Surgical treatment in chronic aortic regurgitation

Timing, results, prognosis
and
left ventricular function

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Medicus curat, natura sanat.

CONTENTS

ABSTRACT

Chronic aortic regurgitation (AR) of varying degree affects 13% of men and 8.5% of women. In persons with severe AR, the expected length of life and its quality   are influenced. Some individuals remain asymptomatic for a long period, due to effective compensatory mechanisms, but dysfunction of the left ventricle (LV) usually begins before symptoms appear and can be irreversible by then. This thesis addresses questions of LV function and optimal time for operation of patients suffering from chronic AR. Moreover, detailed echocardiographic studies of the anatomy of the normal aortic valve have been performed to obtain a better understanding of the in vivo anatomic relations within the aortic root.

Patients with chronic AR, without concomitant cardiac disease, were studied both retrospectively (n=88) and prospectively (n=29) and the aortic valves of persons (n=32) free from cardiac disease were investigated.

For the retrospectively studied patients, survival was 82% at 10 years which is an improvement compared with previously published results. The majority of the patients, however, had LV dysfunction preoperatively. By studying patients prospectively by echocardiography, radionuclide ventriculography (MUGA) and cardiopulmonary exercise testing (CPET) our aim was to evaluate the predictive value of measurements of LV function at rest and during exercise for postoperative outcome. LV diameters were markedly elevated prior to and diminished significantly after surgery. Patients with an abnormal exercise ejection fraction (EF) response by MUGA preoperatively, presented the same reaction postoperatively. This could not be predicted by LV function determination at rest, or by NYHA functional class. In spite of median NYHA class II, these patients had a low work capacity on CPET, which was neither improved 6 months postoperatively nor correlated to echocardiographic LV dimensions. Thus, both MUGA and CPET may be useful complements for timing of surgery in patients with chronic AR.

Assuming that patients would benefit from preservation of their native valves the normal aortic valve was studied to gain detailed information about the echocardiographic anatomy and relations within the normal aortic root. This extended examination of the aortic root may facilitate a better planning of aortic valve-preserving interventions in the future.

LIST OF ORIGINAL PAPERS

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

I. Tamas E, Nylander E, Olin C. Are patients with isolated chronic aortic regurgitation operated in time? Analysis of survival data over a decade. *Clin Cardiol. 2005 Jul;28(7):329-32.*

II. Tamas E, Broqvist M, Olsson E, Franzén S, Nylander E. Exercise radionuclide ventriculography for predicting postoperative left ventricular function in chronic aortic regurgitation. *Submitted manuscript.*

III. Tamas E, Nielsen NE, Vanhanen I, Nylander E. Measurement of physical work capacity in patients with chronic aortic regurgitation: A potential improvement in patient management *Submitted manuscript.*

IV. Tamas E, Nylander E. Echocardiographic Description of the Anatomic Relations within the Normal Aortic Root. *J Heart Valve Dis 2007;16:240-246*

ABBREVIATIONS

AR	Aortic Regurgitation
BMI	Body Mass Index
BSA	Body Surface Area
CPET	Cardiopulmonary Exercise Testing
EF	Left Ventricular Ejection Fraction
ΔEF	Left ventricular Ejection Fraction Response to Exercise
ICD	Intercommissural Distance
LC	Left Coronary
LV	Left Ventricle/Ventricular
LVF	Left Ventricular Function
LVED	Left Ventricular End-Diastolic Diameter
LVES	Left Ventricular End-Systolic Diameter
LVEDV	Left Ventricular End-Diastolic Volume
LVESV	Left Ventricular End-Systolic Volume
maxSiD	Maximal Sinus Diameter
MUGA	Multiple Gated Image Acquisition
NC	Non-Coronary
NYHA	New York Heart Association
OV	Opening of the Valve
RC	Right Coronary
RPE	Rate of Perceived Exertion
SAD	Subaortic Diameter
STJ	Sinotubular Junction
TEE	Transesophageal Echocardiography
$\dot{V}O_{2\,peak}$	Peak Oxygen Uptake

INTRODUCTION

"The heart … is the beginning of life; the sun of the microcosm… for it is the heart by whose virtue and pulse the blood is moved, perfected, made apt to nourish, and is preserved from corruption and coagulation; it is the household divinity which, discharging its function, nourishes, cherishes, quickens the whole body, and is indeed the foundation of life, the source of all action."[1]

William Harvey's lines from 1628 can be considered to mark the beginning of an era of extensive studies on the heart and the circulation. Much has been learned since then but we are still far away from being able to describe and understand anatomy and hemodynamics completely.

The studies presented in this thesis address questions of left ventricular function and optimal time for operation of patients suffering from chronic aortic regurgitation; moreover detailed echocardiographic anatomy of the normal aortic valve is presented.

The aortic root and the left ventricle

The aortic root

The aortic valve is located between the left ventricle and the aorta. Unfortunately, completely different opinions about the nomenclature of this region of the heart still remain[2-4]. The three semilunar cusps are usually referred to as the aortic valve. However, these cusps together with the upper part of the left ventricle and the aortic wall form a functional entity called the aortic root. The three half-moon formed cusps are connected to the aortic wall in such a manner that the deepest part of the pocket formed by the aortic wall and a cusp is in the left ventricular outflow tract. The lower border of the cusps together with the aortic wall forms a fibrous crown which can be interpreted as the annulus[4] in spite of the fact that the Latin word means 'ring'. (Fig.1) Others define the aortic annulus as an imaginary ring laid through the deepest points of the cusps. [5]

Figure 1
Aortic root. A: The crown shaped conception of the annulus is based on histo-pathological studies. B: Surgical interpretation of the annulus.

It is considered common knowledge that the aortic valve is competent when the upper segments of the cusps meet, and this is what prevents blood from regurgitating out of the aorta to the left ventricle. The band-like area

where the cusps meet bears the name of coaptation area. The meeting post between two cusps on the aortic wall is called commissure. The aortic wall bulges between two commissures and the aortic sinus is formed. These sinuses have a role in coronary perfusion through a special pattern of blood flow due to their geometry. Leonardo DaVinci described and showed this pattern but the exact function and mechanism is still unknown. Hence, it is difficult to say how important the sinuses are. [6-9]

As the limit of the aortic root is the deepest point of the cusps towards the left ventricle, the upper limit is the sinotubular junction (STJ) where the sinuses and the commissures end and the aorta takes the shape of a tube.

Left ventricle: anatomy & function

The dominating tissue of the left ventricle is muscle. The fibres of the myocardium are organized in three layers, where the fibres run in different directions: longitudinally under the endocardium, circumferentially in the middle and obliquely close to the epicardium. The longitudinal fibres of the inner muscle layer perform the long axis movement of the heart.

The phase during which the left ventricle is filled with blood is called diastole *(Greek. 'act of dispending or dilating')* while the emptying is called systole *(Greek. 'contraction')*. The original words describe very well what happens to the heart muscle during these phases. Intact contractility, in other words ability to perform contraction and have time to relax between contractions, is the basis of myocardial function. The total function of the left ventricle is a counteraction of systolic and diastolic function of the myocardial fibres, as dilatation is as important as contraction in order to be able to present good pump function and thereby sufficient circulation for the body. [6, 10]

Methods of clinical examination

Measuring contractility in vivo in humans is difficult with standard diagnostic tools but evaluation of function of which contractility is an important component is possible with different methods. Ejection fraction (EF) is one measure of systolic function.

$$EF\,(\%) = \frac{LVEDV - LVESV}{LVEDV} \times 100$$

where LVEDV is left ventricular end-diastolic volume and LVESV is left ventricular end-systolic volume. Nevertheless, EF is influenced by e.g. ventricular volume and valvular regurgitation. Another tool for assessment of systolic function is the longitudinal function.[10, 11] The diastolic function can be estimated by measuring blood flow velocity and inflow pattern to the left heart. The ideal technique for examination should be non-invasive, informative, reproducible, reliable and cost-effective.

Ultrasound imaging

Sound is a pressure wave and its frequency is the number of cycles per second (Hertz; Hz). The range which has higher frequencies than are audible for humans is referred to as ultrasound ($\geq$ 20 kHz). Imaging ultrasound frequencies range from 2 MHz to 40 MHz. Transducer crystals are used to generate ultrasound. An electric impulse causes expansion of the crystal and the adjacent tissues are compressed. After expansion, the crystal contracts and a pressure wave is produced that travels through the tissues by the transfer of the pressure wave from one vibrating particle to the next, in the direction of the wave-front. Ultrasound passes through homogenous tissue without change in velocity (1540 m/s in soft tissue). As the sound beam passes through tissue, it is reflected, refracted and absorbed. Reflection is utilized for creating images, hence the name for cardiac imaging is echocardiography *(Greek. echo – 'reflected sound')*.

Ultrasound technique was first used during World War II and documentation of medical application came first in 1952. Edler in Lund recorded cardiac motion and published this in 1953. However, only the expansion of computer technology made it possible to create compact and fast

equipment for echocardiography and its extensive use could begin in the middle of 1980s.

Two dimensional (2D) images show real-time anatomical images of cardiac structures in a scanned sector of the heart.

M-mode (time – motion) imaging is based on information collected along one scan line only. This results in a higher sampling rate and a very accurate presentation of movement for a particular structure. The position of the M-mode line is usually guided by a 2D image.

Doppler studies (continuous, pulsed wave and colour coded) are used to measure blood flow characteristics. Measurements are based on the Doppler-effect (J.C. Doppler, Austrian physicist, 1803-1853) which is described as a frequency shift when the radiation source is moving.

$\Delta f = \dfrac{2vfcos\theta}{C}$ where v is the velocity of the blood, f is the emitted frequency, θ is the angle between the blood flow and the ultrasound beam and C is the velocity of the ultrasound in soft tissue. The velocity can be calculated as $v = \dfrac{\Delta fC}{2fcos\theta}$. Maximum value for $cos\theta$ is $cos0° = 1$ which means that maximum velocity is detected when blood flow is parallel to the ultrasound beam. A $\theta = 20°$ gives a 6% difference in blood velocity which is accepted as the error limit. This means that the measured velocity is practically always less than the real value. Pulsed wave doppler is used when blood flow velocity is to be measured at a certain depth.
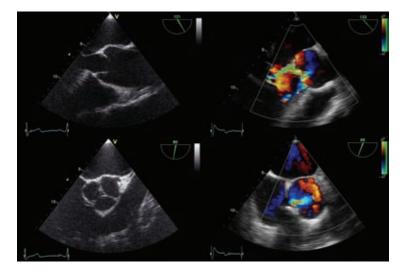

Figure 2
2D and colour flow doppler images of a regurgitant aortic valve.

9

Continuous wave doppler is used to measure high velocities. Measuring the velocities makes it possible to give a good approximation of pressure and thereby flow through regurgitant valves according to the simplified Bernoulli equation $P = 4(v_2^2 - v_1^2)$, where P is the pressure drop, v_2 is the peak flow through the valve and v_1 is the flow just prior to the valve.

Colour coded doppler images give information about flow characteristics. The form, direction and magnitude of the jet are basic pieces of information in grading regurgitant valves but one has to bear in mind that this is still a qualitative method.[10-12]

Radionuclide ventriculography with Multiple Gated Image Acquisition (MUGA)

This method is based on the principle that radioactivity of a certain amount of injected isotope marked red blood cells in a blood pool is proportional to the volume of the blood pool. Radioactivity is detected by NaI crystals in a gamma camera. These crystals work as scintillation detectors and capture γ-radiation with high sensitivity and good resolution. In order to screen radiation beams not perpendicular to the detector, a plate of lead with wholes is placed in the way of the radiation. With absorption of radiation, the scintillation detector gives a light signal. This signal is captured by a photomultiplicator which transforms it into an electric signal and gives information about position in the X and Y directions. The position of a third position signal (Z) is captured by a pulse height analysator (PHA). The PHA accepts the energy signal only if it lies within a previously defined range. This makes it possible to filtrate radiation of unknown origin and thereby improve image contrast and geometrical resolution. The radioactive impulses on the detector are counted (counts), collected and stored by a computer. A certain number of counts are necessary in order to achieve a good image quality and to provide a reliable material for analysis of the blood pool in the imaged organ.

Digital images are stored in the form of a picture matrix, generally 64x64 pixels. Measurements in nuclear medicine are based on evaluation of relative activity within a certain region called region of interest (ROI). The ROI can be delineated manually by an operator or automatically by the computer. Background radiation from blood flow through other tissues than the organ of interest affects analysis of radioactivity therefore background activity is to be subtracted. Images are normalized and filtered to diminish variation and noise, and to enhance contrast.
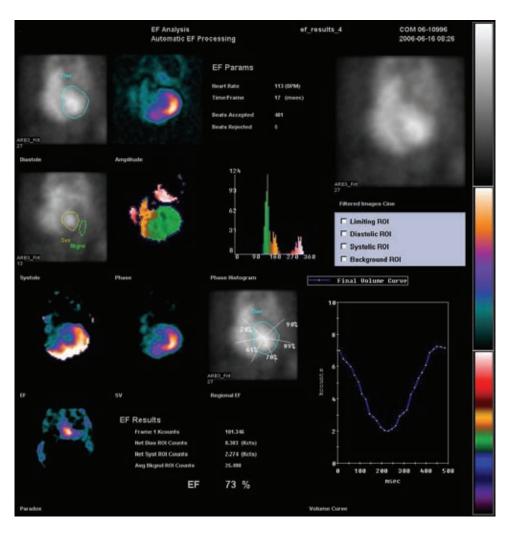
Figure 3
Calculation of EF by MUGA.

Cardiopulmonary Exercise Testing (CPET)

The primary function of the cardiopulmonary system is to provide oxygen (O_2) supply and carbon dioxide (CO_2) elimination. Under steady state conditions, the external respiration (lungs) is equivalent to internal (cell) respiration. Exercise testing using a treadmill or bicycle protocol is commonly used to test exercise capacity. Considerable amounts of additional information can be gained through registration and analysis of respiratory gases. CPET records data about the cardiovascular and respiratory systems under stress

simultaneously, which makes it possible to identify whether the reason for the patient's symptoms is respiratory or cardiac. Physical exercise needs a higher level of oxygen supply ($\dot{V}O_{2\,peak}$) in order to be able to produce the necessary energy for muscle work and results in CO_2 accumulation, which must be eliminated to avoid acidosis.

Chronic aortic regurgitation

Etiology & prevalence

Aortic regurgitation arises when the semilunar cusps between the left ventricle and aorta do not close effectively and a certain volume of blood regurgitates to the left ventricle. When this defect develops and is sustained for a longer period of time, it is called chronic aortic regurgitation. The possible etiology is presented in Table 1.

The prevalence of chronic aortic regurgitation or, as often also referred to in the literature, aortic insufficiency, is 13.0% in men and 8.5% in women, as reported in The Framingham Heart Study in 1999.[13]

The regurgitant blood volume causes volume overload in the left ventricle. The total stroke volume (sum of effective stroke volume and regurgitant volume) is increased. In order to be able to achieve a normal effective stroke volume the heart increases the LV end-diastolic volume. This causes elevation of LV end-diastolic pressure but, nevertheless, LV function can be normal at this stage and the patient is often free of any symptoms. As the illness progresses, a further increase of the LV end-diastolic pressure and impairment of LV function are to be expected. In order to be able to maintain stroke volume, the left ventricle compensates with eccentric hypertrophy. There is an increased demand on oxygen supply due to the volume overload, higher left ventricular pressure and hypertrophy and, at the same time, it is exactly these factors that are limiting coronary perfusion.

1. **Inflammation**
   - 1.1.   Endocarditis lenta
   - 1.2.   Ankylosing spondylitis
   - 1.3.   Rheumatic disease
   - 1.4.   Rheumatiod arthritis
   - 1.5.   Giant cell aortitis
   - 1.6.   Syphilitic aortitis
2. **Tissue degeneration**
   - 2.1.   Marfan's syndrome (cystic medianecrosis)
   - 2.2.   Ehlers-Danlos syndrome
   - 2.3.   Osteogenesis imperfecta
   - 2.4.   Reiters syndrome
   - 2.5.   Myxomatous degeneration
3. **Congenital**
   - 3.1.   Bicuspid aortic valve
   - 3.2.   Outlet supracristal VSD
   - 3.3.   Discrete subaortic stenosis
4. **Other**
   - 4.1.   Chronic severe systemic hypertension
   - 4.2.   Anorectic drugs
   - 4.3.   Idiopathic aortic root dilatation

Table 1
Etiology of chronic aortic regurgitation[6, 14-17]

Natural history & timing of surgery

Less than 6% of asymptomatic patients with normal LVF present with symptoms per year. Nevertheless, 3.5% per year develop LV dysfunction and 0.2 suffer sudden death. Of those who already have LV dysfunction, 25% progress to symptoms and 10% of those who became symptomatic die every year.[16, 17]

In order to avoid irreversible deterioration of LVF, aortic valve replacement or reconstruction is the state of the art treatment for symptomatic patients. As surgery is unavoidable for these patients, natural history has not

been studied on larger groups of patients after the introduction of prosthetic valve implantation in the aortic position in 1953.

Criteria for indication of surgery	Class	Level of evidence
1. Symptomatic patient		
1.1. Severe AR irrespective of LVF	I	B
2. Asymptomatic patient		
2.1. Severe AR		
2.1.1. LV dysfunction (EF < 50%)	I	B
2.1.2. Normal LV function (EF > 50%)		
2.1.2.1. LVED > 75 mm or LVES > 55 mm	IIa*	B*
2.1.2.2. LVED > 70 mm or LVES > 50 mm	IIb*/IIa[†]	C*/ C[†]
2.1.2.2.1. progressive LV dilatation*		
2.1.2.2.2. declining exercise tolerance*		
2.1.2.2.3. abnormal hemodynamic responses to exercise*		
(consider lower threshold values for patients of small stature of either gender)		
3. Asymptomatic and symptomatic		
3.1. Severe & moderate chronic AR while undergoing CABG or surgery on the aorta or other heart valves	I	C
3.2. Whatever/moderate severity of AR undergoing surgery on the ascending aorta	IIb*	C*
3.2.1. patients with Marfan's syndrome[†]	I	C
3.2.2. bicuspid valves[†]	IIa	C

Table 2

Indications of surgery for patients with chronic AR according to present guidelines from the American College of Cardiology* and the European Society of Cardiology[†]. [16, 17]

The above mentioned compensation by the left ventricle keeps the majority of the patients asymptomatic and may disguise a beginning important dysfunction. Therefore, regular follow-up of LVF is recommended

in order to be able to operate before irreversible changes occur. Table 2 shows the indications for surgery for patients with chronic aortic regurgitation.

Finding the optimal time for surgical intervention has remained an art[18-21] during the years of aortic valve surgery, in spite of the evolution of diagnostic methods. Scandinavian studies[22-24] have shown that the relative survival for patients with chronic aortic regurgitation was 67% after 10 years. This group of patients has not only high expected mortality but a relatively high morbidity as well.

Natural history of chronic AR[6, 13, 25] tells us that predominantly young and middle aged persons, with an otherwise long life expectancy, suffer from this disease. A well chosen time for operation of these patients could be essential for their clinical outcome e.g. expected length of life. The "heart of the matter" would seem to be how to determine that point on the timeline when the LVF starts to deteriorate and whether the standard methods of today have the capacity to provide us with these pieces of information.

AIMS OF THE STUDY

I. To analyze the preoperative LVF and survival data in patients suffering from chronic AR without concomitant heart disease, operated on during a ten year interval, 1989-1999.

II. To study

    i) the changes in the EF from rest to exercise, as a measure of LVF both pre- and postoperatively in patients with chronic AR without any other cardiac disease.

    ii) whether any of the measured preoperative LV dimensional or functional parameters could reliably predict LVF after surgery.

III. To evaluate and compare the pre- and postoperative functional capacity of asymptomatic to moderately symptomatic patients with chronic AR by CPET.

IV. To investigate

    i) the aortic valve in detail by TEE, in order to describe the anatomical and, if possible, physiological properties of healthy human aortic valves in vivo.

    ii) if application of echocardiography is reproducible and reliable for measurements of the fine details in the clinical anatomy of the aortic valves.

METHODS

Patients

Paper I

A cohort of patients (n=88) operated on for chronic isolated aortic regurgitation during a ten-year period (1989-1999) was studied. Concomitant cardiac disease was an exclusion criterion. General patient characteristics are indicated in Table 3. Most of our patients were middle aged men with body surface area (BSA) and body mass index (BMI) within normal ranges. The women were somewhat older, had generally lower BSAs and were slightly overweight. The majority of this patient population was moderately symptomatic. All included patients had hemodynamically highly significant aortic regurgitation, judged to need surgical treatment based on clinical signs and echocardiography results.

Papers II & III

Consecutive patients (n=29) with severe chronic aortic regurgitation were included in this study. Patients with concomitant coronary artery disease and with other heart valve disease than chronic aortic regurgitation were excluded. Aortic stenosis was defined as aortic orifice area ≤ 1.6 cm². Moreover, patients who had any history of congenital heart disease or active endocarditis were excluded. Healed endocarditis was not an exclusion criterion. Patients were asymptomatic to moderately symptomatic in this population. Transthoracic echocardiography and MUGA, both at rest and during exercise, were performed 1-2 days before the planned surgery and 6 months postoperatively.

Twenty-six patients completed the study. The reasons for three patients being lost to follow up were: moved abroad, mild claustrophobic symptoms and abstained from the postoperative study, and one patient suffered perioperative stroke with incapacitating neurological symptoms. Preoperative data of these patients were analyzed. In Paper III, the patient in NYHA IV was not included.

Paper IV

Patients (n=32) referred for TEE for suspected cardiac sources of emboli, but diagnosed as normal, were included in this cross-sectional study. Exclusion criteria were concomitant heart valve disease, endocarditis (active as well as healed), history of myocardial infarction or any cardiac abnormality detected during the echocardiographic study, except for trivial valve regurgitation.

	Age (yrs)	BSA (m²)	BMI (kg/ m²)	NYHA
Paper I				
All patients (n=88)	56 ± 13	1.9 ± 0.2	21.0 ± 2.0	III (I-IV)
Men (n=76)	55 ± 14	2.0 ± 0.2	20.6 ±1.7	II (I-IV)
Women (n=12)	65 ± 10	1.6 ± 0.1	23.4 ± 2.2	III (I-IV)
Paper II				
Men (n=29)	51 ± 14	2.0 ± 0.2	27.4 ± 3.1	II (I-IV)
Paper III				
Men (n=28)	50 ± 13	2.0 ± 0.2	27.1 ± 2.8	II (I-III)
Paper IV				
All patients (n=32)	54 ± 14.	1.9 ± 0.2	24.9 ± 3.6	-
Men (n=20)	55 ± 13	2.0 ± 0.1	24.7 ± 3.1	-
Women (n=12)	53 ± 17	1.7 ± 0.2	25.3 ± 4.3	-

Table 3
Demographic data & NYHA functional class

Echocardiography

Global LV function was evaluated using a 4-grade scale, where normal systolic function corresponds to an EF≥50%, slight dysfunction to EF 40-49%, moderate dysfunction to 30-39% and severely reduced function corresponds to EF<30%.[26] The LV diameter was measured in end-diastole and end-systole by M-mode. The aortic root diameter at the level of cusp closure was measured (M-mode) in Paper I.

For transthoracic ultrasound scans a GE Vingmed, Vivid 5 or a Vivid 7 echocardiograph was used in Papers II & III. Images were recorded, stored digitally and analysed off-line.

LV diameters in end-diastole, and in end-systole (LVED, LVES) and LV wall thickness in end-diastole were measured by M-mode and LV mass was calculated according to Devereaux's formula. LV end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and EF according to Simpson's rule were calculated. Volume measurements, an average of three tracings in each registration, were performed by an experienced investigator who was blinded for the EF results of MUGA.

The velocity of E and A waves, E/A ratio and pulmonary venous systolic and diastolic velocity were analysed and used for an integrated description of diastolic function.[27, 28]

In Paper IV, the echocardiograms were recorded using a GE Vivid 5 instrument fitted with a multiplane transesophageal probe. Two-dimensional, electrocardiogram-synchronized cine loops of the aortic valve in the long axis (100-120°) and short axis (45-60°) views, both in mid-systole and end-diastole, were stored digitally and measurements carried out off-line. After scrolling to identify optimal images in end-diastole (defined as the beginning of the QRS) and mid-systole (when the valve was most wide open, coinciding with the top of the T-wave), parameters were measured using the inner edge technique. This method was chosen in order to ensure uniformity for both horizontal and vertical measurements. Anatomic parameters of the entire aortic apparatus, displayed in Fig. 4, were measured three times and the mean value used in the statistical analyses. Two investigators performed the same series of measurements, and this dataset was analyzed for repeatability and reproducibility.
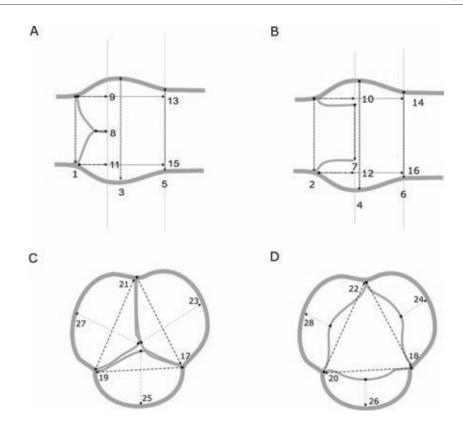
Figure 4

Aortic root and cusp parameters.Panel A: long axis view, diastole, Panel B: long axis view, systole, Panel C: short axis view diastole, Panel D: short axis view, systole.

Identification numbers for parameters: 1, 2: subaortic diameter; 3, 4: maximal sinus diameter; 5, 6: sinotubular junction; 7: cusp separation (valve opening); 8: coaptation; 9, 10: left cusp height; 11, 12: right cusp height; 13, 14: left sinus height; 15, 16: right sinus height; 17, 18: intercommissural distance left coronary sinus; 19, 20: intercommissural distance right coronary sinus; 21, 22: intercommissural distance non-coronary sinus; 23, 24: left coronary cusp diameter; 25, 26: right coronary cusp diameter; 27, 28: non-coronary cusp diameter.

MUGA

Erythrocytes were labelled with 10 MBq/kg Tc-99m pertechnetate using the modified in-vitro technique. Electrocardiogram gated imaging was performed using a General Electric XR/T gamma camera (General Electric Medical Systems, Milwaukee, USA) equipped with a general purpose, low energy collimator and a Genie ACQ collecting station. For optimal separation of the left and the right ventricles, left anterior oblique (LAO 45º) positioning was

used. Supine multigated blood pool imaging was performed first at rest. After this, the patients performed supine bicycle exercise at a pedal rate of 60/min. Besides continuous ECG and heart rate registration, blood pressure was also measured every 2 minutes. The initial workload was 50 W and was increased by 50 W at the next level.

Xeleris Functional Imaging Workstation, EF Analysis (General Electric Medical Systems, Milwaukee, USA) was used for image and data analysis. Five Mcounts in total were collected at rest and 2.5 Mcounts during steady state exercise, with 32 frames per heart cycle in a matrix size of 64 x 64. Left ventricular end-diastolic and end-systolic outlines were marked manually by each of two operators separately, who made 3 measurements each. The mean of these measurements was used. The automatic algorithms of the computer program were used for background (BG) correction. Left ventricular ejection fraction (EF) was calculated as

$$EF\,(\%) = \frac{\left(LV\,counts\,_{diastole} - BG\,counts\right) - \left(LV\,counts\,_{systole} - BG\,counts\right)}{\left(LV\,counts\,_{diastole} - BG\,counts\right)} \times 100\,.$$

Cycle length windowing with dynamic arrhythmia filtration[29] with forward gating was used. A heart rate (cycle length) histogram was generated and observed for 1-3 min. When steady state heart rate was achieved a window was centred round peak heart rate ±10% for patients with sinus rhythm. Beats outside this interval were rejected. In patients with atrial fibrillation the window of acceptable beats was widened up to 15-20% to reduce imaging time.

Subgroups of patients were formed based on preoperative EF exercise response (ΔEF) during MUGA and were categorized as decreasing: ΔEF < -5%, unaltered: -5% $\leq \Delta$EF $\leq$ 5% and increasing: ΔEF > 5%. A 5% or higher increase of EF was considered normal. These subgroups were defined considering the above limits and a 5% bias of the method.[30-32]

CPET

An incremental symptom limited bicycle exercise test using an electrically braked bicycle ergometer (eBike, CE-0459, Ergoline, GE Medical Systems, Freiburg, Germany) at a pedalling rate of 60/min was performed by patients in Paper III. The exercise test was started at 50 Watts (W) steady state for 6

minutes. Thereafter, the workload was increased by 10 or 20 W every min until exhaustion or appearance of any other limiting symptom.

Expired gas was continuously collected through a low resistance tightly fitted mouthpiece with the nostrils clamped. Samples were analysed by MedGraphics CPX (Medical Graphics Corp., St. Paul., Minnesota, US). Oxygen, carbon dioxide and flow sensors were calibrated immediately prior to each test.

A 12-lead electrocardiogram (ECG) was recorded continuously during the test. Systolic and diastolic blood pressure were recorded at baseline and systolic blood pressure was measured at 3 minute intervals during the test, followed by an assessment of dyspnoea, chest pain (Borg CR-10 scale)[33, 34] and Borg's rate of perceived exertion (RPE).[33-35]

The test was performed aiming to reach maximal exertion, "levelling-off" of the oxygen uptake and respiratory exchange ratios clearly above 1. The ECG recording was continued for 5 minutes after termination of exercise.

Statistical methods

Continuous data are presented as mean ± standard deviation (SD), ordinal data as median and range. Significance was set as $p < 0.05$ throughout these studies. Computer analyses were carried out by STATISTICA™ 6.0 - 8.0, StatSoft®, Tulsa, Okla., USA.

Kaplan-Meier product-limit analysis was used to assess cumulative long-term survival. Risk analysis was performed by Cox regression model in Paper I. Comparison of pre- and postoperative data was performed by Wilcoxon's matched pairs test[36] and by sign test in Papers II & III respectively.

General discriminant analysis[37] (forward stepwise) model and general linear models, were used to verify connections among pre- and postoperative variables for data in Papers II & III.

The multivariate method of tree clustering[37] by Ward's method was applied to uncover relationships among data. Cluster analysis is an exploratory technique which organizes observed data into meaningful categories. Ward's method is based on analysis of variance as the linkage rule. The degree of association between variability of two parameters is maximal if they belong to the same group and minimal otherwise.

Multiple regression (forward stepwise regression) was performed to further specify relationships of significance among variables within a cluster

formerly defined by tree clustering. Finally, these variables were plotted against each other in Paper IV.

Reproducibility and repeatability were assessed by correlation coefficient and Bland-Altman analysis[38, 39] in Paper III, and by gage process analysis[40] in a subgroup of 11 randomly chosen patients in Paper IV.
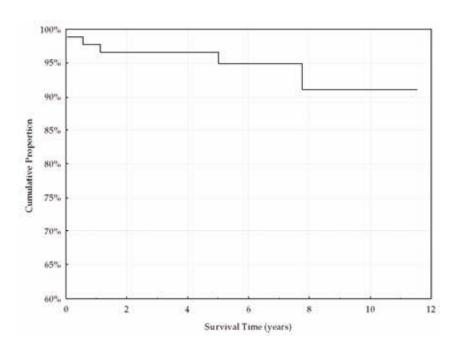
Ethical considerations

The presented studies were performed according to the principles of Human Rights in Declaration of Helsinki and were approved by the Ethics Committee of the Faculty of Health Sciences, University of Linköping. All the patients in the prospective studies (Papers II- IV) gave their informed consent.

RESULTS

Survival analysis (I)

In the group of the retrospectively studied patients 30-day mortality was 1%, due to acute heart failure (preoperative NYHA I and reduced LVF with corresponding EF 30-40%). Late mortality was 11%. Autopsy was performed in the case of early death and 2 of the cases of late death. Neither autopsy reports, nor clinical assessment indicated malfunction of the prostheses. The cause of death was cardiac in 5 cases: 2 cases of heart failure and 3 cases of myocardial infarction. Patients who died from heart failure were in NYHA classes III-IV preoperatively and those who suffered a late, fatal myocardial infarction were all in NYHA class III. Estimated preoperative EF of these five patients was > 50% in one case, 40-50% in two cases, and 30-40% in one case and < 30% in one case. Non-cardiac causes of death were insulin coma in 1, prostatic cancer in 1, pleuracarcinosis in 1 and cerebral bleeding in 2 patients, both of whom had mechanical prostheses and were treated with coumarine.
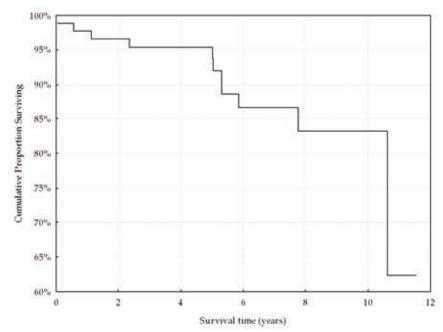
A

B

Figure 5
Kaplan-Meier analysis. Panel A: Cardiac event free survival Panel B: Overall survival.

Survival analysis is shown in Figure 5. Gender, age and LV function could not be shown to be independent risk factors for impaired survival. Thrombosis, dysfunction of the prostheses, embolization or endocarditis were not reported postoperatively.

Left ventricle (I-III)

Left ventricular diameters and volumes

In the retrospective study group, the mean aortic diameter was 37.5 ± 8 mm at the level of the cusps. The end diastolic diameter of the LV was 70 ± 10 mm while the end systolic diameter of the LV was 49 ± 10 mm.

The prospectively studied patents also had a pronounced LV dilatation (LVED = 68 ± 6 mm, LVES = 49 ± 7 mm) with wall thickness within the upper normal range, which resulted in a high LV mass preoperatively. LV diameters diminished markedly, generally falling within normal limits postoperatively

and the overall comparison of pre- and postoperative LV masses and LV end-diastolic volumes showed significant reduction after surgery (Table 2, Paper II).

Preoperative NYHA class had no relation to pre- or postoperative left ventricular end-diastolic or end-systolic diameter (LVED, LVES) or LV mass. However, NYHA and the preoperative left ventricular volume at rest were significantly connected (p=0.02) but no other conclusions could be made concerning volumes.

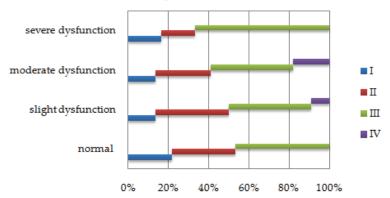*Left ventricular function at rest & during exercise*

Left ventricular function was normal, or only slightly impaired, in the majority of the retrospectively studied patients (Fig. 6A). However, 31 patients had moderate or severe left ventricular dysfunction preoperatively, i.e. estimated EF was ≤ 40%. Figures 6 B & C present the preoperative EF measured by echocardiography and MUGA in the prospective studies. In the same material, preoperatively calculated EF at rest was not a predictor for postoperative EF at rest.

By MUGA we found that both pre- and postoperative EF at maximal workload (EF_{max}) could be predicted from preoperative EF_{rest} (p < 0.001 and p=0.007 respectively).

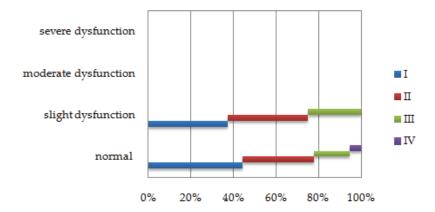Preoperative NYHA class was independent of both pre- and postoperative EF_{rest} and ΔEF.

A

LVF - ECHO & NYHA for patients 1989-1999
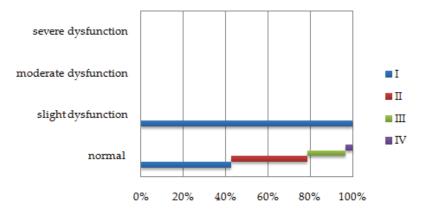
27

B

C

Figure 6

Proportional distribution of NYHA functional class (I-IV) in the different preoperative EF categories at rest for both retrospectively and prospectively studied patients. Panel A: Patients operated on between 1989 and 1999. Panel B: Patients operated on between 2002 and 2006. Panel C: Patients operated on between 2002 and 2006. EF calculated by MUGA.

The semiquantitative description of LVF corresponds to the following EF values: Normal ≥ 50%, slight dysfunction 40-49%, moderate dysfunction 30-39%, severe dysfunction < 30%.

Left ventricle and aortic valve surgery

Preoperative LVED proved to be a predictor for both preoperative and postoperative ΔEF (p=0.003 and 0.04 respectively) in general but did not have any predictive value in allocating the patients in the different subgroups based on EF response postoperatively. LVES, however, was independent of any exercise response. Preoperative left ventricular volumes could not be connected to EF at rest or during exercise.

Analyses of subgroups, formed according to ΔEF, showed that patients with decreasing and unaltered EF preoperatively presented a significantly improved but still abnormal ΔEF during exercise postoperatively. The group of patients with increasing EF preoperatively responded similarly to exercise postoperatively (Fig.3 & Table 2, Paper II). Preoperative ΔEF proved to be a predictor for postoperative ΔEF (p=0.02). Moreover, preoperative ΔEF was the single and only predictor as to which subgroup (EF decreasing: p=0.03, unaltered: p=0.02, increasing: p=0.0008) patients were to be allocated postoperatively.

Physical work capacity (III)

Patients performed the exercise test to maximal exhaustion both pre- and postoperatively. CPET data are shown in Table 3, Paper III. Patient's physical work capacity was classified according to Åstrand's reference values[41], which are corrected for gender, age and weight. According to this classification, the pre- and postoperative work capacity was "low" in 17 cases and 16 cases, "fair" in 4 and 6 cases and "average" in 5 and 3 cases, for pre and post respectively. Figure 1, Paper III illustrates the different groups based on preoperative work capacity and their performance pre- and postoperatively.

Preoperative physical work capacity class according to Åstrand et al.[41] was a predictor of postoperative maximal oxygen uptake ($\dot{V}O_{2\,peak}$) per kg body weight (p=0.03): having a low physical work capacity according to Åstrand´s classification implied a significant probability of remaining in the low performance class after surgery.

Echocardiographic anatomy of the normal aortic valve (IV)

All aortic diameters changed by less than 1 mm between systole (s) and diastole (d). The subaortic diameter (SAD) showed no statistically significant connection to maximal sinus diameter, or to the STJ. However, the STJ could be described as a function of the mean maximal sinus diameter (maxSiD):

$$STJ = 3.7 + 0.76 \times \frac{maxSiD_s + maxSiD_d}{2}.$$

No connection was found between STJ and cusp or sinus length in the long-axis view.

Coaptation was observed in all patients, with length found to be independent of the aortic diameters but related to left coronary (LC) and right coronary (RC) cusp height in diastole;

$$coaptation = 1.3 + 0.45 \times \frac{LC\,cusp\,height_d + RC\,cusp\,height_d}{2}.$$

Neither LC sinus height nor RC sinus height in diastole alone showed any connection with coaptation. Their mean value, however, had a certain relation to coaptation, which was significant. The opening of the valve (OV) as a function of the subaortic diameter can be described as

$$OV = 1 + 0.84 \times SAD.$$

The OV was also significantly related to the mean of the LC and RC cusp height in systole.

The intercommissural distances (ICD) in the right coronary (RC) and non-coronary (NC) sinuses measured in systole were equal and larger than that of the left coronary (LC) sinus. In diastole, the ICD in the RC sinus proved to be the largest, followed by LC sinus and NC sinus, when studied in the short-axis view (Table I, Paper IV). The ICD in the NC sinus changed more than that in either the LC or RC sinuses. The latter two changed equally between systole and diastole. These measurements showed the RC sinus to be deeper than the LC sinus, and the RC cusp to be longer than the LC cusp in the long-axis view. Sinus height was shortened by 2 mm in systole (Table I, Paper IV). The LC and RC cusp diameters were similar, and larger than the NC cusp diameter in

systole. However, this pattern changed in diastole, with LC and NC cusp diameters showing similarity and the RC cusp diameter being smallest (Table I & Fig. 2, Paper IV). Changes in cusp diameter and ICD were largest in the NC sinus and cusp, whereas changes in the LC and RC sinuses and cusps were smaller and of similar magnitude.

DISCUSSION

Aspects of pathophysiology, prevalence & gender

When defining inclusion criteria for these studies, we aimed to form a population with chronic severe isolated AR requiring surgery, without co-existent cardiac disease.

The decision about surgery was then based on either progressive LV dilatation, indication of a declining LV function despite a normal EF, or the appearance of symptoms, together with an awareness not to delay surgery too long.

One fourth of the patients could be considered strictly asymptomatic, those who were NYHA I without medication. The rest of the patients were symptom free while on medication, or had mild to moderate symptoms.
That a few patients were in a higher NYHA class upon entry into the study was, in several of the cases, due to their AR not having been detected until then.

The patients were mainly middle-aged men, and this is influenced by the exclusion of patients with aneurysms, since aneurysm in connection with AR has been shown to be related to female gender.[13, 42-44] Chronic aortic insufficiency occurs predominantly in men between the ages of 20 and 80. The incidence and the prevalence of chronic aortic insufficiency[13, 42] explain the lack of women among patients in the prospective studies.

Previously published studies[22-24] did not, in contrast to our studies, define acute endocarditis as an exclusion criterion. Since acute surgery due to endocarditis was, however, extremely rare during the time period covered by these previous studies, our conclusions concerning comparison of survival data can still be assumed to be valid for the retrospectively studied patient population.

Survival after surgery for chronic AR

Although we have not found statistical comparisons to be justified, due to differences between populations for our retrospective data and results of earlier studies, our data from the last decade indicate a higher survival rate

than that in the earlier Scandinavian samples. One Scandinavian study[22] covered the period 1969 to 1983 and showed a relative survival rate of 67% at 10 years in patients with AR despite a similar mean age at surgery to that of the patient population in our study. Other international studies[42-46] that covered the approximately 20-year period prior to our study have shown that the expected cardiac survival, as well as the overall survival for patients undergoing surgery for chronic aortic insufficiency was lower than that experienced with our patients. Turina et al.[46] published a study on 192 patients with chronic AR operated on between 1970 and 1983. Perioperative mortality was 2.6% and the survival rate after 10 years was 76%. They found that advanced age at the time of surgery and higher preoperative NYHA class were the main predictors of late mortality. However, Morris et al.[45] studied a group of patients who had both AR and aortic stenosis, and only a smaller group of their patients had pure AR.

During follow-up, one fifth of our patients had needed in-patient hospital care because of significant heart problems and a third had symptoms that could be of cardiac origin. The trend in the treatment of aortic regurgitation today is to recommend surgery before signs of obvious LV dysfunction develop; for example, asymptomatic patients often undergo surgery. Looking back one decade, this strategy had not completely penetrated, since the majority of our patients were moderately symptomatic, and substantial preoperative LV dysfunction was present in a third of the cases preoperatively in the retrospectively studied patients.

None of the prospectively studied patients died or suffered perioperative myocardial infarction.

Compensated & decompensated left ventricle in chronic AR

A leaking aortic valve causes a certain fraction of blood ejected at each systole to regurgitate back into the LV during diastole, causing a "pendulum volume". The total stroke volume increases, partly due to the regurgitant volume and partly because the LV increases its volume so as to provide an unaltered effective stroke volume. This leads to volume overload and consequently also to a pressure overload and, in order to compensate, the LV develops eccentric hypertrophy. Thus, an increased myocardial mass is inevitable for this compensation.

While the LV is able to compensate for the regurgitant lesion, LV diameters and mass increase are appropriate for meeting the increased needs

and EF remains within normal range. When reserves begin to languish, distinct alterations arise. A further dilatation of the LV and a drop in EF can be observed and, eventually, the patient becomes symptomatic. Current guidelines[16, 17] recommend operation based on LV diameters and EF to prevent further deterioration and preserve LVF (Table 2), and to avoid premature death.

There is general consensus[16, 17, 47-51] that patients with significant AR should be operated upon when signs of LV dysfunction appear, irrespective of symptoms. EF_{rest} is considered to be an insensitive marker[52-55] and LV function during exercise has proved to be related to prognosis in AR patients. Consequently, even if the time point for surgery of a patient with chronic AR has been theoretically well defined and described[16, 17], this theory often proves to be difficult to apply in clinical practice in asymptomatic or mildly symptomatic patients with normal EF_{rest}.

Our prospectively studied patient population had an overall normal ejection fraction (Fig. 1, Paper II). We did not find any connection or correlation between NYHA functional class and EF, which is concordant with results from earlier studies. This confirms the earlier observations[55, 56] that lack of symptoms cannot be relied upon for judgement of LV function and timing of surgery in AR.

In order to detect imminent LV dysfunction in asymptomatic or mildly symptomatic patients, exercise testing is recommended in addition to follow-up of LV diameters and ejection fraction at rest for further differentiation. The predictive value is, however, considered to be unclear due to lack of sufficient evidence[16, 17].

Previous studies of MUGA have shown that EF during exercise and exercise EF response have predictive value for the predicted length of the period until symptoms develop and there is an absolute indication for surgery.[57, 58] These studies were performed in an era when asymptomatic patients were not operated on. Furthermore, these variables had predictive value for the risk of sudden cardiac death in the natural history of the disease.[59] In the present study, preoperative EF_{rest} was found to be significantly correlated to EF_{max}, separately both pre- and postoperatively, which was in agreement with previous studies.[30, 51, 52, 60] However, preoperative EF_{rest} was not related to postoperative EF increase upon exercise and was, therefore, not found to be informative for LV performance during exercise postoperatively. Moreover, we found that preoperative exercise response was not only a predictor for postoperative exercise response but that preoperative ΔEF predicted which type of exercise response the patient was going to have

postoperatively. This is an extension of results in accordance with earlier studies of cardiac catheterization[57] and echocardiography at rest and post-stress.[58]

Patients in the different subgroups defined by preoperative EF exercise response showed a similar exercise response pattern postoperatively. Decreasing EF during exercise preoperatively meant an improved but still not normally increasing EF during exercise on follow-up. The general pattern was that the group of patients with unaltered EF preoperatively responded to exercise normally after operation while those who had had normal ΔEF had preserved it. This might indicate that at least those with decreasing EF should have been operated on earlier in order to preserve LVF, which had obviously deteriorated at the time of the operation in spite of normal EF_{rest}. The importance of functional evaluation during exercise is emphasized by the left ventricular diameters lying within intervals, where guidelines recommend regular follow-up and consideration of hemodynamic response before a decision about surgery is recommended. LV volumes significantly diminished postoperatively in the whole study group, as expected and described in previous studies.[61, 62] We found that EF calculations by MUGA and by ultrasound were in agreement, although echocardiography gave a lower level of EF in our study, as has been reported by others.[63] This indicates that careful choice and use of validated methods is important for follow-up over the time. Determination of EF by radionuclide ventriculography has high reproducibility, even during exercise[64] and therefore adds valuable information in borderline cases.

Effects of AR on physical work capacity

During exercise, the fraction of the stroke volume that regurgitates into the LV, i.e. the regurgitant fraction, diminishes, due to the heart rate increase with a relatively more pronounced shortening of diastole than of systole. This reduction is reported to be approximately 20%.[65] Due to this reduced regurgitation, patients with significant AR show a reduction of both diastolic and systolic LV volumes during exercise.[65, 66] Thereby, if their LV function is normal, the EF of persons with AR increases upon exercise, even if total stroke volume does not. This hemodynamic reaction to exercise in AR provides an extremely adequate explanation as to, why the exercise capacity may remain normal for a long time despite severe AR. When symptoms occur, initial complaints are usually tiredness or dyspnoea upon exertion, indicating a

reduced capacity to increase effective cardiac output normally and/or elevated LV filling pressures.

During the last 1-2 decades, CPET has been extensively studied[67-69] and reported to be a valuable tool in the evaluation of patients with heart failure. A few studies have also pointed towards the possibility of using CPET to evaluate the results of cardiac rehabilitation after cardiac events or cardiac surgery.[70-73] These studies have shown that CPET is a reliable method and that $\dot{V}O_{2\,peak}$ is a useful predictor of heart failure patients' event free survival, as well as a good measure of the positive effect of cardiac rehabilitation by physical training.

In our patients with severe AR, there was a striking discrepancy between preoperative NYHA class, EF and physical work capacity. The patients as a group (median NYHA II) presented a surprisingly poor physical work capacity preoperatively and failed to show any improvement 6 months postoperatively and patients in NYHA III did not consistently have the lowest physical work capacity.

The expected improvement, as seen in previous studies in patients who entered a cardiac rehabilitation program [71-73], did not occur in this specific group. This could be explained by the fact that our patients did not participate in a cardiac rehabilitation program or, simply, that the follow-up interval needs to be longer for patients with chronic AR[74], assuming a longer recovery period than for patients with coronary disease or other valve disease.[70-73] Further studies are indicated as to whether having a prosthetic aortic valve may also per se impede the physical work capacity.

The lack of postoperative improvement in our patients could also be due to subclinical LV dysfunction that is not possible to identify by preoperative examinations at rest. However, the cardiac compensation by LV dilatation and eccentric hypertrophy, as well as systemic adaptations, may be insufficient and thereby manifested during CPET. Preoperative physical work capacity by Åstrand's classification, a $\dot{V}O_{2\,peak}$ nomogram corrected for age, gender and weight, was a predictor for postoperative physical work capacity. As $\dot{V}O_{2\,peak}$ is an indicator of aerobic work and thereby for the general status of the oxygen transport and utilisation capacity, it may represent potential for detecting latent heart muscle dysfunction at an earlier stage. This would implement a complementary examination to the routine follow-up of the patients with chronic AR who have normal EF and moderately elevated LV diameters and volumes.

Timing of surgery

The treatment of severe chronic aortic regurgitation is surgical, and in the vast majority of cases, means implantation of a prosthetic valve. Although this can be done with low perioperative mortality, the postoperative morbidity is not negligible, e.g. postoperative heart failure, patient prosthesis mismatch[75-78] and bleeding complications due to coumarine treatment.

Timing of surgery for patients with chronic aortic regurgitation remains an art[18, 19, 79, 80] because our standard methods merely estimate LVF and do not provide exact measurement of myocardial contractility. We of course, have to keep trying to give the best possible estimation.

Our retrospective analysis showed that overall survival for patients operated for chronic AR during a defined interval was improved compared to previously published data on survival for chronic AR. One third of these patients had moderate or severe LV dysfunction at the time of the operation and an irreversible LV dysfunction may have affected their postoperative survival and morbidity.

The LVF, based on resting EF alone, for the prospective study group was better compared to the retrospective group (Fig. 6) but a majority of these patients presented abnormal EF reaction and low physical capacity both prior to and after surgery. These reactions may be used to provoke latent LV dysfunction and identify patients on the borderline of developing LV dysfunction and thereby indicate an operation earlier in the natural history of the disease.

As a treating physician, it is a difficult decision to recommend surgery to an asymptomatic person, who will not feel any improvement but rather, in the short term, may suffer complications. The decision to recommend surgery must then rest on the rationale that surgery is highly probable to be beneficial to the patient in the long term, to avoid irreversible LV dysfunction.

Clinical anatomy of the aortic valve

Although supporting data are scarce as to whether patients with chronic AR should have better preserved LVF or have a more favourable outcome of rehabilitation after aortic valve sparing operation[81-84] compared to implantation of a prosthetic valve, it is conceivable that avoiding patient prosthesis mismatch per se would provide better function. Reconstructing a

failing valve requires knowledge about normally functioning valves. Several animal[85-92] and human[93-97] studies describing normal anatomy and function of the aortic valve and root have been performed. The former in vivo but the latter mostly consist of autopsy data. The aortic flow characteristics and opening patterns of the valve have been studied in human series of small size.[9, 85, 98-101]

We have applied an established diagnostic method (TEE) and extended its use, in order to provide a more detailed description[102-105] of the in vivo physioanatomy of the normal aortic root in its entirety in contrast to previous studies.[106-110] Measurements of the aortic root showed overall larger dimensions compared to those found in cadaver studies and reported previously, when the same parameter was measured.[93, 96, 97] Postmortem studies are based on measuring inner size, as in the present study. However, the effect of blood pressure as a factor that can modify dimensions in vivo should also be taken into consideration. A difficulty emerges even when comparing our measurements to earlier echocardiographic studies, due to differences in measuring by inner edge to inner edge, trailing edge to leading edge, or leading edge to leading edge.

There is no ruling consensus about whether the sinuses are alike or if they are different in size.[94, 96] The statement, based on an autopsy material, by Berdajs et al.[96] of a pattern 'R > N > L', meaning that the right coronary sinus is the largest and the left coronary sinus the smallest, was not confirmed by the present data. Indeed, analysis of these data showed the NC sinus and cusp not to resemble the other two, although these relations were shown to depend on the cardiac cycle. Changes in the dimensions of both cusp diameter and intercommissural distance were largest in the NC area and less, but still alike, for the RC and LC parameters. The interpretation here is that the NC sinus and cusp have a more extensive movement than the other two, at least when studied using 2D TEE.

It was also found, somewhat surprisingly, that the subaortic diameter was not related to either the maximal sinus diameter or to the STJ. This may mean that this parameter is influenced by the structures and physiological events in the left ventricle, and that its changes have no impact on maximal width in the sinuses of Valsalva and the STJ. This observation is concordant with the observations of Sutton et al.[111] and Lansac et al.[112] If the subaortic diameter is related to the left ventricular outlet, then a statistically significant relation to the opening of the valve, as found in the present study, would be reasonable. However, as the constant in this equation is less than the standard deviation of the subaortic diameter, it can be stated that a normal valve opens to

approximately 80% of the dimension of the subaortic diameter in the transesophageal long-axis view. When choosing a graft for reconstructive surgery, this means that a graft with a diameter the same as the subaortic diameter would allow valve opening without contacting the graft. Hence, an accelerated leaflet degeneration and thickening caused by contact with the graft might be avoided.

The relation between the STJ and the maximal sinus diameter might be relevant in the reconstruction of aortic root geometry. The regression equation may be simplified to state that, in healthy persons, the STJ is three-quarters of the maximal sinus diameter.

Another parameter that is usually considered important is coaptation; however, such importance is based on common sense as its existence was rarely stated and its length was not measured in earlier studies. The finding that coaptation occurred in all of the patients and that all of the valves were competent, emphasizes its importance. The analysis showed a relation only between the cusps in diastole and the coaptation. The equation describing coaptation considering the standard deviation for coaptation and that the precision of the echocardiographic measurements is 1-2 mm, can be interpreted as, without oversimplifying or neglecting important details, that the length of coaptation was approximately half of the cusp height. It is noteworthy that, although there is frequently a coexistence of root dilatation and an absence of coaptation in AR patients, the length of coaptation in normal subjects was found to be independent of the aortic root diameters.

CONCLUSIONS

I. Retrospective analysis of left ventricular function

 i) A reduced LV function preoperatively could be seen in a substantial number of patients operated on for chronic AR during the period 1989-1999.

II. LV function at rest and during exercise

 i) Preoperative exercise response measured with radionuclide ventriculography can identify patients at risk of an abnormal postoperative LV function response during exercise.

 ii) It can predict what kind of exercise response (decreasing, unaltered or increasing EF during exercise) to expect after surgery.

 iii) An abnormal EF response to exercise might also occur in patients who do not fulfil the criteria for surgery based on LV dimensions by echocardiography or EF at rest.

III. Physical work capacity in patients with chronic AR

 i) Echocardiographic parameters such as EF, LV diameters and volumes at rest did not reflect the preoperative physical work capacity in patients with chronic AR and neither did they predict the postoperative physical work capacity.

IV. Echocardiographic anatomy of the normal aortic valve

 i) The length of coaptation in normal subjects was found to be independent of the aortic root diameters and was approximately half of the cusp height.

 ii) The subaortic diameter was not related to either the maximal sinus diameter or to the STJ.

 iii) A normal valve opens to approximately 80% of the dimension of the subaortic diameter in the transesophageal long-axis view.

CLINICAL IMPLICATIONS

I. Efforts should be made to evaluate LV function and detect LV dysfunction, preferably by a non-invasive method, early in the natural history of patients with AR. The rationale for performing surgery earlier than previously will most probably be justified.

II. Patients with significant chronic AR could benefit from follow-up of LV function during exercise and by considering surgery when the character of the exercise response is abnormal or changes character.

III. We suggest that the use of CPET in preoperative follow up and decision-making as a complement to echocardiography may be a useful tool in identifying patients with poor physical work capacity indicating insufficient compensation and latent LV dysfunction in chronic AR.

IV. Detailed mapping of the aortic root by echocardiography might help to improve techniques for restoring normal functional anatomic relations in the pathologically altered aortic root.

ACKNOWLEDGEMENTS

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