BPsys (mmHg)	BPdia (mmHg)	HR (1/min)	BPsys (mmHg)	BPdia (mmHg)
1	65	103	59	91	124	72
2	62	103	60	93	129	78
3	60	107	54	80	127	55
4	84	114	70	91	136	74
5	58	102	52	74	104	59
6	91	126	81	115	143	94
7	68	112	54	98	126	43
8	66	103	60	98	121	74
9	59	110	51	76	129	63
10	57	111	57	71	122	77
11	75	115	62	89	119	66
12	63	110	60	79	111	79

Table 13: Volunteer's vital parameters at rest and under submaximal exercise

	Rest			Submaximal Exercise		
Patient No	HR (1/min)	BPsys (mmHg)	BPdia (mmHg)	HR (1/min)	BPsys (mmHg)	BPdia (mmHg)
1	57	134	62	83	155	78
2	64	121	51	83	129	68
3	63	120	47	76	121	56
4	87	105	65	90	99	65
5	64	119	51	81	124	62
6	71	102	50	95	107	64
7	78	111	59	96	108	64
8	75	110	60	135	160	90
9	73	97	49	89	105	57
10	70	97	56	89	102	62
11	82	111	55	96	n.a.	n.a.
12	80	105	42	113	123	57

Table 14: Patient’s vital parameters at rest and under submaximal exercise

Appendix D

	Rest	Submaximal Exercise
Volunteer No	Diastole (ms)	Diastole (ms)
1	490	400
2	610	440
3	560	300
4	560	370
5	360	190
6	420	290
7	440	300
8	650	410
9	710	540
10	510	330
11	520	300
12	400	270

Table 15: Volunteer's diastolic filling time at rest and under submaximal exercise

	Rest	Submaximal Exercise
Patient No	Diastole (ms)	Diastole (ms)
1	610	380
2	700	370
3	510	350
4	460	350
5	570	460
6	490	220
7	610	420
8	429	340
9	400	280
10	500	350
11	500	250
12	330	320

Table 16: Patient's diastolic filling time at rest and under submaximal exercise

Appendix E

	Rest				Submaximal exercise			
Volunteer No.	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	SVI(vol) (ml/m^2)	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	SVI(vol) (ml/m^2)
1	68	19	72	49	75	15	79	60
2	70	27	61	42	59	22	62	37
3	79	20	74	59	70	15	78	55
4	59	16	73	43	61	17	72	44
5	70	17	76	53	78	16	80	62
6	74	17	77	56	66	21	68	45
7	86	29	66	57	75	26	65	49
8	68	23	65	45	53	13	76	40
9	99	34	66	65	100	32	68	69
10	86	26	69	60	73	21	72	52
11	79	18	77	61	84	17	79	67
12	73	15	80	58	77	23	70	54

Table 17: Volunteer's volumetric measurements at rest and under submaximal exercise

	Rest				Submaximal exercise			
Patient No.	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	SVI(vol) (ml/m^2)	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	SVI(vol) (ml/m^2)
1	193	66	66	127	156	51	67	105
2	181	49	73	133	173	30	83	144
3	160	49	69	111	155	48	69	107
4	58	21	64	37	56	15	74	41
5	138	48	65	90	126	39	69	87
6	131	37	72	94	107	25	77	82
7	73	27	63	46	55	18	68	38
8	101	42	58	59	79	24	69	55
9	52	18	65	34	54	14	73	40
10	93	26	72	67	91	32	65	59
11	105	28	73	77	97	23	77	74
12	134	39	71	96	131	36	72	95

Table 18: Petient’s volumetric measurements at rest and under submaximal exercise

Appendix F

	Rest					Submaximal exercise				
Volunteer No.	fSV (ml)	nSV (ml)	RF (%)	nCI (l/min/m^2)	fCI (l/min/m^2)	fSV (ml)	nSV (ml)	RF (%)	nCI (l/min/m^2)	fCI (l/min/m^2)
1	113	112	1	3.9	3.9	111	110	1	5.3	5.3
2	101	101	0	2.9	2.9	90	88	3	3.7	3.8
3	101	101	0	3.8	3.8	95	95	0	4.8	4.8
4	88	87	1	3.8	3.9	89	89	0	4.2	4.2
5	104	104	0	3.1	3.1	112	112	0	4.2	4.2
6	87	87	0	5.0	5.0	90	90	0	6.6	6.6
7	106	106	0	3.7	3.7	98	97	1	4.9	4.9
8	86	86	0	3.2	3.2	83	83	0	4.6	4.6
9	127	126	1	3.6	3.6	138	135	2	4.9	5.0
10	128	128	0	3.6	3.6	123	122	1	4.2	4.3
11	122	122	0	5.0	5.0	114	114	0	5.5	5.5
12	86	85	1	3.1	3.1	83	82	1	3.7	3.7

Table 19: Volunteer's flow measurements at rest and under submaximal exercise

	Rest					Submaximal exercise				
Patient No.	fSV (ml)	nSV (ml)	RF (%)	nCI (l/min/m^2)	fCI (l/min/m^2)	fSV (ml)	nSV (ml)	RF (%)	nCI (l/min/m^2)	fCI (l/min/m^2)
1	172	62	64	1.8	5.0	161	94	42	4.0	6.8
2	169	136	20	6.0	7.4	150	122	19	7.0	8.5
3	239	138	42	4.3	7.5	256	171	33	6.5	9.7
4	51	44	14	3.0	3.4	49	44	10	3.1	3.4
5	132	80	39	3.0	4.9	135	108	20	5.0	6.3
6	115	66	43	2.8	4.8	133	119	11	6.7	7.4
7	76	69	9	3.1	3.4	69	64	7	3.6	3.8
8	117	90	23	3.0	4.3	94	83	12	5.5	6.2
9	78	66	15	2.7	3.2	60	52	13	2.6	3.0
10	108	70	35	3.0	4.6	109	80	27	4.3	5.9
11	69	45	35	3.6	5.5	68	49	28	4.5	6.3
12	94	55	41	3.5	5.9	97	85	12	7.6	8.7

Table 20: Patient’s volumetric measurements at rest and under submaximal exercise

Appendix G

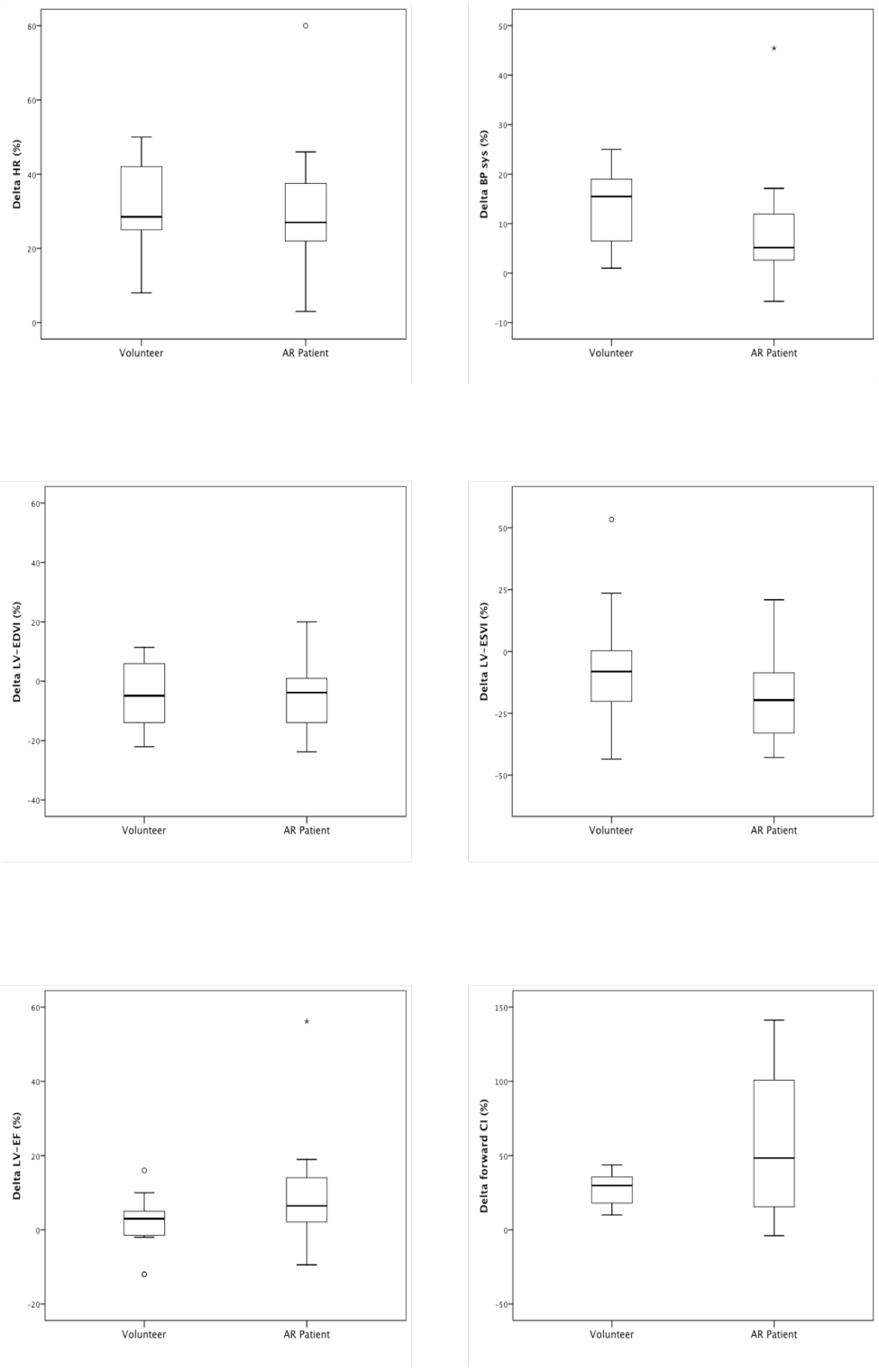

Figure 24: Relative percent changes HR, BPsys, LV-EDVI, LV-ESVI, LV-EF and net CI from rest to submaximal exercise in volunteers and patients

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