Cardiac Function and Aortic Valve Intervention

- Echocardiographic Studies of Myocardial Recovery in Patients with Severe Aortic Valve Disease

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There is nothing like looking, if you want to find something. You certainly usually find something if you look, but it is not always quite the something you were after.

J.R.R Tolkien
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Abstract

In patients with severe aortic valve disease, aortic valve intervention is performed when the risk for mortality or morbidity with conservative management is significantly increased. Left ventricular (LV) longitudinal motion decreases before conventional echocardiographic measures such as ejection fraction, are influenced in patients with severe aortic valve disease. This thesis is devoted to the assessment of cardiac function, including ventricular longitudinal motion, by echocardiography before and after aortic valve intervention in patients with chronic severe aortic regurgitation (AR) or severe aortic stenosis (AS).

Patients with chronic AR (n=29) were studied preoperatively, and 6 months and 4 years postoperatively by echocardiography, including tissue Doppler imaging, at rest and during exercise. LV longitudinal function (atrioventricular plane displacement, AVPD, and peak systolic velocity, PSV) decreased postoperatively, and patients with low PSV continued to show reduced longitudinal function 6 months after surgery. Preoperative exercise echocardiographic variables showed a strong correlation to late LV function variables, while preoperative variables obtained at rest were not useful for prediction. Exercise echocardiography and longitudinal LV function could therefore be useful complements in the timing of aortic valve surgery for AR.

Since 2002, transcatheter aortic valve intervention (TAVI) has been an alternative to conservative treatment in patients with symptomatic severe AS and high surgical risk. We studied pre- and postprocedural (7 weeks
and 6 months) left and right ventricular (RV) function in patients undergoing TAVI and included a matched patient group undergoing surgical aortic valve replacement (SAVR). Longitudinal LV function in the septal and lateral wall increased early after the procedure and remained unchanged after six months. Longitudinal RV function remained unchanged in the TAVI group but decreased in the SAVR group. When analyzing the transapical and the transfemoral TAVI approach separately, improved LV systolic and diastolic function were seen in the transfemoral patient group, while transapical patients showed unchanged ventricular function. Although longitudinal LV function improves after TAVI, postprocedural changes in longitudinal LV and RV function differ considerably between patient groups undergoing transfemoral, transapical or surgical aortic valve intervention.
Populärvetenskaplig sammanfattning

Aortaklaffssjukdomar (aortastenos och aortainsufficiens) är vanliga och antalet drabbade personer ökar med stigande ålder. Vid svår aortaklaffsjukdom kan patienten behöva genomgå en hjärtoperation där den sjuka klaffen byts ut mot en konstgjord klaff, s.k. klaffprotes, för att undvika förtida död eller allvarlig skada på hjärtmuskeln.

Populärvetenskaplig sammanfattning

Resultaten från avhandlingen kommer att kunna användas till att förbättra valet av tidpunkt för hjärtkirurgi hos patienter med aortainsufficiens.

Aortastenos innebär att klaffen inte öppnar sig fullt ut när hjärtat pumpar ut blodet från vänster kammare till kroppsputsåden. Patienter som har en mycket svår förträngning och som besväras av andfåddhet, bröstsmärta eller svimning behöver genomgå hjärtkirurgi, då risken för att annars dö i sjukdomen inom 1-3 år är över 50%. Denna patientgrupp har p.g.a. hög ålder också ofta andra sjukdomar och detta gör att hjärtkirurgi hos en viss grupp patienter innebär en hög risk för död i samband med operationen. Denna grupp av patienter har tidigare inte kunnat genomgå någon behandling. Sedan 2002 finns det en ny metod, som ger möjlighet att behandla denna patientgrupp och metoden kallas kateterimplantation av aortaklaffprotes (TAVI). I avhandlingen har hjärtfunktionen hos patienter som genomgått kateterimplantation studerats med hjärtultraljud dels före ingreppet och vid två tillfällen efter ingreppet. En återhämtning av hjärtats pumpförmåga kunde tydligt ses efter ingreppet. En försämring av högerkammarsunctionen, som är vanligt efter hjärtkirurgi, sågs inte efter kateterimplantationen utan istället sågs tecken på en förbättring.

Resultaten är viktiga då de ger detaljerad information om hjärtats återhämtning efter ett helt nytt sätt att behandla täta aortastenoser.
This thesis is based on the following publications, which will be referred to by their Roman numerals:

I. L Helin, É Tamás, E Nylander. Preoperative longitudinal left ventricular function by tissue Doppler echocardiography at rest and during exercise is valuable in timing of aortic valve surgery in male aortic regurgitation patients.

II. L Forsberg, E Nylander, É Tamás. Preoperative left ventricular function assessed by exercise echocardiography predicts late postoperative left ventricular remodeling in chronic aortic regurgitation patients.
   *Submitted*

III. L Forsberg, É Tamas, F Vánky, NE Nielsen, J Engvall, E Nylander. Left and right ventricular function in aortic stenosis patients 8 weeks post-transcatheter aortic valve implantation or surgical aortic valve replacement.

IV. L Forsberg, É Tamás, F Vánky, J Engvall, E Nylander. Differences in recovery of left and right ventricular function following aortic valve interventions – A longitudinal echocardiographic study in patients undergoing surgical, transapical or transfemoral aortic valve implantation.
   *Submitted*
## Abbreviations

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<tr>
<td>A</td>
<td>Late diastolic filling velocity</td>
</tr>
<tr>
<td>á</td>
<td>Late diastolic myocardial velocity</td>
</tr>
<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
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<td>AS</td>
<td>Aortic stenosis</td>
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<td>AVPD</td>
<td>Atrioventricular plane displacement</td>
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<td>AVR</td>
<td>Aortic valve replacement</td>
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<tr>
<td>BSA</td>
<td>Body surface area</td>
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<tr>
<td>DT</td>
<td>Deceleration time</td>
</tr>
<tr>
<td>E</td>
<td>Early diastolic filling velocity</td>
</tr>
<tr>
<td>é</td>
<td>Early diastolic myocardial velocity</td>
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<tr>
<td>EDD</td>
<td>End-diastolic dimension</td>
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<tr>
<td>EDV</td>
<td>End-diastolic volume</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>ESD</td>
<td>End-systolic dimension</td>
</tr>
<tr>
<td>ESV</td>
<td>End-systolic volume</td>
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<tr>
<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
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<tr>
<td>IVRT</td>
<td>Isovolumic relaxation time</td>
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<td>LV</td>
<td>Left ventricle/ ventricular</td>
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<td>MM</td>
<td>M-mode</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>Preop</td>
<td>Preoperative</td>
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<tr>
<td>Postop</td>
<td>Postoperative</td>
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<tr>
<td>PSV</td>
<td>Peak systolic velocity</td>
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<tr>
<td>PVd</td>
<td>Pulmonary vein peak diastolic velocity</td>
</tr>
<tr>
<td>PVs</td>
<td>Pulmonary vein peak systolic velocity</td>
</tr>
<tr>
<td>PWTd</td>
<td>Posterior wall thickness, diastole</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle/ ventricular</td>
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<tr>
<td>SAVR</td>
<td>Surgical aortic valve replacement</td>
</tr>
<tr>
<td>SWTd</td>
<td>Septal wall thickness, diastole</td>
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<tr>
<td>TAVI</td>
<td>Transcatheter aortic valve implantation</td>
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<td>TDI</td>
<td>Tissue Doppler imaging</td>
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<td>TT</td>
<td>Tissue tracking</td>
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<td>ΔAVPD</td>
<td>Atrioventricular plane displacement response to exercise</td>
</tr>
<tr>
<td>ΔEF</td>
<td>Ejection fraction response to exercise</td>
</tr>
<tr>
<td>ΔPSV</td>
<td>Peak systolic velocity response to exercise</td>
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Moderate or severe valve disease represents an important public health problem having a reported prevalence of 2.5% in a Western population. Moreover patients with valvular disease have an increased mortality risk in relation to expected survival. The prevalence of aortic valve disease increases with age, and since there is a steady increase in life expectancy, the prevalence of valvular disease is expected to rise.

Patients with established valvular disease require repeated follow-up imaging procedures to enable decision-making on long-term management. In some patients, the valvular disease will eventually progress to a severe grade with or without symptoms, and valvular intervention will be required to prevent morbidity and delay death. For this patient category major advances in diagnostics and diagnostic techniques, interventional cardiology and surgical procedures have evolved in recent decades.

The objective of this thesis was to evaluate ventricular function by echocardiography, before and after valve intervention in patients with severe aortic valve disease.
Left Ventricular Function

The cardiac pump is the result of contraction and relaxation of myocardial fibres organized in different directions and layers. With insufficient contraction during systole the forward volume will be too small. Moreover if relaxation of the left ventricle (LV) is incomplete during diastole filling will be suboptimal. Ventricular emptying and filling is a complex process with interdependence between systole and diastole, as well as between the right and left ventricle.

The myocardium of the LV is arranged in several layers with longitudinally and obliquely orientated fibres in the sub- and epicardium, and with circumferential fibres concentrated to the middle layer. LV pump function was, for many years, mostly attributed to the contractility of the circumferential myocardial fibres in the LV. However, ventricular contraction also occurs in the longitudinal direction and with a twisted motion called torsion resulting from the apex and the base rotating in opposite directions.

Although Leonardo da Vinci described the longitudinally oriented fibres, it is only recently that the importance of their contribution to LV function in both systole and diastole first gained interest.

Longitudinal LV Function

Lundbäck found in the 1990’s that the outer contour of the heart is practically unchanged during the cardiac cycle, while the atroventricular plane motion is significant. This longitudinal motion of the atroventricular plane involves a movement of the mitral annulus towards the apex in systole and towards the left atrium in diastole. The ventricular long axis motion contributes significantly to the total LV volume change during systole and diastole, and it has been suggested that without this...
contribution normal sarcomere shortening would lead to a shortening fraction of 12% and an EF less than 30%.8–10

The longitudinal movement is derived as atrioventricular plane displacement (AVPD) by M-mode echocardiography, myocardial peak systolic velocity (PSV) by tissue Doppler, and strain/strain rate by 2D speckle-tracking echocardiography or tissue Doppler.11

AVPD and PSV have both shown a strong correlation to measurements of global systolic function and are used in everyday clinical practice as measures of global and regional LV and RV function.12, 13 Both PSV and AVPD are age-dependent and fall with ageing in a healthy population.5, 14, 15 Measuring mean mitral annular velocities by averaging inferoseptal and anterolateral wall movements and by averaging velocities of the 4 myocardial walls, yielded similar results in a large healthy population.14

LONGITUDINAL LV FUNCTION DURING EXERCISE
Motion of the atrioventricular plane towards a relatively stationary apex in systole plays a significant role in LV pump function. During exercise echocardiography there is an increase in longitudinal motion and PSV has been reported to increase by 70–85 % from rest to submaximal exercise.16–19 Long axis function during exercise has shown to be valuable in detection of myocardial ischemia and heart failure with normal EF.19, 20

LONGITUDINAL LV FUNCTION IN DISEASE
Long axis LV function has shown to be a useful early marker of LV dysfunction in several cardiac conditions; valvular heart disease, heart failure with normal EF, myocardial ischemia, cardiomyopathy, hypertension, type 2 diabetes mellitus, and systemic diseases affecting the heart.6 The longitudinal fibres, located in the subendocardium, are suggested to be sensitive to increased wall stress induced by pressure or
volume overload in the LV. More, wall stress induces ischemia and fibrosis causing a decrease in long axis motion detectable by imaging technology.

**LV Diastolic Function**

The diastolic phase of the cardiac cycle takes place between aortic and mitral valve closure. When the aortic valve closes, the isovolumetric relaxation phase starts with a rapid drop in LV pressure due to energy-demanding relaxation of the myocardium. When LV pressure falls below the pressure in the left atrium the mitral valve opens and the rapid early filling phase starts. During this phase pressures in the ventricle and atrium equalize. When the heart rate is low there can be a period of diastasis, during which there is little movement of blood between the cavities. Atrial contraction then causes the mitral annulus to be pulled further from the apex and the difference in pressure between the atrium and ventricle increases again. In healthy young persons this phase is of little importance, whereas subjects with cardiac disease can be heavily dependent on the atrial contribution. When pressures in the two chambers have again equilibrated the mitral valve closes and systole begins.

**LV Diastolic Dysfunction**

Catheterization has long been the gold standard method for assessing diastolic function. Today, however, Doppler echocardiography is the technique mostly used due to its possibility to obtain data indirectly without invasive procedures. Systolic function is traditionally frequently assessed by one widely accepted parameter - ejection fraction (EF). Evaluation of diastolic function, however, is not so straightforward. When evaluating diastolic function it is necessary to bare in mind factors that influence LV filling such as breathing, heart rate, age and the PR
interval, as well as preload, LV systolic function, atrial contractile function and mitral valvular disease. LV diastolic dysfunction is first seen as ventricular relaxation disturbance, and if the cause of the dysfunction is not treated, increased diastolic filling pressures may supervene. By using echocardiographic variables diastolic dysfunction can be graded as disturbed relaxation (mild), pseudonormal filling (moderate) and restrictive filling (severe), (Figure 1).
Diastolic dysfunction appears early in cardiac disease and may be detected before changes in systolic function are seen. It has also been shown that diastolic function has prognostic value for both mortality and morbidity in a wide variety of cardiac diseases.23-26
Figure 1 Classification of LV diastolic function by echocardiography. Representative images from Doppler echocardiography (mitral inflow and pulmonary vein) and tissue Doppler imaging (TDI) in patients with normal diastolic function, disturbed relaxation pattern, pseudonormalization or restrictive filling pattern.
Right Ventricular Function

The right ventricle (RV) is thin-walled, crescent shaped, and embraces the LV. In contrast to the LV, the distribution of myocardial fibres is such that the longitudinal fibres have a more dominating role. RV function is more difficult to evaluate by echocardiography than LV function due to its complex shape and its anatomical position that makes echocardiographic visualization a challenge. However, longitudinal motion in the RV free wall by M-mode echocardiography (AVPD) or tissue Doppler (PSV) has been shown to correlate with RVEF as well as providing prognostic information in cardiac disease, and is now commonly used in the clinical setting.

RV Longitudinal Function and Cardiac Surgery

Reduced longitudinal motion of the RV free wall after open heart surgery is a common finding. Long-term follow up has shown that RV function continues to be depressed up to at least one year postoperatively. The reason for this phenomenon is unknown and two main theories have been postulated: myocardial damage (due to perioperative myocardial ischemia, cardioplegia, right atrial damage from cannulation) and changes in heart motion (due to sternotomy, pericardial disruption and adhesions). Furthermore, postoperative paradoxical septal motion has been suggested to be a compensatory mechanism for the surgically induced fall in longitudinal RV contraction, in order to maintain RV stroke volume.
Echocardiography

The first successful attempt to image the heart by ultrasound was made in 1954 by Edler and Hertz, although the theory behind ultrasound waves has been known since the 18th century. The first variant of echocardiography was electrocardiogram-synchronized M-mode. Since then echocardiography has undergone extensive development including such techniques as 2D, 3D and 4D echocardiography, Doppler echocardiography, transesophageal, tissue Doppler imaging, and contrast agents. Today the technique can produce such clear and detailed images that it seems as though one sees the heart directly, but in fact we are looking at images constructed through extensive mathematical and physical calculations.

Basic Physics

The ultrasound image is generated by the physical interaction of sound with tissues in the body. For sound to be audible for humans, it must have a frequency <20 000 Hz and sound with frequencies above this value is named ultrasound. The ultrasound used in medical imaging has a wave frequency of 1-20 MHz.

When sending high frequency sound from piezocrystals via a transducer through tissue, the waves are reflected and an echo formed. This echo is registered by a receiver in the transducer and converted to an image by computer technology. The quality of an echocardiographic image is dependent on the appropriateness of the ultrasound (frequency, wavelength), the interaction between ultrasound and tissue (acoustic impedance, reflection, scattering, refraction and attenuation), and the properties of the transducer. This is a combination of technical factors and the user.
Doppler Echocardiography

Doppler echocardiography is used to evaluate valvular and diastolic function. The technique is based on the Doppler principle that the frequency of the reflected ultrasound is altered by a moving target. This physical principle provides information on blood flow direction and velocity non-invasively. There are three Doppler echocardiography modalities (Figure 2):

Pulsed wave Doppler is used to measure velocities within a specific depth, but due to aliasing no maximal velocities can be estimated. The velocities can be estimated because the transducer alternates between sending and receiving signals. The length of the sending and receiving cycle is dependent on the depth of region of interest, equaling the position of the sample volume.

Continuous wave Doppler is used to measure maximal velocities by continuously transmitting and receiving signals. Localization of the origin of the registered velocities, however, is lost.

Pulsed and continuous wave Doppler are used to quantify flow velocities in the diagnosis of valve disease.\textsuperscript{40,41}

Color flow Doppler reveals pathological blood flow over a valve by color-coding the flow according to direction and mean velocities over a large region of interest.

TISSUE DOPPLER IMAGING

In the beginning Doppler echocardiography was mainly used to assess blood flow. Echoes from erythrocytes, the moving targets, have low amplitude and high frequency, and the high amplitude and low frequency signals from the moving myocardium were filtered to improve image quality. However, with improved technology it became possible to also register the ultrasound signal from the myocardium. This technique,
tissue Doppler imaging (TDI), estimates regional and global LV and RV function by measuring peak systolic velocity (PSV), early diastolic (é) and late diastolic myocardial velocities (á). TDI is applicable in the diagnosis of early reversible or irreversible LV dysfunction, myocardial ischemia, diastolic function and RV function.6

There are two TDI modalities in clinical use. Pulsed TDI measures the peak systolic and diastolic velocities in one separate segment with high

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**Figure 2** Examples of blood flow over the aortic valve by color Doppler (top), velocities in the left ventricular outflow tract by pulsed Doppler (left) and aortic flow velocity by continuous-wave Doppler (right).
temporal solution (Figure 3a). This method, however, is limited by low spatial resolution and can only record one segment at a time. 44 In color TDI (Figure 3b) each pixel of the Doppler spectrum is colored depending on myocardial velocity and direction. 45 Images can be saved for off-line analysis and, after choosing regions of interest, systolic and diastolic velocity profiles are obtained. However, instead of “true” peak systolic and diastolic velocities a calculated mean of the region of interest is given.

The TDI technique is clinically available, can objectively quantify LV regional function, and has shown satisfying reproducibility. The use of TDI is limited by the angle dependency of the Doppler technique and the possibility that velocities recorded are influenced by global heart motion (translation, torsion, rotation). 11

TISSUE TRACKING

By mathematical processing of the velocities in the pixels saved from color TDI, new color-coded information can be presented. By calculating the integral of the velocities, the distance which each segment moves can be visualized by color-coding. This method is called tissue tracking (TT) and provides the opportunity of a fast real-time presentation of longitudinal movement in the LV wall. By selecting a region of interest at the mitral annulus it is possible to quantify the total AVPD (Figure 3c). 46 Furthermore, tissue tracking provides the opportunity to obtain a fast overview of the total AVPD by color-coding the segments according to different ranges of longitudinal motion. Total AVPD by M-mode echocardiography and TT have shown a strong correlation and the reproducibility for TT has shown to be high. 37-49
**Figure 3** Different modalities of tissue Doppler imaging (TDI) recorded in the 4-chamber view. Example of (a) pulsed TDI and a velocity curve from the LV basal septal wall, (b) color TDI and a velocity curve from the basal septal wall, (c) tissue tracking showing displacement coded as different colors, and as a displacement curve.
Systolic AVPD by M-mode Echocardiography

The total AVPD is measured from the lowest to the highest point of contraction in the M-mode image. This total AVPD includes a diastolic contribution through atrial contraction and relaxation as well as an isovolumetric relaxation and postsystolic shortening after aortic valve closure. Together these two components have been shown to overestimate true systolic AVPD. Furthermore postsystolic shortening has been observed in patients with myocardial ischemia and hypertension, and contributes 11-14% to the total AVPD. In Figure 4 total and systolic AVPD are shown.

Figure 4 M-mode echocardiography is one available method to measure AVPD (left). The drawing to the right visualizes the differences between systolic AVPD (1) and total AVPD (2).

Stress Echocardiography

Stress echocardiography, either pharmacologic or exercise, can be used to assess inducible myocardial ischemia secondary to coronary artery disease. Moreover, the method is a non-invasive approach diagnosing the physiological effects of cardiac disease, including the significance of valvular stenosis, and to predict myocardial viability.
the supine position during bicycle exercise echocardiography, it is possible to save images during exercise. Exercise echocardiography is preferred because, in contrast to pharmacologic stress echocardiography, additional information regarding exercise capacity is obtained.
**Aortic Valve Disease**

The healthy aortic valve is a one-way entrance between the LV and the aorta. It normally consists of three leaflets: the left coronary, right coronary and non-coronary cusps. Over a lifetime the valve will open and close 3.3 billion times in a constantly high pressure system. This explains why the prevalence of aortic valve disease, both regurgitation and stenosis, increases with age. Cardiac auscultation remains the most widely used method for screening for valvular heart disease, and has shown acceptable sensitivity and specificity. However, after the primary diagnosis has been made, regular medical follow up and imaging investigations are necessary to evaluate progression rate and optimal timing of surgery so as to avoid the severe consequences of malfunction of the valve.

**Chronic Aortic Regurgitation**

Chronic aortic regurgitation (AR) is a state in which both preload and afterload are increased (Figure 5). An increase in LV end-diastolic volume (EDV) constitutes the major compensation for AR (preload). As consequences of increased EDV there are increased LV dimensions, increased LV compliance and myocardial hypertrophy. With increased LV volumes and dimensions there is a rise in wall stress according to Laplace’s law (afterload). Together the compensation mechanisms can balance the increased pre- and afterload over a long period without resulting in symptoms or a decreased LVEF. In the Framingham study the incidence of AR of any degree was 13% in men and 8.5% in women. Chronic AR can be either primary valvular or secondary to aortic root dilatation, the latter being the most common etiology in patients undergoing AVR today. Rheumatic disease used to
be the most frequent etiology of AR, but now it has been demonstrated that degeneration is by far the most frequent origin in AR. Each year 4.3% of severe AR patients develop symptoms or echocardiographic findings fulfilling the criteria for aortic valve surgery. Indications for aortic valve replacement (AVR) according to American and European guidelines are shown in Table 1. Optimal timing

![Schematic figures of the normal aortic valve and the aortic valve in aortic regurgitation (AR) and aortic stenosis (AS, upper). The pressure-volume loop in chronic AR: end-diastolic volumes (EDV) are increased due to filling from both the atrium and the aorta during diastole. The increase in EDV activates the Frank-Starling mechanism and so also the force of contraction, the peak systolic ventricular pressure and the stroke volume. As long as the ventricle can compensate the volume overload the end-systolic volume (ESV) is near normal. The pressure-volume loop in AS: a high outflow resistance, due to the decreased aortic valve opening during systole, leads to increased ventricular systolic pressure. This in turn increases afterload with subsequent decrease in stroke volume. The ESV increases and this results in increased EDV and activates the Frank-Starling mechanism with increased force of contraction compensating for the outflow resistance.](image-url)
of aortic valve surgery is essential, and surgery should be performed before irreversible damage to the LV myocardium occurs.

AORTIC REGURGITATION AND LONGITUDINAL LV FUNCTION

It has been shown that asymptomatic chronic AR patients can have reduced systolic LV function while maintaining a normal LVEF. This was found by studying longitudinal function assessed as PSV by TDI at rest in asymptomatic patients with normal EF. That longitudinal LV function is affected before EF declines can be explained by the fact that the subendocardial fibres, which perform longitudinal LV contraction, are exposed to the increased wall stress at an early stage, and that this initiates a fibrotic process.

AORTIC REGURGITATION AND EXERCISE ECHOCARDIOGRAPHY

During exercise demands on the cardiovascular system rise and a heart with healthy myocardium increases stroke volume by increasing end-diastolic volume (EDV) and decreasing end-systolic volume (ESV). Based on this the hypothesis has been made that exercise unmasks early LV dysfunction. Exercise data have been shown to be a better predictor of postoperative LV function than resting LV indices in this patient category. An abnormal EF response to exercise can be seen preoperatively in AR patients not fulfilling the guideline criteria for AVR, suggesting that exercise data are valuable in identifying early LV dysfunction. Moreover, it has been demonstrated that patients with a decrease in EF during exercise preoperatively, do not increase resting EF at postoperative follow up.
### Table 1 Indications of surgery for patients with chronic AR according to present guidelines from the American College of Cardiology* and the European Society of Cardiology†, 57,68

<table>
<thead>
<tr>
<th>Criteria for indication of surgery</th>
<th>Class</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Severe AR regardless of LVF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>Asymptomatic patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe AR and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. LV dysfunction (EF&lt;50%)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2. Normal LVF (EF&gt;50%) and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. LVEDD &gt;75 mm or LVESD &gt;55 mm</td>
<td>IIa*</td>
<td>B*</td>
</tr>
<tr>
<td>b. LVEDD &gt;70 mm or LVESD &gt;50 mm</td>
<td>IIa†/IIb*</td>
<td>C†/C*</td>
</tr>
<tr>
<td>Criteria 2a and 2b can be supported by signs of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Progressive LV dilatation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Declining exercise tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abnormal hemodynamic responses to exercise</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Symptomatic and asymptomatic patients**

1. Severe and moderate chronic AR while undergoing other cardiac or aortic surgery
2. Whatever/moderate severity of AR undergoing surgery on the ascending aorta
   a. Patients with Marfans syndrome
   b. Bicuspid valves

*By courtesy of Éva Tamás, Linköping.*
It is unclear at which point in the natural history of AR irreversible LV dysfunction develops and to improve timing of chronic AR there is a need for further studies on this subject. In Papers I and II longitudinal LV function and exercise echocardiography as markers of early myocardial dysfunction in patients with chronic AR are investigated.

**Aortic Stenosis**

Aortic stenosis (AS) is a frequent valve disease in elderly people in the Western world and it is most often caused by calcification of a normal trileaflet or a congenital bicuspid valve.\(^{57,69}\) This calcification process includes lipid accumulation and inflammation similar to atherosclerosis.\(^{70}\) The severity of AS is classified according to echocardiographic measurements of blood flow velocity through the valve, the mean pressure gradient, and the aortic valve area. Research has shown that this is a progressive disease and that when the AS is graded as moderate, the aortic valve area decreases by 0.1 cm\(^2\) per year. However, the variability between individual patients is large. It is therefore that international guidelines recommend regular follow ups in AS patients - including a detailed history, physical examination and an echocardiographic examination.\(^{57,68}\)

Patients with severe AS, normal LV function and no symptoms have a low risk for sudden death, and according to today’s guidelines these patients should not undergo aortic valve surgery. On the other hand, when patients with severe AS develop symptoms such as breathlessness, fainting and angina due to the valve disease, there is an average survival of 2-3 years in the case of conservative treatment. Aortic valve replacement (AVR) is thus recommended in these patients.\(^{57}\) AVR has been shown to improve survival as well as symptoms in this patient
category. However, there are risks with open heart surgery, and one third of elderly patients are not offered interventional treatment even though fulfilling criteria according to guidelines. Surgical high risk patients were previously referred to medical therapy and in some cases balloon aortic valvuloplasty, although these therapeutic options do not improve survival.

TRANSCATHETER AORTIC VALVE IMPLANTATION

In 2002 the first transcatheter aortic valve implantation (TAVI) in humans was performed in Rouen. Since then this therapeutic option in surgical high risk patients with symptomatic severe AS has expanded. The approach may be transfemoral, transapical, transsubclavian or transaortic depending on the patient’s peripheral vessel status and the centers’ choice of aortic valve bioprosthesis. Thirty-day mortality has been reported to be between 5.0-11.3%. Two prospective clinical trials have been published recently, PARTNER A and B. In a population of symptomatic severe AS patients denied surgical aortic valve replacement (SAVR) the patient cohort randomized to TAVI had significantly higher 1-year survival than the cohort randomized to standard conservative therapy (69 vs. 49%, p<0.001). The second trial demonstrated that in a surgical high risk population the survival rates did not differ between patients undergoing SAVR or TAVI.

AORTIC STENOSIS AND LONGITUDINAL LV FUNCTION

During the natural history of AS the LV adapts to the systolic pressure overload through hypertrophy of the myocardium (Figure 5). Wall stress is balanced by this compensation mechanism, but if wall stress increases beyond the degree of compensation possible, LV function starts to deteriorate. It is proposed that subendocardial myocardial fibres that
produce longitudinal LV contraction are the first cells to be damaged by this wall stress. It has been demonstrated that with increasing severity of AS, longitudinal LV function decreases with maintained EF. There are conflicting opinions on whether or not longitudinal LV function can provide prognostic information in AS. Whatever, correlation between the degree of myocardial fibrosis and septal AVPD has been demonstrated in severe AS.

Because of the limited time TAVI has been a treatment option for surgical high risk patients, our knowledge of how the procedure affects LV and RV function is scarce. Furthermore we do not know if ventricular recovery differs between TAVI and SAVR, as well as between the transapical and transfemoral approach. This is analyzed in Papers III and IV.
Aims of the thesis

The general aim of this thesis was to explore how LV and RV function assessed by echocardiography responds to aortic valve intervention in patients with either AS or AR.

I. To explore the mid- and long-term effects of aortic valve surgery on longitudinal LV systolic function in patients with chronic AR by TDI. (*Papers I and II*)

II. To investigate whether or not preoperative LV function assessed by exercise echocardiography including TDI predicts mid- and long-term postoperative LV function in chronic AR patients undergoing aortic valve surgery. (*Papers I and II*)

III. To determine early and mid-term changes in LV and RV global and longitudinal function in AS patients undergoing TAVI assessed by echocardiography and pulsed TDI. (*Papers III and IV*)

IV. To analyze potential differences in preservation or recovery of LV and RV function between patients accepted for TAVI or SAVR. (*Papers III and IV*)

V. To evaluate potential changes in early and mid-term systolic and diastolic LV function in patients with severe AS undergoing either transfemoral or transapical TAVI, by echocardiography and pulsed TDI. (*Paper IV*)
Subjects & Methods

Study population

Chronic Aortic Regurgitation Patients (I-II)

Between January 2002 and February 2006 a total of 29 patients with severe chronic AR, accepted for aortic valve surgery according to guidelines, were included. Exclusion criteria were: active endocarditis; previous cardiac surgery; concomitant valve disease; and coronary artery disease. Twenty-one patients with complete preoperative and 6-month postoperative echocardiographic examinations were available for late follow up examination during 2008 (Figure 6). Although the cohort consisted solely of men, female gender was not an exclusion criterion.

Aortic Stenosis Patients (III-IV)

TRANSCATHETER AORTIC VALVE IMPLANTATION

Patients with severe AS, denied SAVR by a multidisciplinary team due to high surgical risk or contraindications to SAVR, and who underwent TAVI between September 2008 and January 2010/June 2011 (Papers III/IV) were included (Figure 6). Exclusion criteria were: an aortic annulus diameter less than 18 mm or greater than 25 mm (when 29 mm prosthesis became available 27 mm became the upper limit); and where survival with a reasonable quality of life or duration was unlikely. The default approach was transfemoral, with transapical as a second choice if the femoral access was judged to be inappropriate. Table 2 summarizes patients included in Papers I-IV.
SURGICAL AORTIC VALVE IMPLANTATION

Patients accepted to SAVR were matched according to age (±10 years), gender and LV function (normal/slightly reduced ejection fraction or moderately/severely reduced ejection fraction) to TAVI patients.

Table 2 Summary of characteristics of patients included in the studies

<table>
<thead>
<tr>
<th></th>
<th>Aortic Regurgitation</th>
<th>Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paper I</td>
<td>Paper II</td>
</tr>
<tr>
<td>Number, n</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Age, years</td>
<td>51±14</td>
<td>49±12</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.0±0.2</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>NYHA, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>AF, n</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

BSA, body surface area; NYHA, New York Heart Association; AF, atrial fibrillation. *Exclusively patients undergoing TAVI.
Subjects & Methods

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Figure 6 Study flow chart for Paper I-IV
**Echocardiography**

The studies were performed with a GE Vivid 5 or 7 (GE Medical Systems, Norway), equipped with software for TDI. The routine examination was performed with the patient in the left lateral position. In the presence of atrial fibrillation all recordings were performed during an interval with as normal heart rate and regular heart rhythm as possible.

**Exercise Echocardiography (I-II)**

Exercise echocardiography was performed with patients in a semi-supine left lateral position on a bicycle ergometer designed for this purpose. After recording echocardiographic images at rest, exercise started at a load of 50 W and increased after 5 min to 100 W and then to 150 W. To study steady-state physiology, echocardiographic and color TDI images were recorded after 5 minutes at a workload of 100W. Blood pressure and heart rate were also measured at each work load. Apical 2- and 4-chamber views with and without color TDI were saved for offline analysis which included EF, LV volumes, PSV and AVPD. All examinations were performed by the same person.

**LV Systolic Function (I-IV)**

LV end diastolic and end-systolic dimensions (LVEDD and LVESD), septal and posterior wall thickness in end-diastole (SWTd and PWTd) were measured according to guidelines. The Devereaux formula was used to calculate LV mass:

\[
LVmass = 0.8 \times (1.04[(LVEDD + PWTd + SWTd)^3 - (LVEDD)^3]) + 0.6g
\]
Subjects & Methods

Because LV dimensions indexed to body surface area (BSA) have been shown to improve prediction of unfavorable postoperative outcome in AR patients, dimensions and volumes were indexed for BSA.\(^3\)

In Paper II, EF at rest and during exercise was obtained by 2D measurements for volume calculations using the biplane method of disks (modified Simpson’s rule) in apical 2- and 4-chamber views at end-diastole and at end-systole.

In Papers III and IV, EF was estimated in four intervals after evaluation of short axis view, long axis view and apical 2- and 4-chamber views by an experienced observer (Figure 7).\(^4\)

![Figure 7 EF by visual estimation.](image)

Doppler Echocardiography

TO DIAGNOSE AND GRADE SEVERITY OF AORTIC VALVE DISEASE (I-IV)

Color Doppler was used to identify regurgitation. Evaluation of aortic valve function was performed according to guidelines using appropriate Doppler modalities.\(^4\) Severe AR was determined on the basis of an integrated echocardiographic evaluation taking LV dimensions, vena contracta width, back-flow in the descending aorta and forward stroke volume into consideration.\(^4\) Severe AS was defined as maximal aortic velocity >4.0 m/s, mean aortic gradient >40 mmHg and aortic valve area <1.0 cm\(^2\) or aortic valve area indexed to BSA <0.6cm\(^2\)/m\(^2\).\(^5\)
Subjects & Methods

DIASTOLIC FUNCTION (III-IV)

Mitral flow velocities were obtained from the apical 4-chamber view with the sample volumes placed at the tips of the valve leaflets. The pulmonary venous flow velocities were then recorded by adjusting the image if necessary, and moving the sample volume to the right upper pulmonary vein. Isovolumetric relaxation time (IVRT) was calculated by subtracting the duration of aortic valve opening from the beginning of the QRS to the time between beginning of QRS and the early mitral wave. To estimate LV diastolic function, the following variables were included:

- Early diastolic filling velocity (E)
- Late diastolic filling velocity (A)
- Deceleration time (DT)
- IVRT
- Pulmonary vein peak diastolic velocity (PVd)
- Pulmonary vein peak systolic velocity (PVs)
- Average of septal and LV lateral é by TDI and E/é

In Papers III-IV diastolic function was classified using an integrated evaluation of mitral inflow, pulmonary vein velocities and average é-velocities by pulsed TDI from the basal septal and lateral LV walls with age-related changes taken into consideration (Table 3).³ ⁸⁵ ⁸⁶ Patients with atrial fibrillation formed a separate group.
### Table 3 Classification of diastolic function

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Impaired relaxation</th>
<th>Pseudo-normal</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E/A)</td>
<td>1.2</td>
<td>&lt;0.8</td>
<td>0.8-1.5</td>
<td>≥2.0</td>
</tr>
<tr>
<td>(DT (ms))</td>
<td>150-200</td>
<td>&gt;200</td>
<td>150-200</td>
<td>&lt;160</td>
</tr>
<tr>
<td>(IVRT (ms))</td>
<td>50-100</td>
<td>≥100</td>
<td>60-100</td>
<td>≤60</td>
</tr>
<tr>
<td>(PSV/PSd)</td>
<td>PSV≈PSd</td>
<td>PSV&gt;PSd</td>
<td>PSV&lt;PSd</td>
<td>PSV&lt;&lt;PSd</td>
</tr>
<tr>
<td>(e) (cm/s)</td>
<td>&gt;10</td>
<td>&lt;8</td>
<td>&lt;8</td>
<td>&lt;5</td>
</tr>
<tr>
<td>(E/e)</td>
<td>≤8</td>
<td>&lt;8</td>
<td>9-12</td>
<td>&gt;13</td>
</tr>
</tbody>
</table>

### Tissue Doppler Imaging

**COLOR TISSUE DOPPLER IMAGING (I-II)**

Apical 2- and 4-chamber views with TDI were recorded aiming at a frame rate >100/s, and were saved for offline analysis. Myocardial velocity profile was obtained from the basal segments in the lateral, septal, anterior and inferior LV walls at rest and during exercise at 100W. The PSV was measured at the highest velocity recorded during the systolic interval. Velocities during isovolumetric contraction were excluded. Diastolic early and late velocities (\(e\) and \(a\)) were obtained at rest.

**PULSED TISSUE DOPPLER IMAGING (III-IV)**

With an apical 4-chamber view, the sample volume was placed in the basal segments in the LV lateral, LV septal and RV free wall. It was carefully checked that the sample volume was within the myocardial borders during the cardiac cycle, and that the ultrasound beam was aligned with the longitudinal motion. PSV, \(e\) and \(a\) were measured for all ventricular walls.
AVPD BY TISSUE TRACKING (I)

Displacement (d) can be obtained from color TDI images showing myocardial velocities, by calculating the integral of the myocardial velocity (v)\(^1\):

\[ d = \int V \, dt \]

In the post-processing program, the sample volume was placed in the mitral annulus at the LV lateral, septal, anterior and inferior wall. From the displacement curve obtained, the AVPD was measured as the distance between the lowest and highest point. The mean AVPD of the four sites was calculated.

**Systolic AVPD by M-mode Echocardiography (I-IV)**

From apical 2- and 4-chamber views, systolic AVPD was measured by M-mode with guidance from 2D echocardiography. The cursor was placed over the septal, lateral (Papers I-IV), anterior and inferior LV wall (Papers I-II), but also over the RV lateral free wall (Papers III-IV) as described by Höglund et al. and Kaul et al.\(^5, 13\). To identify true systole, AVPD was measured from 60 ms after QRS, corresponding to mitral valve closure, to the first peak on M-mode, which has been shown to concur with aortic valve closure.\(^50\)
Subjects & Methods

Radionuclide Ventriculography (I)

Radionuclide ventriculography with multiple gated acquisition was performed to measure EF and LV volumes in Paper I. Using a GE XR/T gamma camera, supine multigated blood pool imaging was first performed at rest and during exercise. Initial work load was 50W which was increased to 100W. Xeleris Functional Imaging Workstation, EF analysis was used to measure EF.

Statistics

All data analyses were performed using SPSS version 15.0-19.0. Continuous data are expressed as median (interquartile range, Paper I) and mean values ± standard deviation (Papers II-IV). Categorical variables were expressed as numbers or percentages, apart from degree of AR and mitral regurgitation in Paper III expressed as median and interquartile range. Significance was defined as p<0.05.

To perform pre- and postoperative comparison with paired data, Wilcoxon’s signed rank test was used in Papers I and III, and paired t-test in Paper IV. Mann-Whitney U test was used to analyze unpaired groups in Papers I, II and IV, and unpaired t-test in Paper IV. In Papers II and IV, ventricular function was obtained at three time points for each patient, and therefore repeated measurement ANOVA followed by Bonferroni correction for multiple comparisons was used. Because of small sample size Wilcoxon sign rank test was used in Paper II to analyze differences within Low and High PSV groups.

Categorical data were analyzed by χ²-test, Fischers exact test or McNemar’s test (Paper IV), while ordinal data were analyzed by either Wilcoxon sign rank test or Mann-Whitney U-test (Papers III and IV).
Correlation between preoperative longitudinal function and postoperative EF, LV dimensions, and LV volumes were determined using Spearman’s correlation coefficient in Paper I and Pearson’s correlation coefficient in Paper II.

Bland-Altman analysis was used to evaluate agreement between tissue tracking and M-mode echocardiography (Paper I). 87

In Paper I, missing data due to missing images were treated as true missing data, whereas missing values due to inability of the patient to perform exercise because of their heart condition were replaced by zeroes in Wilcoxon’s matched-pairs tests, and by approximated low values in the Mann-Whitney analysis, so as to preserve information about the low performance patient group.

To evaluate inter-observer and intra-observer variability, studies from 10 randomly selected patients were separately analyzed preoperatively and postoperatively by two observers and remeasured by the first observer (Paper I). Mean differences and reproducibility coefficients (1.96xSD) were calculated.

Ethical considerations

All patients included in this thesis gave their written informed consent prior to their participation. The studies comply with the Declaration of Helsinki and have been approved by the Regional Ethical Review Board in Linköping.
Results

Chronic Aortic Regurgitation (I-II)

Twenty-nine patients with severe AR were examined preoperatively and 6 months postoperatively. The etiology behind AR was prolapse (n=19), degeneration (n=7), or dilatation (n=2). A bicuspid valve was found in 16 patients. Twenty-one of the patients were further examined on average 4 years after surgery.

Preoperatively, in paper I, one patient had EF at rest <50%, ΔEF was negative in 10 patients, LVESD was >50mm in 9 patients, and LVEDD was >70mm in 6 patients. Six months postoperatively EF, LV end-diastolic and end-systolic volumes and dimensions, all at rest, had decreased significantly (All p<0.001). In paper II, LV dimensions and volumes including EF were only obtained by echocardiography and not radionuclide ventriculography. EF at rest was unchanged at the long-term follow up (Figure 8).

LV Longitudinal Function at Rest Pre- and Postoperatively

In papers I and II LV longitudinal function was evaluated as PSV and AVPD by TDI, including TT (Paper I), and M-mode echocardiography. PSV and AVPD assessed by both methods (AVPD_{TT} and AVPD_{MM}) decreased in the early postoperative period and no further changes were observed at the late follow up (Table 3, Paper I, and Table 1, Paper II).
Figure 8 Ejection fraction, end-diastolic and end-systolic volumes (LVEDV and LVESV), end-diastolic and end-systolic dimensions (LVEDD and LVESD), and LV mass obtained by echocardiography two days preoperatively, and 6 months (6 mo) and 4 years postoperatively in 21 chronic AR patients. All data apart from EF are indexed (i) to body surface area (BSA).
**Results**

**Exercise Echocardiography and Aortic Valve Surgery in AR**

Preoperatively there was no change in EF or LV end-systolic volume index (ESVI) in response to exercise, while LV end-diastolic volume index (EDVI) decreased significantly during exercise (All p<0.01). LV longitudinal function, assessed as AVPD and PSV, increased during exercise (All p<0.05).

Six months postoperatively both LVEDVI and LVESVI had decreased significantly (Both p<0.001) and there were no changes in LV volumes between rest and exercise. EF during exercise showed a tendency to increase, and ∆EF improved significantly compared to preoperative data (p=0.059 and p<0.001). As regards LV longitudinal function, AVPD during exercise decreased compared to preoperative data, while PSV remained unchanged (Table 3, Paper I).

At the long-term follow up, no further decreases in LV volumes during exercise were seen, whereas ∆EF increased significantly (p<0.05). LV longitudinal function was stable between the short- and long-term follow ups, with the exception of an increase in ∆PSV (p<0.05).

**Prediction of Postoperative LV Function**

**LOW AND HIGH PSV GROUP**

The patients were divided into two groups with a previously published PSV reference value as the cut-off (5.9±1.3 cm/s) giving low PSV (n=13) and high PSV (n=14) groups. For two patients preoperative color TDI images were not available, either because of missing images or unacceptable image quality. The two groups did not differ with respect to baseline and echocardiographic characteristics, iLVESD being an exception (Tables 1 and 2, Paper I). Patients in the low PSV group had lower LV longitudinal function preoperatively and 6 months
Results

postoperatively, both at rest and during exercise, than those in the high PSV group (Table 4). In Paper II, data from 13 patients in the high PSV group and 7 patients in low PSV group were available for analysis. At the long-term follow up, LV longitudinal function in the high PSV group remained unchanged compared to the short-term follow up, while the low PSV group had increased AVPD_{MM} both at rest and during exercise (Figure 2, Paper II).

**Table 4 Low and High PSV group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low PSV group (n=13)</th>
<th>High PSV group (n=14)</th>
<th>P-value (Low vs High)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Postop</td>
<td>Preop</td>
</tr>
<tr>
<td>PSV rest(cm/s)</td>
<td>5.3 (4.7-5.5)</td>
<td>5.3 (4.6-5.7)</td>
<td>7.2 (6.4-7.7)</td>
</tr>
<tr>
<td>ex (cm/s)</td>
<td>7.5 (6.7-7.9)</td>
<td>6.3 (6.1-7.6)</td>
<td>9.6 (8.3-10.1)</td>
</tr>
<tr>
<td>Δ (cm/s)</td>
<td>2.1 (1.7-2.7)</td>
<td>1.1 (0.7-2.7)</td>
<td>2.2 (1.2-3.0)</td>
</tr>
<tr>
<td>AVPD_{TT} rest (mm)</td>
<td>11 (10-13)</td>
<td>9 (8-12)</td>
<td>14 (13-16)</td>
</tr>
<tr>
<td>ex (mm)</td>
<td>12 (11-13)</td>
<td>11 (10-13)</td>
<td>17 (16-19)</td>
</tr>
<tr>
<td>Δ (mm)</td>
<td>0.5 (-0.3-3.3)</td>
<td>1.6 (0.0-2.3)</td>
<td>2.5 (0.7-3.4)</td>
</tr>
<tr>
<td>AVPD_{MM} rest (mm)</td>
<td>11(10-12)</td>
<td>10 (8-10)</td>
<td>13 (11-14)</td>
</tr>
<tr>
<td>ex (mm)</td>
<td>12 (11-15)</td>
<td>11 (10-12)</td>
<td>16 (14-17)</td>
</tr>
<tr>
<td>Δ (mm)</td>
<td>1.5 (0.1-3.8)</td>
<td>1.3 (0.4-4.3)</td>
<td>2.8 (1.3-3.9)</td>
</tr>
<tr>
<td>EF rest (%)</td>
<td>61 (57-63)</td>
<td>59 (54-66)</td>
<td>65 (56-68)</td>
</tr>
<tr>
<td>ex (%)</td>
<td>58 (54-63)</td>
<td>61 (55-72)</td>
<td>70 (61-71)</td>
</tr>
<tr>
<td>ΔEF (%)</td>
<td>-3 (-7.4)</td>
<td>3 (-3-4)</td>
<td>3.5 (1-5)</td>
</tr>
</tbody>
</table>

Values expressed as median (25th-75th percentiles). Ex = exercise; Δ = the change from rest to exercise. x: not analysed since subgroups was defined on basis of PSV at rest. Rest vs. exercise; § p < 0.05, §§ p <0.01, §§§ p <0.001. Rest preop vs. rest postop, ex preop vs. ex postop; † p <0.05, †† p <0.01, ††† p <0.001
CORRELATION BETWEEN POSTOPERATIVE LV FUNCTION AND PREOPERATIVE DATA

In *Paper I*, correlation analyses between preoperative LV longitudinal function and conventional LV measures 6 months postoperatively indicated a stronger correlation when using preoperative exercise variables rather than data obtained at rest (Table 4, *Paper I*).

In *Paper II*, preoperative EF during exercise, $\Delta$EF, AVPD$_{MM}$ during exercise and $\Delta$AVPD$_{MM}$ showed strong inverse correlations to late postoperative LVESVI at rest ($r=-0.68$, $r=-0.58$, $r=-0.81$ and $r=-0.74$, all $P<0.01$) and LVEDVI at rest ($r=-0.68$, $r=-0.71$, $r=-0.86$ and $r=-0.81$, all $p<0.01$), while corresponding preoperative variables at rest showed no correlation ($r<0.02$ for all variables).

**Aortic Stenosis (III-IV)**

Transcatheter Aortic Valve Implantation

Thirty-three patients who were accepted for TAVI were studied regarding systolic and diastolic LV and RV function pre- and 8 weeks postprocedurally (*Paper III*). In *Paper IV* the total number of patients was 60, and subgroup analyses were performed in patients undergoing either transapical or transfemoral TAVI.

LV SYSTOLIC FUNCTION

Most of the TAVI patients had a normal global LV function preprocedurally (*Paper III* 76%, *Paper IV* 79%) and this proportion remained unchanged early and 6 months after the intervention. Systolic AVPD and PSV in the lateral and septal wall improved significantly between the pre- and early postprocedural investigations (Figure 9). The study presented in *Paper IV* showed that this early improvement was maintained at the 6-month follow up.
Results

Figure 9 Longitudinal LV function in the septal and lateral walls one day before, and 7 weeks and 6 months after TAVI. Both lateral and septal walls show improved longitudinal function early after TAVI and no further changes were seen after 6 months.

LV DIASTOLIC FUNCTION

LV diastolic function was classified according to criteria shown in Table 3. TAVI patients did not improve their diastolic function classification in the early postprocedural period. However, data from the 6-month follow up showed a significant improvement (Figure 3, Paper IV). Diastolic data obtained by TDI showed an early improvement in é-septal, and E/é-average had also decreased significantly after 8 weeks. When analyzing the patients grouped according to previously published reference values for é-septal, é-lateral, E/é-septal and E/é-lateral, only patients with abnormal é or E/é preoperatively showed improvement (Figure 4, Paper IV). 85
RV FUNCTION
A significant increase in PSV in the RV lateral wall in the early postprocedural period was seen (p=0.006 and p=0.001) (Papers III and IV) while AVPD remained unchanged (Figure 2, Paper III).

**Transapical vs. Transfemoral Approach**
In *Paper IV* comparative analyses were performed between patients undergoing the transapical (n=25) and the transfemoral (n=35) TAVI approach. The transapical patients had lower BSA, poorer kidney function and higher logistic EuroSCORE (Table 1, Paper IV). The frequency of coronary artery disease was 60% in the transapical group and 34% among the transfemoral patients (p>0.05).

Whereas the transfemoral group improved their longitudinal function in the lateral and septal walls in the early postprocedural period, the transapical group showed unchanged AVPD and PSV. The transapical group had lower AVPD preprocedurally, and AVPD and PSV were both higher in the transfemoral than in the transapical group postprocedurally.

As regards diastolic function, the transapical patients had a more pathological diastolic function at the first and second follow up (Figure 3, Paper IV).

**TAVI vs. SAVR**
Seventeen TAVI patients in *Paper III* and 27 in *Paper IV* were matched with SAVR patients according to age, gender and global LV function. The SAVR patients showed improvement in longitudinal function in the lateral wall after surgery, and had at the two postoperative examinations higher PSV and AVPD than the TAVI group. The SAVR group did not show changes in PSV and AVPD in the septal wall despite a higher
AVPD preoperatively in this group. The SAVR and TAVI groups did not differ in septal AVPD postoperatively (Figure 1, Paper III).
Although the SAVR patients did not improve their LV diastolic function class after surgery, the group had better diastolic function than the TAVI patients preoperatively as well as at the two postoperative investigations (Figure 3, Paper III, and Figure 3, Paper IV).
The SAVR group had higher longitudinal motion in the RV free wall preoperatively, but this decreased after the procedure and the situation became the opposite, with lower PSV in the SAVR group than in the TAVI group. In Paper IV an incomplete recovery of AVPD between the early and 6-month follow up was shown in the SAVR group (p=0.008).

**Regional LV Function after Aortic Valve Intervention**
Changes in regional LV function in the septal and lateral walls of patients undergoing aortic valve intervention differed in three patient categories: the TAVI group (n=60), the SAVR-AS group (n=27) and SAVR-AR group (n=29). The TAVI group increased PSV and AVPD in both the septal and lateral wall postoperatively (Figure 10). The SAVR-AS group remained unchanged regarding PSV and AVPD in the septal wall, while both variables increased in the lateral wall after surgery. The SAVR-AR group had decreased longitudinal motion in the septal wall while the lateral wall was unchanged postoperatively.
Figure 10 Longitudinal LV function after aortic valve intervention in patients undergoing TAVI, SAVR due to AS or SAVR due to chronic AR. PSV and systolic AVPD were measured in the septal (blue) and lateral (green) LV walls one or two days prior to intervention (light colored) and 6 months postoperatively (dark colored). Pre- vs. 6 months postoperatively *p<0.05, **p≤ 0.01, ***p≤ 0.001.
The left ventricle plays an important role in aortic valve disease and the evaluation of LV function is an important component in the serial follow ups and in the timing of aortic valve surgery.

EF has for a long time been used in the assessment of LV function. It is widely available and has gained an important role in numerous studies that have formed today’s guidelines regarding cardiac and non-cardiac disease. However, EF obtained by echocardiography has some important drawbacks regarding image quality, mathematical assumptions of cardiac size, and load dependence.\textsuperscript{88} LVEF, often used synonymously with global LV function, is dependent on radial, twisting and longitudinal myocardial contraction. Radial contraction is performed by radially orientated myocardial fibres located in the middle layer of the myocardium. These fibres have been shown to be influenced late in cardiac disease, preceded by a reduction in long axis function. Because of this, the measurement of long axis function has gained interest in recent years. Early diastolic velocity obtained by TDI is one example, and has been important in the formulation of the latest guidelines concerning assessment of diastolic function.\textsuperscript{86}

**LV function in chronic AR before and after surgery**

**LONGITUDINAL LV FUNCTION**

Table 5 shows a summary of the publications covering longitudinal LV function in patients with chronic AR. Several studies have shown that longitudinal LV function measured as PSV, AVPD, strain and strain rate
**Table 5** Overview of publications regarding chronic aortic regurgitation and longitudinal LV function.

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Study design</th>
<th>Pat, n</th>
<th>Male, n</th>
<th>NYHA</th>
<th>EF rest</th>
<th>Long LVF</th>
<th>Exercise data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinereanu et al (21)</td>
<td>2001</td>
<td>Cross sectional</td>
<td>21</td>
<td>16</td>
<td>≤IIa</td>
<td>54±4</td>
<td>PSV - s* AVPD - septal†</td>
<td>EF, ΔEF, after symptom limited exercise</td>
</tr>
<tr>
<td>Sokmen et al (52)</td>
<td>2007</td>
<td>Cross sectional</td>
<td>32</td>
<td>17</td>
<td>I</td>
<td>63±8</td>
<td>PSV-s, l, a, i*</td>
<td>-</td>
</tr>
<tr>
<td>Paraskevaidis et al (61)</td>
<td>2006</td>
<td>Cross sectional</td>
<td>84</td>
<td>48</td>
<td>≤IIa</td>
<td>65±8†</td>
<td>PSV - s, l*</td>
<td>EF, ΔEF, peak exercise †</td>
</tr>
<tr>
<td>Marciniak et al</td>
<td></td>
<td>(90)</td>
<td>2009</td>
<td>Cross sectional</td>
<td>59</td>
<td>37</td>
<td>≤II</td>
<td>63±5 - 55±9</td>
</tr>
<tr>
<td>Yurdakul et al (89)</td>
<td>2011</td>
<td>Repeated cross sectional (2 years)</td>
<td>30</td>
<td>17</td>
<td>≤IIa</td>
<td>59±4</td>
<td>Strain, strain rate – s, l, a, i</td>
<td>-</td>
</tr>
<tr>
<td>Tayyareci et al (91)</td>
<td>2010</td>
<td>Cross sectional</td>
<td>40</td>
<td>23</td>
<td>≤IIa</td>
<td>56±5</td>
<td>PSV – s, l and RV 6, 8, i*</td>
<td>-</td>
</tr>
<tr>
<td>Paraskevaidis et al (63)</td>
<td>2007</td>
<td>Repeated cross sectional (1 year)</td>
<td>85</td>
<td>39</td>
<td>≤IIa</td>
<td>65±8</td>
<td>PSV – s, l, RV*</td>
<td>-</td>
</tr>
<tr>
<td>Name</td>
<td>Year</td>
<td>Study design</td>
<td>Pat, n</td>
<td>Male, n</td>
<td>NYHA</td>
<td>EF rest</td>
<td>Long LVF</td>
<td>Exercise data</td>
</tr>
<tr>
<td>----------------------</td>
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<td>--------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Olsen et al (92)</td>
<td>2011</td>
<td>Repeated cross sectional (19±8 months, n=35)</td>
<td>64</td>
<td>46</td>
<td>39%&gt;II</td>
<td>55±9</td>
<td></td>
<td>Strain, strain rate† Total AVPD = average of 6 walls** PSV – average of 6 walls***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeated cross sectional (6 months postop, n=29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smedsrud et al (93)</td>
<td>2011</td>
<td>:58±77 days preop &amp; 229±159 days postop</td>
<td>44</td>
<td>30</td>
<td>23%&gt;II</td>
<td>59±5</td>
<td></td>
<td>Strain - global PSV – s, l AVPD – s, l</td>
</tr>
<tr>
<td>Paper I</td>
<td>2010</td>
<td>Repeated cross sectional: 2 days preop &amp; 6 months postop</td>
<td>29</td>
<td>29</td>
<td>21%&gt;II</td>
<td>62 (56-68)</td>
<td></td>
<td>PSV- s, l, a, i Total AVPD - s, l, a, i Systolic AVPD - s, l, a, i 100W EF, ΔEF, LV volumes§ Long LVF</td>
</tr>
<tr>
<td>Paper II</td>
<td>Subm.</td>
<td>Repeated cross sectional: 2 days preop, 6 months &amp; 4 years postop</td>
<td>21</td>
<td>21</td>
<td>14%&gt;II</td>
<td>55±7</td>
<td></td>
<td>PSV- s, l, a, i Systolic AVPD - s, l, a, i 100W EF, ΔEF, LV volumes Long LVF</td>
</tr>
</tbody>
</table>

s, septal; l, lateral; a, anterior; i, inferior; RV, right ventricular lateral wall; VVI, velocity vector imaging; *pulsed TDI, †M-mode, ‡Radionuclide cineangiography, || mid-severe AR, § by 2D strain, **by tissue tracking, ***by color TDI
Discussion

decreases before conventional echocardiographic measurements show a fall in function in patients with severe chronic AR and EF >50%. Furthermore, few studies have investigated the prognostic value of longitudinal LV function. Pre- and postoperative longitudinal LV function measured as strain, strain rate, PSV and longitudinal displacement have previously been studied in two studies comprising 29 and 44 patients respectively. Remaining symptoms or LV dysfunction postoperatively could be best predicted by strain variables from speckle tracking. Preoperative PSV and displacement were also associated with postoperative outcome. In Paper I longitudinal LV function was studied during exercise in chronic AR patients. This was the first study of its kind, moreover this study included a postoperative follow up after six months including an echocardiographic examination with TDI at rest and during exercise. We showed that preoperative PSV at rest predicts postoperative longitudinal function, and that preoperative longitudinal function assessed during exercise was more strongly correlated to postoperative conventional echocardiographic parameters than the corresponding variables at rest.

EXERCISE PHYSIOLOGY IN AR
Change in longitudinal LV function as a response to exercise in chronic AR patients has, until now, never been published. We showed that longitudinal LV function parameters increased during exercise in this patient category.

In normal individuals the LV responds to exercise and the demands of increased cardiac output with increased heart rate, increased myocardial contractility and alterations in pre- and afterload. The increase in stroke volume is due to increased LVEDV and decreased LVESV. In patients with chronic AR this is complicated by a large regurgitation volume and
LV dilatation. With exercise diastolic filling time is shortened and the regurgitation volume decreased. Furthermore, studies have shown that AR patients with normal LV function decrease EDV and ESV as a response to exercise, while patients with depressed LV function instead increase ESV and EDV or have unchanged volumes. An increase in ESV is a direct sign of ventricular failure while an increase in EDV has been proposed to be an attempt to adapt according to the Frank-Starling Law. However, the net effect of this dilatation is higher wall tension to produce equivalent intraventricular pressure. In our patient population, where all patients were accepted for surgery, we saw a decreased EDV but an unchanged ESV as a response to exercise. Although ∆EF improved postoperatively, neither EDV nor ESV changed during exercise as would be expected in a normal response to exercise. This suggests remaining LV dysfunction in these patients.

PROGNOSTIC VALUE OF EXERCISE ECHOCARIOGRAPHY IN AR

It is a challenge to recognize patients with subclinical reversible myocardial dysfunction in order to operate early enough to prevent postoperative LV dysfunction, but not so early as to subject the patient to unnecessary operative morbidity and mortality risks. LV data obtained during exercise (∆EF and EF_{exercise}) have been proposed to be valuable in identifying subclinical LV dysfunction and as prognostic information. ∆EF and change in ESV from rest to exercise as measured by echocardiography during exercise has also been shown to be of prognostic importance regarding LV function in conservatively treated patients as well as in surgically treated patients. In Paper II we found that preoperative EF, LV volumes and longitudinal LV function, measured during exercise did relate to late postoperative LV function. This correlation could not be found when considering data obtained at
Discussion

rest only. Furthermore LV function variables that play a major role in guidelines regarding surgery in AR patients (EFrest and LVESDI) did not correlate to corresponding late postoperative LV function variables.57

LV Function after Aortic Valve Intervention in AS Patients

LONGITUDINAL SYSTOLIC LV FUNCTION

There is a progressive decline in longitudinal LV function in AS patients, and EF is not affected until late in the natural history.22, 103 AVPD has been shown to decline gradually with the development of fibrosis of the myocardium, and in the same study AVPD >7mm preoperatively was associated with an improvement in NYHA class after aortic valve surgery.81 Furthermore, long axis function by pulsed TDI has prognostic implications, where PSV≤4.5 cm/s predicts development of symptoms, SAVR or cardiac death in patients with asymptomatic severe AS.80 On the other hand Stewart et al concluded that TDI variables have no prognostic value in AS patients.79

In AS patients with normal LVEF preoperatively, little or no change in EF has been shown after SAVR and TAVI, while regression of myocardial hypertrophy is common.104-106 We and others have shown that after SAVR, LV longitudinal wall motion parameters increase in the lateral wall, while septal longitudinal function remains unchanged.107, 108 However, in patients undergoing TAVI there is a more homogenous improvement in long axis function. A possible explanation for this could be the absence of paradoxical septal motion after TAVI, which is a common finding after SAVR.109

Thirty-day mortality is in a majority of studies higher with transapical TAVI than with transfemoral TAVI,75, 78, 110 while in others comparable clinical and echocardiographic outcomes have been seen.111 Potential
differences in LV function between the two approaches have not been studied previously. We looked at longitudinal function in patients accepted for transapical or transfemoral TAVI, the transapical patients showing no improvement in longitudinal LV function. This could have been due to irreversible LV dysfunction caused by longstanding AS or coronary artery disease. However, we cannot rule out a possible influence on cardiac motion or myocardial damage caused by surgical opening of the pericardium, the transapical puncture or apical suture performed in transapical TAVI.

DIASTOLIC FUNCTION IN AS
Although LV hypertrophy is a key adaptive mechanism to the pressure load imposed by AS, it has adverse pathophysiological consequences by increasing myocardial stiffness, increasing resistance to diastolic filling and eventually increasing LV diastolic filling pressures. Diastolic dysfunction has been proposed to appear before changes in systolic function and the incidence of diastolic dysfunction in AS patients has in general been reported to be 50% with normal systolic function, but 100% in the case of abnormal systolic function. The majority of patients accepted for TAVI in Papers III and IV had normal global systolic function, but >90% had preprocedural abnormal diastolic function. Diastolic function variables – E/é, á, and degree of dysfunction - have been shown to have a prognostic role in AS patients. The treatment of diastolic dysfunction in AS is SAVR, followed by regression of LV hypertrophy. However, changes in diastolic function after pressure overload reduction have been shown as soon as 24 hours after TAVI, long before changes in LV mass were evident. These results suggest that afterload reduction per se contributes to improvement in diastolic function. We saw increased early diastolic myocardial
Discussion

velocities among TAVI patients at the first follow up. Six months after the intervention diastolic function classification had also improved significantly. Furthermore, a decrease in E/é was observed after six months, which suggests decreased LV filling pressures.117

RV FUNCTION AND AORTIC VALVE SURGERY
Longitudinal RV function decreases after cardiac surgery and we could confirm this in the SAVR group in Papers III and IV. Although the SAVR patients had higher longitudinal RV function than the TAVI patients preoperatively, both AVPD and PSV were lowered to values significantly below those of TAVI patients after the intervention. As discussed in the introduction, the cause of this decrease is not known but several theories have been proposed. The patients undergoing TAVI had instead unchanged or improved longitudinal RV function suggesting that these procedures are more favorable for the RV.
Studies have shown unchanged postoperative RVEF and that there is no relationship between postoperative exercise capacity and reduction in longitudinal RV function.31, 118 It has been suggested that the septal wall is recruited to the right side to compensate for this decrease, explaining the paradoxical septal motion.37
The clinical importance of the decrease in longitudinal RV function is unknown, but when evaluating RV function in patients who have previously undergone cardiac surgery, isolated use of longitudinal RV function variables can be misleading.
**Regional LV Function after Aortic Valve Intervention**

When we compared septal and lateral LV wall responses to aortic valve intervention we found significant differences between patients with chronic AR, patients with severe AS undergoing open heart surgery and patients with severe AS undergoing TAVI.

The significant impact of stroke volume on longitudinal LV motion together with paradoxical septal motion could explain the decrease in septal motion and the unchanged lateral motion in the AR group.\textsuperscript{119, 120}

With a decline in stroke volume and LV dimensions a decline in myocardial wall movement also occurs.\textsuperscript{92}

While TAVI patients showed a homogenous increase in regional LV function after the intervention, the SAVR-AS group did not. The longitudinal motion in the lateral wall increased significantly, while the septal wall remained unchanged. Even here the paradoxical septal motion can be an explanation for this phenomenon as also described by others.\textsuperscript{121}

These findings have led to an improved understanding and knowledge of regional LV function after aortic valve intervention. This is valuable in the postoperative evaluation of LV function performed by echocardiography.

**Methodological consideration**

**PATIENT POPULATION**

Although female gender was not an exclusion criterion there were only men in the study population of Papers I and II. This can partly be explained by chronic AR being more common in men.\textsuperscript{55} In this patient cohort there was also a high prevalence of bicuspid aortic valve which is a more common finding in men.\textsuperscript{122} Furthermore, the exclusion of patients...
with aortic dilatation could have contributed to the absence of females because it has been shown to be more prevalent with aortic root disease among women with concurrent AR.123 Forty-five percent of the TAVI patients in Paper IV had concurrent coronary artery disease. We defined this as previous myocardial infarction or significant coronary artery stenosis on preprocedural angiography, and not stable angina because of its relationship to AS. Although there is a high likelihood of diffuse fibrosis due to long-standing excess afterload, we cannot exclude the presence of focal fibrosis due to the presence of coronary artery disease and this could have resulted in a further decrease in longitudinal motion in these TAVI patients.124, 125

TDI & PRELOAD DEPENDENCY

When TDI first was introduced this modality was presented as less load-dependent than already existing techniques. Animal studies showed that $\ddot{e}$, in the presence of normal and enhanced relaxation states, was load-dependent. However, when impaired LV relaxation was present, $\ddot{e}$ became load-independent.126 With changes in volume status, changes in the annular or myocardial tissue velocities have been noted to be less than the corresponding changes in mitral flow velocities.127-130 This information was used to offset the preload-dependent E-wave by creation of a ratio - the E/$\ddot{e}$. E/$\ddot{e}$ has shown to correlate with LV filling pressures.131, 132 However later studies in humans have showed significant correlation between stroke volume and mitral annulus velocities suggesting load dependency that should be kept in mind. One of these studies comprised patients with left-sided valvular regurgitation, lowered stroke volume due to coronary artery disease or dilated cardiomyopathy, and normal subjects.119 Studies of TDI variables before and after hemodialysis have shown both load-dependency and load-independency,
and this difference in results could possibly be explained by the amount of fluid extraction during dialysis. In Paper I we showed decreased long axis function parameters at rest and during exercise after aortic valve surgery. The marked decrease in stroke volume could partly explain this. However due to a relationship between LV size and PSV, the marked decrease in stroke volume and LV volumes could also lead to the diminished long axis motion.
Clinical Implications

A vision for the future is to be able to optimise the timing of aortic valve surgery in patients with chronic AR, using reliable and simple measurements that unmask early deterioration in LV systolic function. Papers I and II demonstrate that tissue Doppler echocardiographic measurements at rest and during exercise can detect subnormal systolic velocities when EF is still >50%. This technique seems to fill the criteria and may thus have a role in the timing of aortic valve surgery by detecting early subclinical and reversible LV dysfunction in patients with chronic severe AR.

Papers III and IV demonstrate improved LV systolic and diastolic function in a patient population undergoing TAVI, and in Paper IV a detailed analysis of differences in recovery of LV function after the transapical and the transfemoral approach is also included. These two papers expand our understanding of biventricular function after aortic valve intervention.

Transapical patients have been suggested to represent a patient population with higher surgical risk. Our data demonstrate that longitudinal LV and RV function did not improve significantly after transapical TAVI, suggesting irreversible LV dysfunction in this patient category. Moreover, these results show that longitudinal myocardial contractility does not necessarily improve after aortic valve intervention. Even so, we cannot rule out the possibility that the differences between the approaches were procedure-related.
The decrease in longitudinal RV function and the paradoxical septal motion, often seen after SAVR, are avoided with TAVI, and instead there is a tendency towards improved RV function.
Concluding Remarks

The work comprising this thesis has deepened our knowledge of ventricular function before and after aortic valve intervention in patients with either chronic AR or AS. Furthermore, data suggesting that echocardiography during exercise can provide prognostic information with regard to LV remodeling after aortic valve surgery in chronic AR patients are presented.

In a chronic AR patient cohort with EF and LV dimensions not fulfilling criteria for surgery according to present recommendations, a subgroup of patients with high preoperative PSV had higher longitudinal motion 6 months postoperatively than the subgroup with preoperative low PSV. Furthermore, chronic AR patients with impaired exercise echocardiographic variables preoperatively were more likely to have suboptimal LV remodeling late postoperatively. Exercise echocardiography and TDI at rest and during exercise can become a valuable complement in the preoperative screening of patients in order to optimise timing of AR surgery thus minimizing postoperative irreversible LV dysfunction.

Early after TAVI, an improvement in LV systolic and diastolic function assessed by echocardiography and TDI could be seen. At the 6-month follow up the early increase in longitudinal motion remained unchanged, and diastolic function class was improved indicating LV remodeling in progress. Furthermore, RV function, assessed by tricuspid annular motion...
and PSV, was unaffected or improved in this patient category in the early postprocedural period.

The results presented in Papers III and IV show that TAVI prevents the reduction in longitudinal RV function frequently seen after SAVR via sternotomy. RV systolic function improved in TAVI patients, but was impaired in the SAVR group at the early follow up. Both TAVI and SAVR patients seem to gain improvement in LV function in the lateral wall. Although the matched TAVI patients had significantly lower PSV_{Septal} and PSV_{Lateral} than did the SAVR patients, a similar reaction with improved LV lateral wall longitudinal function could be observed in both groups postprocedurally.

There is a considerable difference in the longitudinal LV and RV function response between patients assigned to the transapical or to the transfemoral aortic valve implantation approach. The absence of improvement in LV function in transapical patients could be due to irreversible LV dysfunction, but an influence on cardiac function caused by the invasive nature of the intervention cannot be ruled out.
Acknowledgements

I would like to express my great appreciation to everyone who has in many different ways helped me along the way during this journey. I would like to especially mention the brilliant help and support I have been given from following people:

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