Aortic Valve Surgery

Clinical studies
after autograft, homograft and prosthetic valve replacement

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To my beloved family

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Introduction and Aims: Aortic valve disease in symptomatic adult patients often requires surgery. Several alternatives are available: repair, mechanical and biological prostheses, homograft and the Ross procedure. In the process of choosing valve substitute, the individual patient's characteristics are matched against the characteristics of the different valve alternatives. This thesis includes clinical studies addressing outcome after the Ross procedure, after homograft replacement in endocarditis and Doppler versus catheter findings in patients with prosthetic valves.

Methods: In *Study I,* surgical correction of autograft mismatch in the Ross operation (n=77) was investigated. In *Study II* we established the normal aortic dimensions using echocardiography in normal controls (n=38) and compared these findings with Ross operated patients (n=71) in a long-term follow up (101±31 mo). In *Study III,* patients with prosthetic (n=31) or native valve endocarditis with abscess (n=31) were operated with a homograft replacement, and followed for 37±11 months. In *Study IV* we investigated the flow resistance of mechanical and biological aortic valves using simultaneous Doppler and left ventricular and aortic pressure measurements (high-fidelity catheters).

Results: *Study I:* Among the 24 patients without surgical correction an early moderate aortic regurgitation was present in eight patients (33%) compared with two of the following surgically corrected 53 patients (4%, p=0.001). *Study II:* A large proportion of the patients showed dilatation of the autograft (43%) and native aorta (32%) at late follow-up, and 5 were re-operated due to dilatation. There was a progression in both autograft and native aortic dimensions from the baseline to the follow-up. Only baseline autograft size did predict late dilatation (>4 cm). *Study III*: Nine patients (15%) died within 30 days. Variables associated with early mortality were higher Cleveland Clinic Risk Score (p=0.014), ECC-time (p=0.003), inotropic support (p=0.03), bleeding (p=0.01) and myocardial infarction (p<0.001). Cumulative survival was 82%, 78%, 75% and 67% at one, three, five and ten years, respectively. Quality of life (SF36) was not significantly different to a matched healthy control group. *Study IV:* There was a strong linear relation between catheter and Doppler gradients (r = 0.85 to 0.92). Doppler overestimated catheter gradients in both the mechanical and stented biological valve.

Conclusions: Aortic regurgitation immediately after the Ross procedure can be minimized with surgical correction of anatomical mismatch in the aortic root. The autograft as well as the native aorta continues to dilate and this may lead to reoperation. Severe acute aortic endocarditis treated with homograft replacement is still associated with a substantial early complication rate and mortality. Long-term survival, quality of life and homograft function is satisfactory in patients surviving the immediate postoperative period. In the first in vivo study of the relation between Doppler and catheter gradients in prosthetic valves, we found a significant Doppler-catheter discrepancy in bioprostheses. Doppler overestimates the net gradients in both mechanical and biological prostheses.

Original papers

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

I.   Gunnar Svensson, Obaid Aljassim, Sven-Erik Svensson, Odd Bech-Hanssen and Ulf Kjellman.
      Anatomical Mismatch of the Pulmonary Autograft in the Aortic Root May Be the Cause of Early Aortic Insufficiency After the Ross Procedure.
      Eur J Cardiothorac Surg. 2002 Jun; 21(6):1049-54.

II.   Obaid Aljassim, Gunnar Svensson, Sossio Perrotta, Anders Jeppsson and Odd Bech-Hanssen.
      Dilatation of the Pulmonary Autograft and Native Aorta after the Ross Procedure: A Comprehensive Echocardiography Study.
      (Submitted)

III. Sossio Perrotta, Obaid Aljassim, Anders Jeppsson, Odd Bech-Hanssen and Gunnar Svensson.
      Survival and Quality of Life After Aortic Root Replacement With Cryopreserved Homograft in Acute Endocarditis.
      (Accepted for publication June 22, 2010 in Ann Thorac Surg).

IV.   Obaid Aljassim, Gunnar Svensson, Erik Houltz, and Odd Bech-Hanssen.
      Doppler-Catheter Discrepancies in Patients With Bileaflet Mechanical Prostheses or Bioprostheses in the Aortic Valve Position.
      Am J Cardiol. 2008 Nov 15;102(10):1383-9. Epub 2008 Sep 11.

Contents

Abbreviations

ACC	American college of cardiology
AHA	American heart association
AR	aortic regurgitation
AS	aortic stenosis
AVA	aortic valve area
AVR	aortic valve replacement
CABG	coronary artery bypass grafting
CPB	cardiopulmonary bypass
ECC	extracorporeal circulation
EOA	effective orifice area
LV	left ventricle
LVOT	left ventricular outflow tract
NVE	native valve endocarditis
NYHA	New York heart association
PR	pressure recovery
PVE	prosthetic valve endocarditis
QoL	quality of life
SD	standard deviation
SF-36	short form
SV	stroke volume
TAVI	transcatheter aorticvalve implantation
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
VTI	velocity time integral

1. Introduction

The aortic valve function is to open and allow blood to be ejected from the left ventricle (LV) into the aorta in systole, and to prevent blood from flowing backward into the left ventricle during diastole. Aortic valve dysfunction is the most common cardiac-valve lesion and can be caused by either narrowing (stenosis) or leaking (regurgitation). In adults, aortic valve disease is often progressive and requires surgery in symptomatic patients. Aortic valve dysfunction places the patient at increased risk of heart failure and sudden death if untreated. Treatment of aortic valve dysfunction by aortic valve replacement (AVR) has improved the outcome for the patients dramatically.[1, 2]

Etiology and pathophysiology of aortic valve lesions

Aortic stenosis(AS)

AS is a degenerative and calcific process in the majority of patients and rheumatic, congenital (bicuspid valve) or post-infective in the remaining.[3] The outflow obstruction in AS develops gradually – usually over decades – and the left ventricle compensate the systolic pressure overload by increasing the LV wall thickness (hypertrophy).[4]

Aortic regurgitation (AR)

The etiologies of AR are congenital (bicuspid valve), annular ectasia (root dilatation), cusp-prolapse due to unknown reasons (idiopathic), infective, aortic dissection, fenestration or trauma.[5, 6] AR may be acute or develop gradually over time as a chronic condition. The majority of lesions produce chronic AR with slow, insidious LV dilatation and a long asymptomatic phase. Other lesions, in particular infective endocarditis, aortic dissection, and trauma, more often produce acute severe AR, which can result in sudden, catastrophic, elevation of LV filling pressures and reduction in cardiac output.

Both pressure (AS) and volume (AR) overload result in increased cardiac workload, decreased efficiency, arrhythmias, and ultimately decreased survival. A surgical valve procedure may reverse this process if the intervention occurs before the damage on the LV becomes permanent.

Natural history

Aortic stenosis

The initial phase of the disease process leading to stenosis of the aortic valve is called aortic sclerosis. This process causes thickening of the aortic valve leaflets without obstruction of the ventricular outflow. The sclerosis gradually increases and in approximately 16% of patients the sclerosis progresses to stenosis within 8 years.[7, 8] AS appears to progress more rapidly in degenerative calcific disease than in patients with congenital or rheumatic disease.[9] The onset of symptoms (angina, syncope and heart failure) in AS identifies a critical point in the natural history of the disease. However, in severe AS many patients remain asymptomatic for many years and the risk of death by the disease in these asymptomatic patients is then < 1% per year.[10, 11] With symptoms, the prognosis is usually poor without surgery. Mortality is sharply increased after onset of symtoms[12] and the survival rate is approximately 50% after two years, and 20% after five years. Sudden death is known to occur in patients with severe AS and is rare without prior symptoms.[10, 13, 14]

Aortic regurgitation

There are no recent large-scale studies on the natural history of chronic AR in symptomatic or asymptomatic patients. Available data indicate that patients with dyspnea, angina, or overt heart failure have a poor prognosis without surgery[15, 16] analogous to that of patients with symptomatic AS. Mortality rates of 10% per year have been reported in patients with angina pectoris and AR, and 20% per year in patients with AR and concomitant heart failure.[15, 16]

Clinical features of aortic valve disease

Aortic stenosis

Patients with AS are usually asymptomatic in its early stages. As the disease progresses, the patient may develop shortness of breath, angina (chest pain), dizziness, and even fainting, especially upon physical exertion. The classical symptom triad of aortic stenosis is angina, syncope and heart failure.

Aortic regurgitation

As in AS, patients with AR are usually asymptomatic in the early stages of the disease, and symptoms, when occurring, are often vague. Angina pectoris is commonly a part of the presenting complaint as well as shortness of breath, which is especially common at exercise. In contrast to AS, syncope is rare.

Diagnosis of valvular heart disease

Cardiac auscultation remains the most widely used method of screening for valvular heart disease. Presence of a heart murmur is an essential clinical finding, which leads to an echocardiography assessment. Echocardiography has become the key tool for the diagnosis and evaluation of valve disease, and is the primary non-invasive imaging method of the heart and its valves.[17] Transthoracic echocardiography (TTE) imaging is usually adequate, although transesophageal echocardiography (TEE) may be helpful when image quality is suboptimal or a dissection is suspected in acute AR. Other investigation tools are electrocardiography (ECG) and chest x-ray. Cardiac catheterization for measurement of pressure gradients, severity of AR and calculation of aortic valve area (AVA) is not necessary in most patients and is reserved for patients in whom echocardiography is inconclusive.[18] Coronary angiography is routinely performed in patients at risk for coronary disease before aortic valve surgery. However, ECG-gated high resolution computed tomography provides information of the aortic root anatomy and coronary arteries that might be useful in selected cases.[19] Future developments in cardiac imaging techniques adding information in cardiac assessment may be magnetic resonance imaging (MRI), positron emission tomography (PET), and 3-dimensional echocardiography.

Indications for operation

In the vast majority of adults, aortic valve replacement (AVR) is the only effective treatment for severe AS and AR. However, younger patients with AS may be candidates for valvotomy. Newer techniques for valve repair are developing. Older patients with comorbidity may be candidates for transcatheter aortic valve implantation (TAVI).

Aortic stenosis

According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines from 2006[6] the only class I (evidence and/or general agreement that the procedure is useful and effective and for which there is no conflicting evidences) indications for AVR in AS are: "Symptomatic patients with severe AS" (Mean Doppler gradient > 40 mmHg, AVA < 0.6 cm²/ m^2), or "Patients with severe AS undergoing coronary artery bypass surgery," "Patients with severe AS undergoing surgery on the aorta or other heart valves" and "Patients with severe AS and LV systolic dysfunction" (ejection fraction < 0.50).

Aortic regurgitation

According to the ACC/AHA guidelines mentioned above[6] class I indications for AVR in AR are: "Symptomatic patients with severe AR," "Asymptomatic patients with chronic severe AR and LV systolic dysfunction (ejection fraction ≤ 0.50) at rest" or "Patients with chronic severe AR while undergoing CABG or surgery on the aorta or other heart valves."

History of aortic valve substitutes

In 1960, Harken[20] and Starr[21] implanted the first mechanical valve prosthesis in the aortic position, thereby introducing a new type of treatment for a difficult medical problem. The first stent-mounted biological valve (bioprosthesis) was implanted by Binet in 1965.[22] The first homograft replacement of the aortic root was reported in 1962[23] and the first autograft replacement (Ross operation) was conducted in 1967 by sir Donald Ross.[24] David and co-workers designed a subcoronary stentless porcine valve in 1985 and reported the initial clinical series with this valve in 1990.[25] The first transcatheter aortic valve implantation (TAVI) was performed in 2002.[26] This is a new procedure, in which a bioprosthetic valve is inserted through a catheter and implanted within the diseased native aortic valve. The last forty years have seen major advances in aortic valve surgery which is now considered a routine procedure with low perioperative morbidity and mortality, as well as long-term improvement in survival and quality of life.[12, 27]

Surgical options

The surgical options are repair or replacement of the diseased aortic valve. Techniques for repair of the diseased aortic valve are available but, due to the greater technical difficulty, aortic valve repair is not yet as common as repair of the mitral valve.

Several alternatives for replacement of the aortic valve are available, including mechanical prostheses or biological prostheses. Bioprostheses are of animal origin and include; stented and stentless valves. Other alternatives for valve replacement are human biological material as homograft and pulmonary autograft. Modern technology is still unable to create a bioprosthesis with the same durability as the human heart valve. Improvements in materials and engineering have essentially eliminated this problem in mechanical valves, but these valves require anticoagulation therapy. Prior to year 2000, more mechanical valves than bioprostheses were implanted, but with technical improvements of bioprostheses and younger age of the patients at time of implantation, older population and concerns regarding complications from anticoagulation therapy,

this trend has reversed and currently the majority of valves implanted are bioprostheses.[28]

Figure 1. Mechanical prosthesis: St. Jude Medical® Masters HP (Courtesy of St. Jude Medical)

Mechanical prostheses

Mechanical valve prostheses are made totally of mechanical parts and have evolved through several design changes since 1960.[29] The clear advantage of mechanical valves is the excellent long-term durability with almost nonexistent structural fractures.[30, 31] The disadvantage is the need of life-long anticoagulation, such as Warfarin to prevent thrombus formation and embolism.[30, 31] This medication carries an inherent risk of bleeding and stroke.[30] Another disadvantage with the mechanical valve is the clicking mechanical sound resulting from the opening and closing of the valve leaflets, which can be disturbing for some patients. Moreover, pregnancy in patients with mechanical valves may present a high risk due to the need for anticoagulation. Mechanical valves are otherwise especially appropriate for younger patients because of the durability of the valve (for whom anticoagulation are not contraindicated). With mechanical prostheses the risk for reoperation is low. The bileaflet valve is the most common type of the mechanical valves used today. This valve consists of two semicircular carbon leaflets in a ring covered with polyester knit fabric. The two leaflets are connected to the orifice housing by a butterfly hinge mechanism. The leaflets swing apart during opening, creating three flow areas, one central and two side orifices (Figure 1).

Biological prostheses

Biological valve prostheses are manufactured from either porcine valve tissue or bovine pericardial tissue (Figure 2). Bioprostheses gained popularity because these valves do not require lifelong anticoagulation therapy after surgery, and thus the risk for anticoagulation therapy complications is reduced. Another advantage in comparison with mechanical valves is the absence of the click sound. The major disadvantage of biological alternatives is the risk of structural deterioration and malfunction of the valve. Tears and calcification of the leaflets can occur and the risk of failure (stenosis or regurgitation) and limited durability increases with time.[32, 33] The age of the patient at the time of a biological prostheses implantation is the most important determinant of structural valve deterioration.[34] Estimated median time to reoperation for structural valve deterioration for patients aged 30, 45 and 60 years after AVR with a bioprosthesis is approximately 10, 12 and 14 years respectively.[35]

Figure 2. Biological prosthesis:
Carpentier-Edwards Perimount Magna Ease
(Courtesy of Edwards Lifesciences)
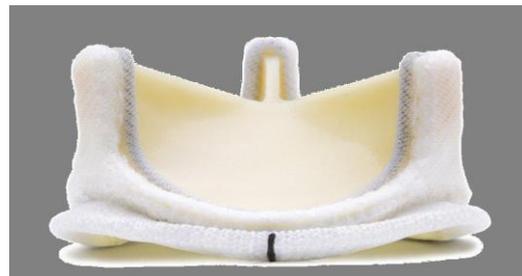
Homograft

Homografts are human donor heart valves (Figure 3). Homografts are harvested from the explanted heart in heart transplant recipients, from multiorgan transplant donors or donor hearts from diseased humans. Both the aortic and the pulmonary valves can be processed. The valves are dissected under sterile conditions, sterilized in an antibiotic solution, cryopreserved and stored in vapors of liquid nitrogen or in a freezer at a very low temperature (<-150°C). The homograft may be implanted as a freehand subcoronary implantation or as a full root replacement in the aortic position. Advantages for the homograft are its superior hemodynamic characteristics, low thromboembolic event rates, the avoidance of lifelong anticoagulation therapy and the low risk of prosthetic valve endocarditis. The homograft has a durability advantage of 2 years over a stented bioprosthesis.[35] Disadvantages are limited availability of homografts and a valve technically more demanding to implant compared to prostheses.

Figure 3. Aortic Homograft prepared for implantation. (Courtesy of Sahlgrenska University Hospital Homograft Bank)

Autograft

The autograft is the pulmonary valve translocated within the same individual to the aortic position. The autograft valve replacement procedure requires the pulmonary valve to be replaced in the pulmonary position with a pulmonary homograft, and this surgical procedure is referred to in this thesis as the "Ross operation" or the "Ross procedure." Autografts have low transvalvular gradient, high resistance to endocarditis, requires no anticoagulant therapy and has superior long-term durability among biological valve replacements in the aortic position.[36-39] It is the valve of choice for small children and infants due to its ability to grow with the child.[40] Disadvantages are technical challenges with regard to the implantation techniques, and limited availability of pulmonary homografts.

2. Study objectives of the thesis

In selection of an aortic valve substitute, the valve-related factors, such as durability, thrombogenicity, and hemodynamic performance, should be carefully matched to patient-related factors such as age, body mass, life expectancy, comorbidities, plans for pregnancy and lifestyle. In addition, surgeon and operation-related factors should be considered. Technical aspects of implantation, future reoperation, and operative mortality affect the selection of optimal valve substitute.

The study objective of this thesis was to obtain further knowledge of performance and characteristics of different aortic valve substitutes, and gain insights in and understanding of how the quality of valve substitutes may influence and facilitate optimal valve selection.

The Ross Procedure (study I & II)

The Ross procedure, also known as the autograft replacement, is considered a valuable option for AVR. The main advantages of the use of a patient's own valve as the aortic substitute, compared to other biological alternatives, are excellent hemodynamic, low risk of endocarditis, no need for anticoagulation, and superior long-term durability. After promising reports of long-term results after the Ross procedure, we extended the indication for total aortic root replacement with an autograft to adults in 1995.[38] At that time, the autograft appeared to be an ideal aortic valve substitute.[38]

In our first series of patients (24 patients), postoperative echocardiography at one week revealed AR grade 2 (moderate) or more in eight patients (33%). Although this did not necessitate immediate surgical intervention, it was still of concern because of the risk of progressive regurgitation and dilatation with time, and it was an unacceptable result with a procedure for which a safer alternative exists. The aim of study I, was to evaluate the short term results at one week after the Ross operation, and to assess the efficacy of a modified surgical technique adjusting anatomical mismatch, to reduce the early autograft valve failure.

Dilatation of the autograft is not a trivial complication after the Ross procedure. Several reports indicate that progressive pulmonary autograft dilatation, with or without regurgitation, may occur after the full root replacement and this may be a cause of reoperation.[37, 41] The magnitude of the problem is controversial and most reports do not include measurements of the native aorta. However, in our series, routine follow-up echocardiography investigations occasionally showed a dilated autograft but in some cases also dilatation of the native aorta. This finding prompted us to perform a comprehensive transthoracic investigation of the aorta, from the annulus to the proximal

part of the descending aorta including the aortic arch. The aim in study II was to evaluate the prevalence and severity of pulmonary autograft and native aortic dilatation after the Ross procedure in adults, to study the progression of dilatation over time and to identify possible predictors.

The Homograft operation (study III)

Although advances in surgical techniques have reduced the morbidity and mortality of prosthetic valve endocarditis (PVE)[42-44] and acute native valve endocarditis (NVE) with periannular abscess formation,[43] it remains a life-threatening condition. The use of a homograft as valve replacement is the generally accepted treatment, but whether to use biologic material (homograft, autograft) or prosthetic material (prosthetic composite) is a matter of controversy and debate. A similar implantation technique as the autograft implantation used in the Ross procedure may be used for homograft implantation in the aortic position. We have used the aortic homograft as our valve of choice for treatment of complicated aortic valve endocarditis.

Quality of life (QoL) is an important factor after cardiac surgery. However, there are only a few reports describing the QoL specifically after AVR.[45, 46] The aim in study III was to retrospectively analyse our single-centre experience with implantation of cryopreserved homografts in patients with aortic PVE or aortic NVE with periannular aortic root abscess formation, regarding short-term and mid-term survival, complications, early homograft function, reoperation due to homograft failure, and QoL.

Mechanical and biological prosthetic valves (study IV)

Patients with aortic valve stenosis develop LV hypertrophy as an adaptive response to the increased LV pressure.[4] Following AVR, most patients will improve their functional status and the LV mass will decrease.[2, 47] The LV mass is closely related to long-term mortality and is an important issue for long-term survival.[2, 48]

The autograft and homograft replacements have low transvalvular gradients and superior hemodynamics among available valve substitutes, but in the vast majority of patients with aortic valve disease the choice of valve substitute used for aortic valve replacement is either mechanical or biological prostheses. It is well known that a prosthetic valve causes some degree of transvalvular pressure gradients[2, 48, 49] which are routinely investigated using Doppler echocardiography. Reports on the relation between Doppler and catheter gradients in prosthetic valves have been conflicting[50] and this relation has previously been investigated in vitro.[51, 52] The discrepancies between Doppler and catheter gradients in mechanical bileaflet valves has been explained by the

pressure recovery phenomena.[51-53] From the in vitro studies it remains controversial if there is a discrepancy between Doppler and catheter pressure gradients in patients with stented biological valves. Study IV was designed as the first in vivo study using high-fidelity pressure catheters simultaneously with Doppler echocardiography to study the pressure recovery phenomenon by investigating the relation between Doppler and catheter pressure gradients in mechanical prostheses and bioprostheses in the aortic valve position.

3. Aims of the thesis

1. To assess the effect of changes in the surgical technique and patient selection on reduction of the observed early pulmonary autograft failure after the Ross procedure.

2. To describe the prevalence and severity of autograft and native aortic dilatation over time after the Ross procedure, and to search for possible predictors.

3. To analyse short- and mid-term survival, complications, early homograft function, reoperation frequency and quality of life after implantation of cryopreserved homografts in patients with aortic prosthetic valve or native valve endocarditis with periannular aortic root abscess formation.

4. To investigate in vivo the Doppler–catheter transvalvular pressure relation in bileaflet mechanical and stented biological aortic valve prostheses.

4. Material and methods

The human ethics committee at the Sahlgrenska Academy of the University of Gothenburg approved the studies and waived informed consents for the studies II and III. The human research ethics committee approved the study IV and all patients provided written informed consent.

Patients and study protocol

All the patients included in study I-IV were operated upon at the Department of Cardiothoracic Surgery and Anaesthesia at the Sahlgrenska University Hospital, Gothenburg, Sweden.

Study I

A total of 77 patients [mean age 44 years (range 17–66 years)], underwent the Ross procedure from January 1995 to February 1999 for AS (n=36), AR (n=23) and combined defects (n=18). Patients included in the study underwent preoperative and one week postoperative TTE investigations. After the first 24 patients, the results were evaluated. Modifications in the surgical technique were defined in order to reduce the observed problem with AR in the autograft. The results from the first 24 patients were compared to the late series of the patients (53 patients, surgically-corrected group) concerning the degree of early postoperative AR.

In the last 53 cases, the surgical technique was changed as follows:

1. Reducing the aortic annulus diameter in cases with moderate dilatation (Figure 4).

2. Excluding patients with severe dilatation of the aortic annulus from the Ross operation. If the aortic annulus, measured with valve sizers, differed by more than two valve sizes compared to the calculated diameter of the pulmonary annulus, the procedure was not performed.

3. Adjusting the diameter of the sinotubular junction of the aorta to the diameter of the sinotubular junction of the pulmonary artery (Figure 5).

4. Reimplanting the left coronary artery ostium in the autograft (Figure 6).

5. Changing the proximal anastomosis technique (Figure 6).

The efficacy of changing the surgical technique and correction of the anatomical mismatch between the aortic root and the autograft root was evaluated by echocardiography. The clinical outcome of both groups was also evaluated.

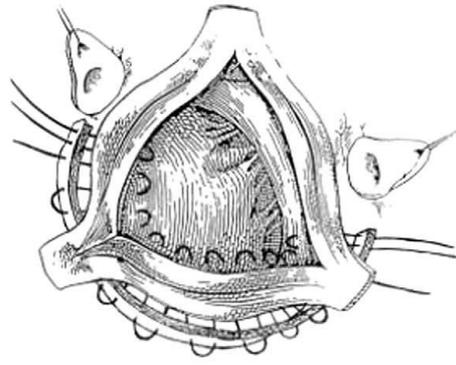Figure 4. Annuloplasty (reducing the aortic annulus).

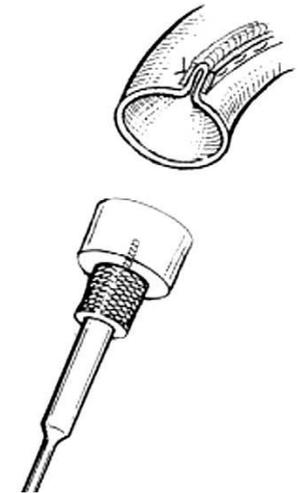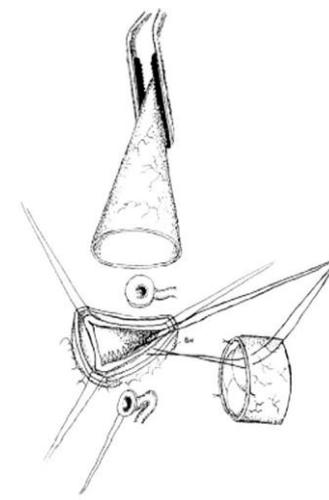Figure 5. Checking the diameter after aortoplasty.

Figure 6. The left ostium dissected from the aortic wall and proximal anastomosis with interrupted sutures.

Study II

A total of 91 patients [mean age 45 ± 12 years (range 17–66 years)] underwent the Ross procedure between January 1995 and January 2002. Thirty-eight healthy adult individuals served as control group.

The patients underwent an echocardiography investigation within the first postoperative week (baseline investigation). These baseline investigations were performed by different investigators and the distal part of the ascending aorta and the aortic arch was not regularly examined. In seventy-one patients (78%) a comprehensive echocardiography follow-up investigation (one investigator) was performed 8.9 years (2.2-14.1 years) after the initial procedure. Eight patients were not alive at the time of echocardiography follow-up and 12 patients (14%) were unavailable for investigation. In 29 patients an intermediate investigation, using the same comprehensive protocol as at the end of follow-up, was performed 7.6 years (3.8-10 years) postoperatively. In this group, the aortic dimensions were investigated at three occasions.

The late clinical outcome was analysed including reoperations due to autograft or homograft failures. The autograft and native aortic dimensions (annulus, sinus of Valsalva, sinotubular junction, ascending aorta, aortic arch and proximal part of the descending aorta) were measured and the progression of dilatation from baseline, intermediate to final follow-up investigations was analysed. Analysis to find contributing factors for dilatation from patient's characteristics was undertaken and the efficacy of surgical correction due to mismatch between the aortic root and the pulmonary autograft was compared with the aortic dimensions of the control group.

Study III:

All patients [n = 62, mean age 57 ± 15 years (range 19 to 80 years), 48 male patients (77%)] operated with a cryopreserved homograft for active aortic PVE (n=31) or aortic NVE with periannular aortic root abscess (n=31) between January 1997 and June 2008 were included. Thirty-two (52%) patients had previously undergone one (n = 28), two (n = 3), or three (n = 1) previous cardiac operation. The subset with NVE includes one case of previous aortic valve and tricuspid valve repair. An age and gender matched general Swedish population of 180 individuals served as control group.

Preoperative, perioperative, and postoperative variables were registered prospectively in a database. Mortality beyond the immediate postoperative period was collected from the Swedish Civil Registry. Mean follow-up time was 37 ± 11 months and was 100% complete.

The early and, mid-term results, complications and survival rates were analysed and compared in both groups. Analysis to determine the preoperative and postoperative variables associated with early mortality was also carried out.

Study IV

A total of 35 patients scheduled for elective AVR from January 2005 to June 2006 were included. Inclusion criteria were severe AS, regular rhythm, and no other surgical valvular procedure. Doppler and catheter measurements of LV and ascending aortic pressure gradients were recorded simultaneously after weaning the patient from cardiopulmonary bypass (CPB) (Figure 7 A and 7B).
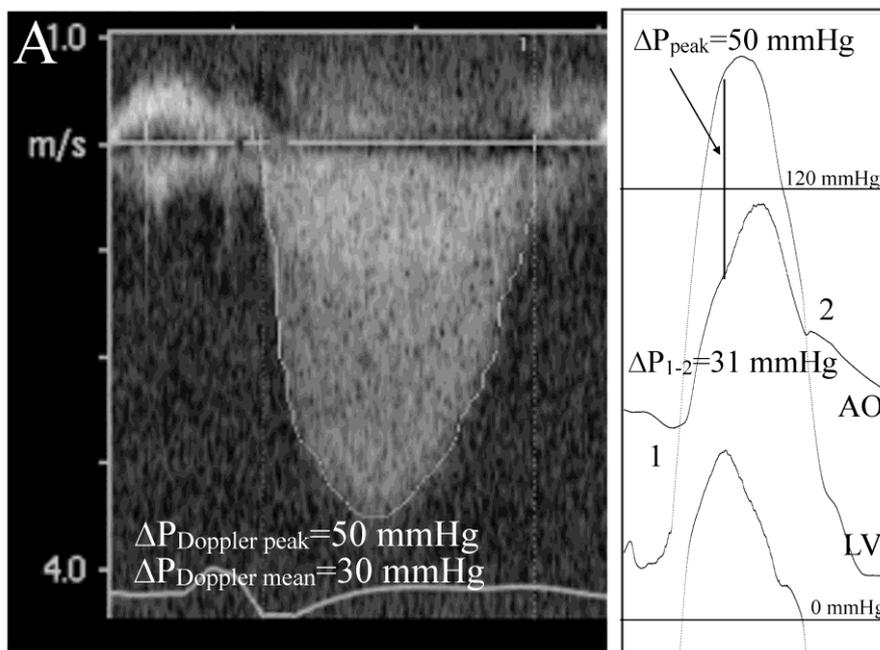

Figure 7 A. Simultaneous continuous Doppler and catheter measurements in a patient with an SJM Biocor valve size 21. The peak and mean Doppler gradients correspond to the catheter gradients. The second pressure crossover (2) corresponds to the incisura of the aortic pressure curve.
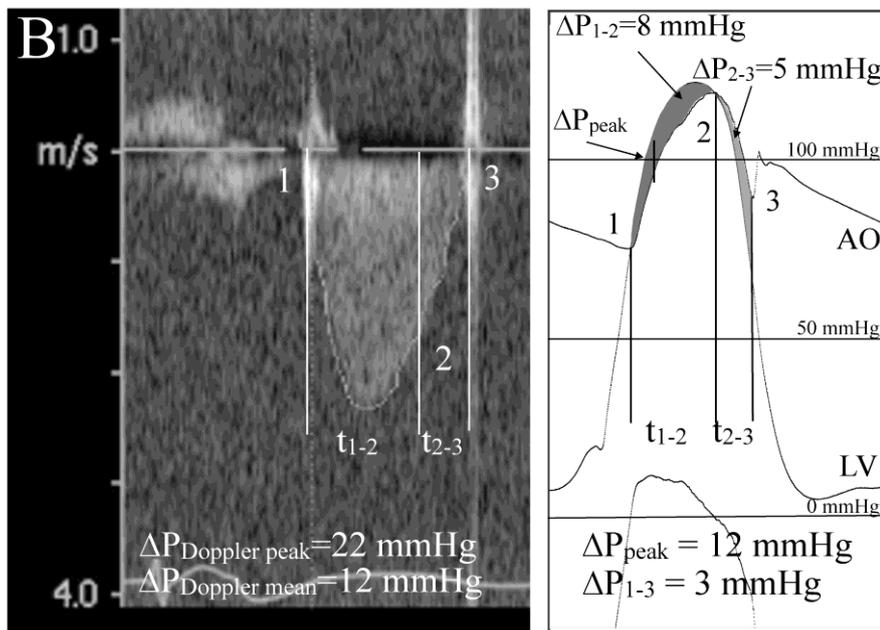
Figure 7 B. Simultaneous continuous Doppler and catheter measurements in a patient with a St. Jude HP valve size 27. The peak/mean Doppler gradients were 22 mmHg/12 mmHg. The corresponding catheter gradients were 12 mmHg (ΔP_{peak}) and 3 mmHg ($\Delta P_{1-2} - \Delta P_{2-3}$).

During data acquisition, all patients were in sinus or atrial-paced rhythm and were hemodynamically stable. After standard calibration of the catheters, Doppler and catheter measurements were obtained. Data were collected using a Biopac A/D system (Acknowledge software; Biopac Systems Inc, Goleta, California) for data acquisition and analyses. The high-fidelity tip manometer catheters with the incoming analogue signals were connected to a pressure control unit (Millar model PCU 2000).

Operative Procedures

After standard median sternotomy all operations were performed using standard CPB techniques under moderate hypothermia (Study I-III) or normothermia (Study IV). After cross-clamping the aorta cold intermittent antegrade (antegrade crystalloid only for the first 24 cases in Study I) and retrograde blood cardioplegia was delivered in the coronaries and the coronary sinus respectively for myocardial protection.

*The Ross Procedure (*study *I & II)*:

The surgical technique used was a full free-standing aortic root replacement with a pulmonary autograft in all cases. The aortic root was completely resected and the right coronary ostium was excised from the aortic wall with a cuff and reimplanted into the pulmonary autograft in all cases. The autograft was harvested and the outflow tract was reconstructed with a fresh or cryopreserved homograft (Figure 8).

In the first 24 patients (early series) the left ostium was retained with a tongue of the aortic wall and the proximal autograft anastomosis was performed with the autograft inverted into the left ventricular outflow tract and with a continuous 4:0 polypropylene (Prolene, Ethicon, Inc, Johnson & Johnson, Somerville, NJ, USA) suture line.

In the later series [n=53 (study I), n=67 (study II)], the left ostium was reimplanted in the autograft and the proximal anastomosis was performed with interrupted suture lines (Figure 6). In cases with diameter mismatch between the pulmonary root and the aortic root, the aortic root (annulus and/or proximal ascending aorta) was adjusted to the size of the pulmonary root. A reduction of the annulus was performed in cases with moderate dilatation (<5mm), with a strip of Teflon (PTFE-felt, Meadox Medical Inc, Oakland, USA) in the area between the two fibrous trigones where dilatation occurred (Figure 4). If the diameter of the aorta was larger than the diameter of the distal end of the pulmonary autograft, the aorta was reduced with an aortoplasty in which the aortic wall was duplicated, sutured and reinforced with a Teflon strip at each side (Figure 5). If an aneurysm of the aorta was present, the ascending aorta was removed and a synthetic graft was implanted.

Figure 8. The Ross Procedure
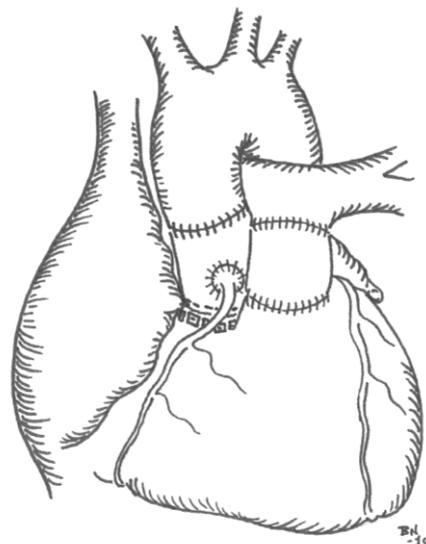
*The homograft operation (*study *III)*:

The infected prosthetic or native aortic valves were excised. The aortic root was completely resected and the right and left coronary ostia were excised from the aortic wall with a cuff. All infected and necrotic tissue was radically resected. In some of the cases, the remaining aortic annulus was possible to measure with valve sizers and a corresponding homograft was selected. In most cases, the aortic annulus was destroyed by infection and the homograft with the maximal available diameter was selected. The outflow tract was reconstructed with a cryopreserved aortic homograft as full free-standing aortic root replacement in all cases. The proximal anastomosis was performed with interrupted sutures placed in a subannular horizontal line in the remaining left ventricle outflow tract. The left and the right ostia were reimplanted in the homograft. The distal anastomosis was performed with one continuous 4:0 polypropylene (Prolene, Ethicon, Inc, Johnson & Johnson, Somerville, NJ, USA) suture line.

The Aortic valve replacement (study IV):

The aortic valve was exposed through a transverse aortotomy. The valve was resected and according to local clinical practice, patients received either a bileaflet mechanical valve (St. Jude Medical HP, St. Jude Medical Inc., St. Paul, Minnesota, USA) or a stented porcine bioprosthesis (St. Jude Medical Biocor, St. Jude Medical Inc., St. Paul, Minnesota, USA). Implantation of the prosthesis was performed in the supraannular position with noneverting interrupted sutures reinforced with pledgets.

Echocardiography

Transthoracic echocardiography (study I & II)

The severity of AR was assessed in a preoperative examination by combining several parameters as recommended by the American Society of Echocardiography.[5] The variables included the width of the vena contracta using colour Doppler, the colour Doppler regurgitation area, the intensity of the continuous Doppler signal and the degree of diastolic flow reversal in the proximal descending aorta. AR was graded on a four-point scale. Grades 3 and 4 indicate severe AR.

All measurements of the aortic dimensions (annulus, sinus Valsalva, sinotubular junction, ascending aorta, aortic arch and proximal part of the descending aorta) were performed with the patient in standard left lateral position, but also in the right lateral position with the transducer at the right parasternal border. With the transducer at this site it is possible to visualize the middle and distal part of the ascending aorta (Figure 9 and 10). This measurement was especially important in the Ross operated patients

where the measurement in the middle or distal part represents the native aorta, while the measurement in the standard parasternal long-axis projection might be either the autograft or the native aorta. The aortic arch and the distal part of the descending aorta were also investigated. The two-dimensional data were stored digitally and measurements were performed off line on a GE workstation (Echo PAC, Horten, Norway). One experienced investigator performed all measurements.
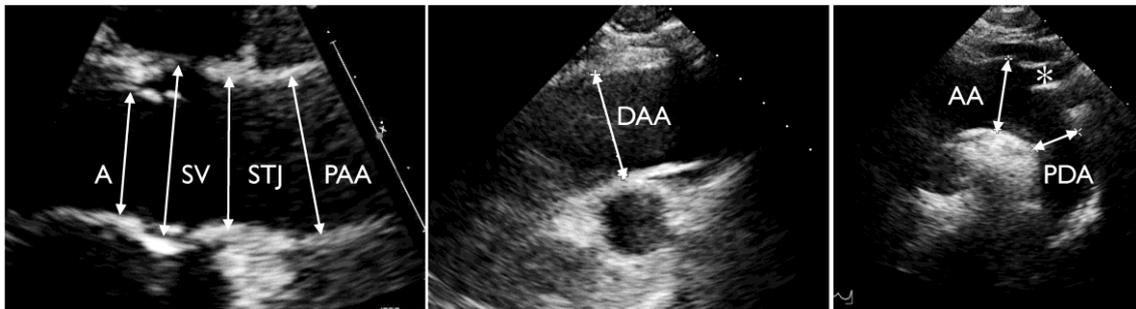

Figure 9. Parasternal long axis (*left*) of the aortic root in a control subject showing the annulus (A, 2.5 cm), sinus Valsalva (SV, 3.1 cm), sino-tubular junction (STJ, 2.7 cm) and proximal ascending aorta (PAA, 3.0 cm). To evaluate the middle and distal part of the ascending aorta we investigate the patient in the right lateral position (*middle*). The long axis projection through the aortic arch was obtained with the transducer in the suprasternal notch (*right*). The diameter (AA, 3.0 cm) was measured proximal to the left common carotid artery (*). The proximal part of part of the descending aorta (PDA) was 2.1 cm.
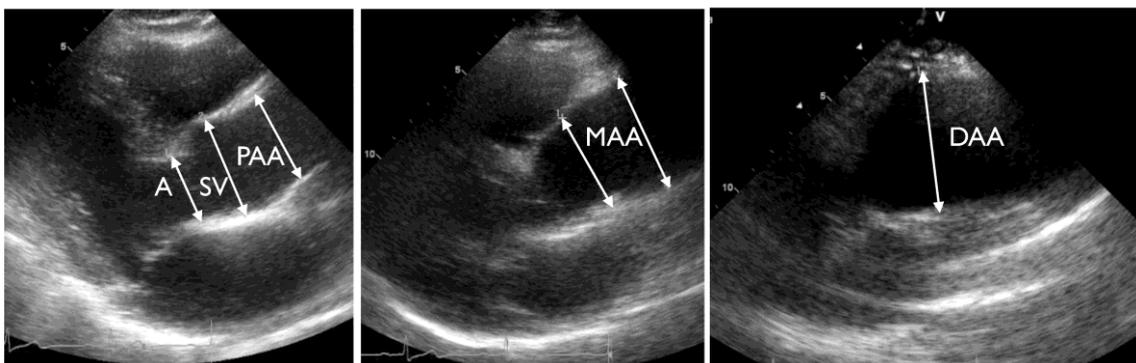
Figure 10. Parasternal long axis (*left*) of the autograft showing the annulus (A, 2.7 cm), sinus Valsalva (SV, 4.0 cm) and proximal ascending aorta (PAA, 3.7 cm). Observe that there is no distinct sino-tubular junction as in the control subject shown in Figure 1. To investigate the native aorta either the transducer was moved one intercostal space in cranial direction (*middle*) and/or the patient was investigated in the right lateral position (*right*). With this approach the middle part of the native ascending aorta (MAA) was 4.9 cm and the more distal part (DPP) 5.1 cm

We measured the annulus from the insertion of the aortic cusp towards the interventricular septum and the anterior mitral leaflet respectively[54] (Figure 9). In controls we measured the diameter of the sinus of Valsalva and the ST-junction. In patients with autograft it was in most cases not possible to define any ST-junction (Figure 10). Therefore, only the sinus of Valsalva diameter and the proximal part of the ascending aorta are reported. In the proximal ascending aorta or the ascending aorta from the right parasternal window (distal ascending aorta) measurement were performed at the site with the widest diameter. In the aortic arch we measured the diameter between the brachiocephalic trunk and the left common carotid artery. The proximal descending aorta was measured distal to the left subclavian artery.

Transesophageal echocardiography (study IV)

Doppler investigation of the prosthetic valve was performed from a deep transgastric long-axis view. The left ventricular outflow tract, prosthetic valve, aortic root, and ascending aorta were investigated. The diameter of the ascending aorta was measured 4 to 6 cm from the prosthetic valve.

All Doppler echocardiography measurements were performed off line. Doppler gradients were calculated using the simplified Bernoulli equation (pressure gradient = 4 x velocity²). The diameter of the left ventricular outflow tract was measured and the blood flow velocity was recorded using pulsed Doppler. The velocity time integral (VTI) from the pulsed Doppler recordings was determined using the modal velocity contour. Ejection time was measured from the pulsed Doppler recordings in the left ventricular outflow tract. Stroke volume was calculated as the product of the cross sectional area and the VTI. Prosthetic effective orifice areas (EOAs) were calculated using the continuity equation (EOA = SV/VTI), where SV is stroke volume derived from pulsed Doppler recordings in the left ventricular outflow tract and VTI is the prosthetic valve velocity obtained using continuous wave Doppler.

High fidelity Catheter measurements (study IV)

Left ventricular and ascending aortic pressures were recorded using 2 separate Millar Mikro-Tip (model MPC-500, Millar Instruments, Inc., Houston, Texas) high-fidelity catheters with a sensing element placed at the distal end. The LV catheter was put in position using the apical puncture site used for venting the LV. The puncture site was secured for bleeding using a 4/0 polypropylene suture with pledgets. We aimed to position the catheter in the central part of the LV. The antegrade cardioplegia cannula was left in the ascending aorta after weaning from bypass and was used to insert the ascending aorta catheter. The catheter tip was inserted aiming at a position 4 to 6 cm

distal of the prosthetic valve. The peak transprosthetic catheter gradient was defined as the peak instantaneous gradient between the ventricle and aorta. The mean transprosthetic catheter gradient was obtained by integrating the difference between the simultaneously recorded ventricular and aortic pressure waves over the period with forward aortic flow (Figure 7A and 7B).

Quality of Life (study III)

The short-form 36 (SF-36) is a validated multipurpose, short-form health survey with 36 questions.[55] It yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures. In short, the results of the survey are divided into the eight following subsets: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The first four scales (PF, RP, BP, GH) are then combined to a physical component scale and the latter four (VT, SF, RE, MH) to a mental component scale.[56-58]

Statistical analyses

Categorical data are given as total numbers; continuous variables are given as mean ± standard deviation (SD). A p value less than 0.05 was considered statistically significant.

Study I
Differences between groups were assessed by Fisher's test to compare proportions.

Study II
The dimensions of the aortic root and aorta are dependent on body surface area. From the healthy controls, regression equations were calculated, as well as the standard error of the estimate. For each patient in the study group, the expected dimensions were predicted. The observed values in patients were regarded as being increased if they differed by more than 1.96 SD from the predicted value, using the Z score. Continuous variables with normal distribution are expressed as the mean ± SD and median (range) when the distribution is not deemed normal. A Student's t-test was used to compare continuous data and Fisher's test to compare proportions.

Study III
Cumulative long-term survival was calculated according to the Kaplan-Meier method. Group comparisons were performed with the nonparametric Mann-Whitney test (continuous data) or χ^2 test (categorical data).

Study IV
The relation between catheter measurements and Doppler echocardiography was assessed using linear regression and Bland-Altman analysis.[59] To compare continuous data, we used paired Student's t test or Wilcoxon's signed rank test, when appropriate. Results from mechanical and bioprosthetic valves were compared using the Mann-Whitney test.

5. Results

The Ross Procedure

Thirty-day mortality was 4/91 (4.4%) for the total series of 91 patients. There were 9 late deaths. Thirteen patients (14%) underwent reoperation during follow-up. Five of these underwent a second reoperation. Nine patients (10%) were re-operated due to autograft dysfunction. Five had dilatation of the autograft with significant secondary AR, three had cusp defects and one patient had endocarditis. Reoperation on the homograft in the pulmonary artery position was performed in three patients (3%) and one patient was reoperated due to mitral regurgitation.

Study I

Postoperative echocardiography at 1 week revealed grade 2 regurgitation in eight patients (33%) of the first 24 patients and in two patients (4%) in the other 53 consecutive patients (p = 0.001).

Study II

At the end of follow-up, all parts of the aortic root and aorta, except the proximal part of descending aorta, were significantly larger in Ross operated patients compared with controls (Figure 11). Forty-eight percent (34/71) had dimensions outside the expected normal range for the aortic root and aorta (Z-score >1.96SD from the predicted value). In twenty patients (28%) both the autograft and the native ascending aorta were enlarged, eleven patients (16%) showed an isolated enlargement of the autograft and three patients (4%) had only enlarged native ascending aorta. In 6 patients aneurysmal dilatation (>5 cm) of the autograft and/or native aorta was present.

The proportion of patients with enlarged sinus of Valsalva of the autograft (Z-score >1.96SD) at the baseline investigation increased from 13% (8/63) to 30% (21/71) at the end of follow-up (p=0.02). The proportion with enlarged proximal ascending aorta was 16% (10/62) at baseline and 43% (30/71) at the end of follow-up (p=0.001), indicating progression of autograft and native aorta dilatation.
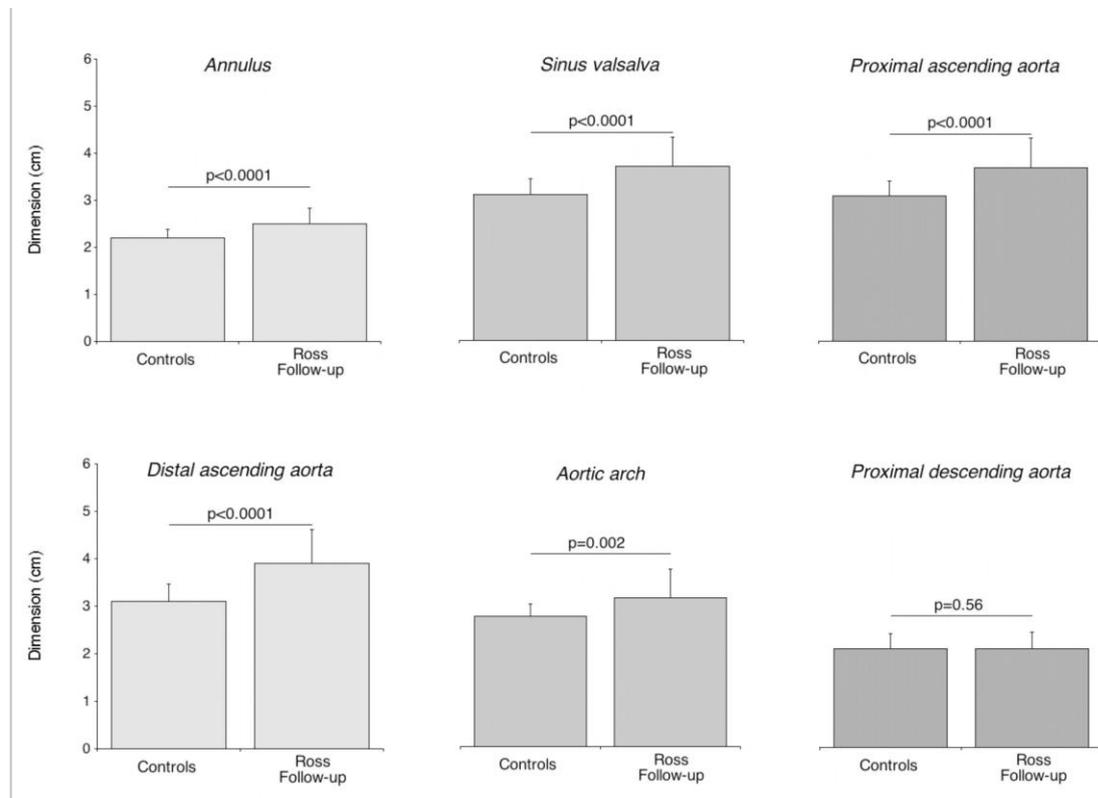
Figure 11. Aortic dimensions in Ross patients at the final follow-up and in age-matched control subjects.

In the 29 patients with three complete postoperative echocardiographic investigations the annulus diameter did not change significantly between baseline and the intermediate follow-up investigation. The diameter of the sinus Valsalva and the proximal part of the ascending aorta increased significantly from baseline to the intermediate investigation and continued to increase until the end of follow-up (Figure 12).

Figure 12. Aortic dimensions in Ross patients investigated at three occasions (n=29).

TABLE 1. Determinants of aortic enlargement (Z-score > 1.96) at the end follow-up. Mean ± standard deviation or number (%).

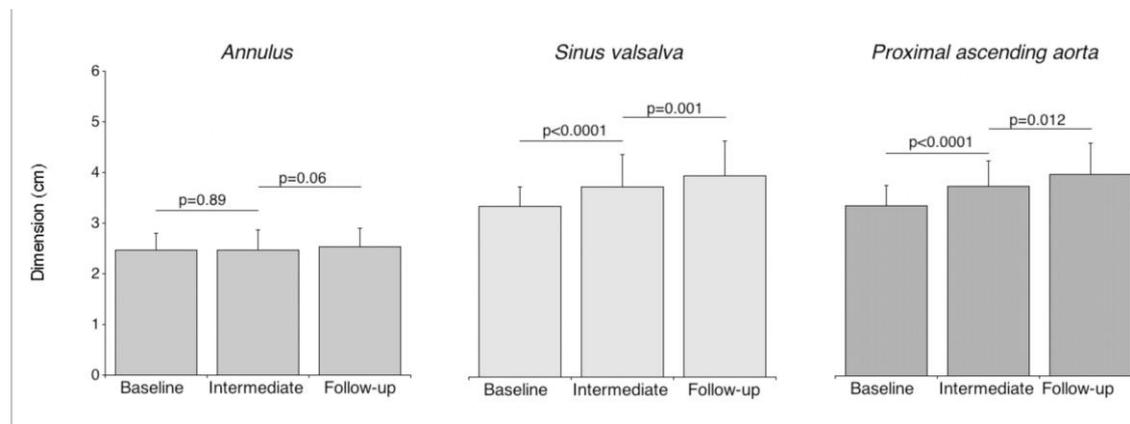|	Not enlarged (n=36)	Enlarged (n=35)	p-value
Age at follow-up (years)	55±12	53±11	0.39
Female	13 (36%)	9 (26%)	0.44
Hypertension	5 (14%)	6(17%)	0.75
Bicuspid	16 (44%)	17(49%)	0.81
Preop AS	22 (61%)	15 (43%)	0.16
Preop AR	12 (33%)	11 (31%)	1.00
Baseline			
Annulus	2.3±0.24	2.4±0.3	0.03
Sinus of Valsalva	3.1±0.37	3.4±0.32	0.003
Proximal ascending aorta	3.2±0.40	3.5±0.34	0.004

Key: AS; aortic stenosis, AR; aortic regurgitation.

Enlargement of the aorta was not related to the presence of a bicuspid valve or to postoperative hypertension. The pulmonary autograft dimension at the early baseline investigation was significantly larger in those who were enlarged at the 2nd follow-up compared with those who were not (Table 1).

TABLE 2. Patients from the second series (n=54) surgically corrected (n=31) due to RVOT/annulus mismatch compared with not-corrected patients (n=23). Mean ± standard deviation or number (%).

	Not-corrected surgically	Corrected surgically	p-value
BSA (m^2)	1.91 ± 0.32	1.91 ± 0.22	0.88
Preoperative (cm)			
Annulus	2.4 ± 0.19	2.6 ± 0.36	0.011
Sinus Valsalva	3.4 ± 0.6	3.6 ± 0.5	0.23
Proximal ascending aorta	3.4 ± 0.75	3.9 ± 0.7	0.03
Baseline (cm)			
Annulus	2.2 ± 0.29	2.4 ± 0.26	0.02
Sinus Valsalva	3.3 ± 0.4	3.3 ± 0.4	0.93
Proximal ascending aorta	3.3 ± 0.39	3.3 ± 0.43	0.69
Follow-up (cm)			
Annulus	2.4 ± 0.29	2.5 ± 0.33	0.07
Sinus Valsalva	3.7 ± 0.60	3.6 ± 0.62	0.66
Proximal ascending aorta	3.7 ± 0.53	3.7 ± 0.66	0.81
Distal ascending aorta	3.7 ± 0.61	3.8 ± 0.61	0.65
Aortic arch	3.1 ± 0.53	3.2 ± 0.69	0.68
Proximal descending aorta	2.2 ± 0.26	2.1 ± 0.44	0.55
Enlarged aorta (Z-score > 1.96) at the end of follow-up (%)	11 (49)	17 (55)	0.78
Reoperations with dilatation at the end of follow-up (%)	3 (13)	1 (3)	0.30
Aortic regurgitation (≥moderate)/reoperations at the end of follow-up (%)	5 (22)	9 (29)	0.75

At the baseline postoperative investigation there was no difference in dimensions of the sinus of Valsalva or the proximal ascending aorta between groups, but patients undergoing annular reduction had a larger aortic valve annulus. At the end of follow-up there was no significant difference in autograft or native aortic dimensions between surgically corrected and not-corrected groups (Table 2).

The homograft operation (Study III):

There was no statistically significant difference between patients operated with homograft and an age- and gender-matched general population in the combined physical component scale or in the combined mental component scale. In contrast, homograft patients had statistically significant inferior results in four of the eight subscales (Figure 13).
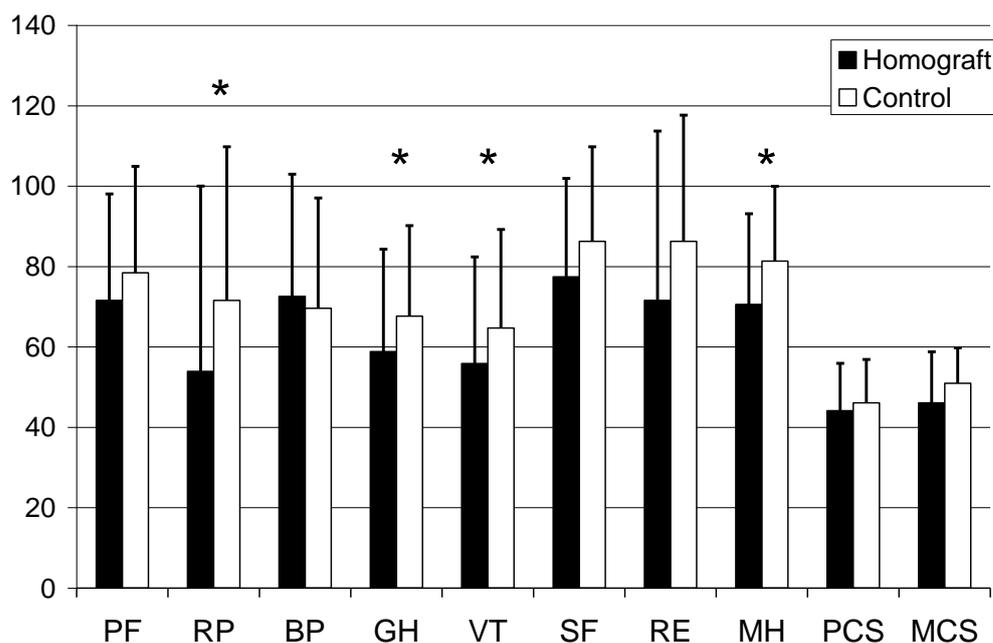

Figure 13. Quality of life as assessed by shortform 36 in homograft patients (n = 40) compared with an age-matched and gender-matched general Swedish population (n = 160) (mean and standard deviation). (■= homograft; □ =control; BP = bodily pain; GH = general health; MCS = mental component scale; MH = mental health; PCS = physical component scale; PF = physical functioning; RE = role-emotional; RP = role physical; SF = social functioning; VT = vitality.)

Preoperative and perioperative variables significantly associated with early mortality in univariate testing were higher Cleveland Clinic risk score (p = 0.014), extracorporeal circulation (ECC) time (p = 0.003), prolonged inotropic support (p = 0.03), reoperation for bleeding (p =0.01), perioperative myocardial infarction (p<0.001), and postoperative serum creatinine (p = 0.04).

Cumulative survival in the whole patient population was 82%, 78%, 75%, and 67% at one, three, five and ten years, respectively (Figure 14). In the patients with prosthesis endocarditis the corresponding figures were 78% at one year, 70% at three years, 70%

at five years, and 51% at ten years, and in the native valve endocarditis group 88% at one year, 84% at three years, 79% at five years, and 79 % at ten years (p = 0.12) (Fig 15). Three patients (6%) underwent late reoperation; one patient for mitral regurgitation and two for homograft failure. One of the patients showed homograft degeneration and the other one presented with endocarditis in the homograft 9 months after the first operation.
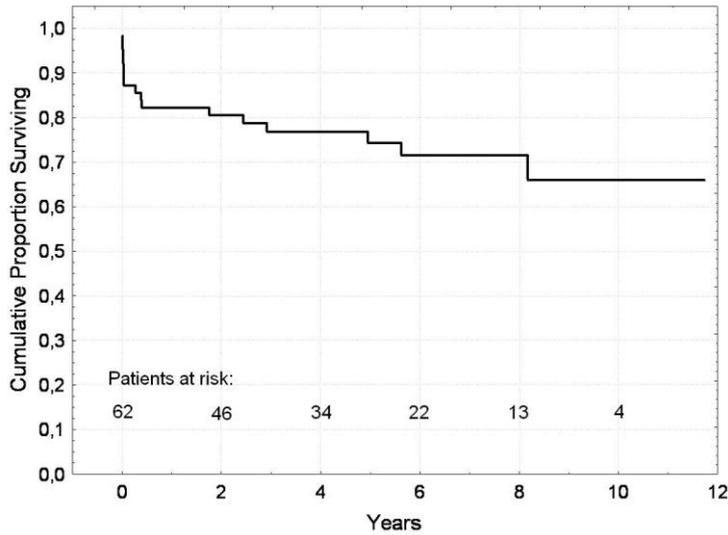

Figure 14. Cumulative survival in 62 patients operated with homograft due to infective endocarditis
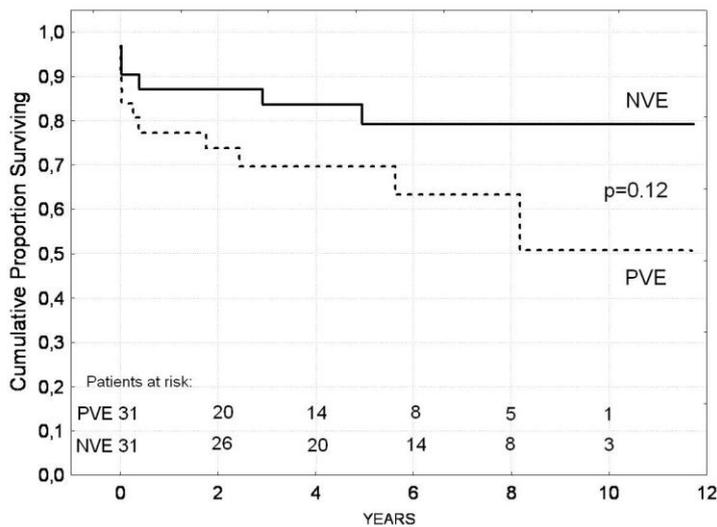

Figure 15. Cumulative survival in patients with prosthetic valve endocarditis (dotted line) and native valve endocarditis (continuous line), p=0.12

Nine patients (15%) died during the first 30 postoperative days; six (19%) in the prosthetic endocarditis group and three (10%) in the native endocarditis group (p = 0.28). Eight of the nine (89%) patients who died had a periannular abscess.

Twenty two patients (35%) had one or more severe perioperative complications in form of renal failure requiring dialysis, perioperative stroke, pacemaker implantation for permanent atrioventricular block, perioperative myocardial infarction, respiratory failure and prolonged mechanical ventilation required tracheotomy and requirement of inotropic support more than 24 hours. Fourteen patients (23%) underwent early reoperation for bleeding.
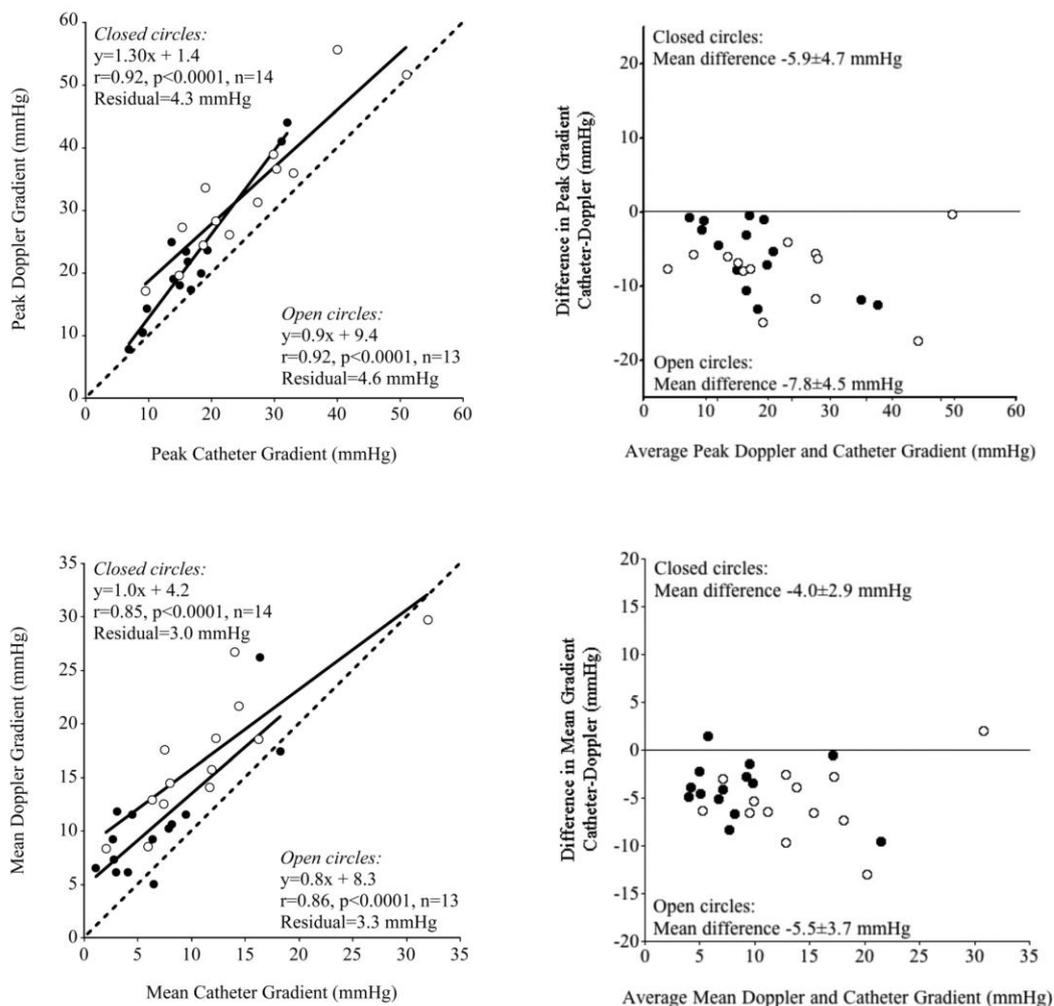

Figure 16. Peak *(upper left)* and mean *(lower left)* Doppler gradients versus catheter gradients in mechanical prostheses *(closed circles)* and bioprostheses *(open circles)*. *Dotted line* indicates the line of identity. *Right panel:* Bland-Altman analysis.

Aortic valve replacement (Study IV):

Seven patients from the total study group (n=35) were excluded because of the poor quality of Doppler recordings, and one patient, because of the poor quality of the pressure recording. Correlation between peak Doppler and peak catheter gradients, as well as mean Doppler and mean catheter gradients, was strong for both mechanical prostheses and bioprostheses (Figure 16). Peak and mean Doppler gradients were significantly higher than catheter gradients for both mechanical prostheses and bioprostheses. There was no difference between mechanical prosthesis and bioprosthesis regarding degree of discrepancy between Doppler and catheter gradients (Figure17).
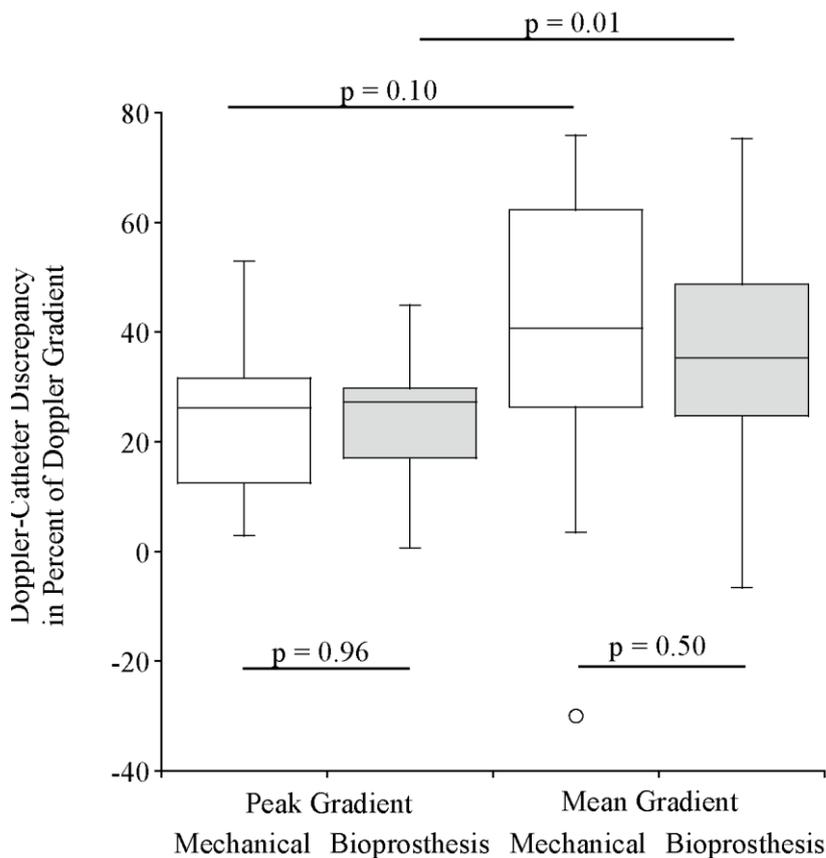

Figure 17. Box plots show the discrepancy between Doppler and catheter peak and mean gradients as a percentage of Doppler gradients.

6. Discussion

The choice of the aortic valve substitute is changing over time as a consequence of patient outcome and newer findings of valve related factors such as durability, thrombogenicity and hemodynamic properties. In selection of optimal aortic valve substitute, the valve related factors should be matched to patient-related factors and technical aspects of the implantation. In quest of the best performing aortic valve substitute for different patient groups we have studied: early autograft regurgitation, autograft and native aortic dilatation over time after the Ross operation, outcome and quality of life after homograft implantation and Doppler and catheter gradients in aortic prosthetic valves.

Replacement of the diseased aortic valve by a pulmonary autograft was introduced by Ross in 1967[24] and follow-up data of this technique has been described for a considerable number of patients.[38, 60-62] The Ross operation has previously been reported to have advantages such as excellent hemodynamic adaption, no need for anticoagulation, low risk for thromboembolism, resistance to infection, limited effect on active lifestyle and a superior survival when compared with the survival of patients with other valve substitutes.[36, 61, 63] After reports on positive long-term results after the Ross procedure, we extended the indication for aortic root replacement with an autograft to adults in the beginning of 1995.[38] We used the full free standing root technique and not the subcoronary implantation technique. As reported by several groups at that time, the durability or failure of the substitute implanted into the right ventricular outflow tract was the expected potential risk factor for reoperation[64] and it was also our concern initially. The durability of the pulmonary autograft was at that time not considered a problem. Our analysis of the early series of the first 24 patients operated using the free standing root technique showed an unacceptable high frequency of early AR of the autograft (eight patients of 24 had moderate postoperative autograft regurgitation). We suspected that the AR might be caused by an anatomical mismatch or an incorrect surgical technique and this could lead to distortion of the normal pulmonary valve geometry and subsequent incorrect leaflet coaptation. This problem can be caused by mismatch both at the level of the proximal and the distal anastomosis. Therefore, in the later series (n=53), a systematic technical approach to the Ross operation was performed and we modified the surgical strategy according to two main principles; correction of anatomical mismatch and optimizing the surgical technique to achieve less AR. Correction for the autograft to aortic annulus and aortic sinotubular junction mismatch requires reproducible and reliable measurements. We used intraoperative TEE to measure the pulmonary and aortic root.[65] In almost half of our patients (25 out of 53) the aortic root (the aortic annulus and/or the ascending aorta) required modifications to match the autograft. This analysis was not performed in the early series where eye-

balling was used to exclude anatomical mismatch due to a dilated aortic root. As a consequence of this change in surgical approach to the Ross procedure, we achieved improved results, and postoperative echocardiography one week postoperatively revealed less than mild or mild autograft regurgitation in all but two patients (4%) compared to eight patients (33%) in the early series. Our findings are supported by other investigators who recommend correction of the aortic annulus dilatation and reduction of an aortic sinotubular junction larger than the autograft.[65, 66]

The introduction of new procedures in surgery usually implies that results follow the so-called learning curve (morbidity rates decrease with experience). The Ross operation is a technically challenging procedure and is significantly more complex than that of implanting a prosthetic valve.[67] Our observation that a number of patients exhibited moderate AR at baseline (in our early series) motivated a critical analysis of the surgical technique and selection of patients. By identifying a number of factors related to surgical technique and selection of patients we probably influenced the slope of the learning curve and thereby the results. We emphasize the necessity of assessment of surgical performance throughout the learning curve period to identifying suboptimal results when new surgical procedures are introduced.[68]

During our follow-up of the Ross operated patients, echocardiography investigations showed enlargement of the autograft and in some cases also of the native aorta. At that time there were a few reports on autograft dilatation following the Ross procedure[41, 61, 69] but no reports describing dilatation of the native aorta. Today, autograft dilatation after the Ross procedure is well described[70, 71] and many authors suggest modified surgical techniques to reinforce the pulmonary autograft to prevent dilatation and subsequent regurgitation.[72, 73] The magnitude of the problem is still controversial. We performed a comprehensive TTE investigation of the aorta from the annulus to the proximal part of descending aorta, and to our knowledge this study is the first that includes an investigation of the native aorta (study II). In this study with up to 14 years follow-up, we observed that the dimensions of the native aorta increased in a significant number of patients over time after the Ross procedure. In addition, we found a gradual dilatation of the autograft and in some cases subsequent AR.

The mechanism underlying the aortic dilatation after the Ross operation is unclear. Many factors have been discussed in native aortic dilatation; genetic syndromes, such as the Marfan syndrome, bicuspid aortic valve disease and the importance of atherosclerosis. The patients in study I and II, had no or only mild signs of atherosclerosis and the group that where enlarged at follow-up where not older than those who were not. A genetic analysis was not performed in our patients but known Marfan syndrome is a contraindication for the Ross procedure at our institution. David et al has reported histological evidence that patients with bicuspid aortic valve disease have more severe degenerative changes in the media of the ascending aorta and main

pulmonary artery than patients with tricuspid aortic valve disease.[69] Whether patients with bicuspid valves should be candidates for the Ross procedure are therefore controversial.[41] Our study includes a large proportion of patients with bicuspid aortic valve (42%). Our results do not support the hypothesis that bicuspid valve disease is a risk factor for dilatation of the autograft or native aorta since postoperative aortic dilatation was not more common in patients with bicuspid valves than in the patients with tricuspid valves. The dilatation of the aorta at the end of the follow-up was related to the baseline dimension of the autograft. We may only speculate that the observed native aortic dilatation is secondary to the proximal autograft dilatation, and not due to aortic valve pathology. The pulmonary autograft tissue might dilate when exposed to the much higher systemic pressure, especially in patients with a preoperative dilated or deformed aortic root. In two patients with the same blood pressure will, as follows from the law of Laplace, the wall tension be higher in the patient with the widest aortic root. The pulmonary autograft does not have a sino-tubular ridge and this might further destabilize the root. The importance of the sino-tubular ridge has been recognized by others, David et al. has recommended stabilization with a circumferential piece of Dacron graft[41], Koul et al has recommended support of the entire pulmonary autograft with a Dacron vascular prosthetic jacket.[74]

In our series 9 patients were reoperated due to AR. Five patients developed AR secondary to root dilatation with subsequent inadequate cusp coaptation that was the main reason for reoperation in our material. In the remaining four patients the reason for reoperation was cusp defects (one endocarditis, two perforations of unclear reasons and one rupture). Cusp defects with regurgitation not related to autograft dilatation is not always well defined and described in previous studies.[63, 75]

The long-term importance of aortic dilatation is unclear, and only a close follow-up will definitely demonstrate if native ascending aortic dilatation is a risk for reoperation after the Ross procedure. A close follow-up, with echocardiography investigations extended to include the native aorta is necessary to assess the dilatation of the pulmonary autograft and the native aorta after the Ross procedure.

The Ross procedure is a surgical alternative for treatment of aortic valve disease with good long term follow up including survival rates.[39] Such results may, be achieved only if the procedure is conducted in dedicated centres with extensive experience of the Ross operation. Autograft dysfunction may possibly be minimized by new surgical solutions such as reinforcing the autograft in the aortic root. The problem of homograft dysfunction in the right ventricular outflow tract can be approached by new and less invasive solutions such as transcatheter pulmonary valve replacement.[76, 77]

Based on our results and our experience of the Ross procedure, our practice has been changed. Today, we are more restrictive and recommend this procedure to a more selected group of patients, such as young women of child-bearing age and subgroups of

young adult patients who require a high level of physical activity after the operation. Any candidate for the Ross procedure should receive comprehensive preoperative information including the risk for reoperation.

Infective endocarditis is a life-threatening disease.[44] The most commonly affected valve in infective endocarditis is the aortic valve.[78] Despite advances in medical and surgical management of endocarditis, the mortality and morbidity remains high[44, 79, 80] particularly in prosthetic valve endocarditis (PVE)[42-44] and in native valve endocarditis (NVE) with periannular abscess formation.[43, 81] To eradicate the infection in this group of patients, antibiotics alone is rarely successful and accepted principles of treatment include surgical excision of infected valve tissue and valve replacement.[44] Even with aggressive surgical therapy, in-hospital mortality ranges from 8 to 39%, according to the literature.[78, 82]

Aortic valve replacement as treatment of aortic valve endocarditis was first reported by Wallace et al in 1965 and a mechanical prosthesis was then used for replacement. [83] Advances in surgical technique offer several options in order to treat aortic valve endocarditis, including valve replacement with a mechanical prosthesis,[84] biological prosthesis,[84] aortic homograft[80, 85] and pulmonary autograft.[86] However, there is still controversy whether to use biologic material (homograft or autograft) or prosthetic material (mechanical or biological prosthesis) in these patients.[85, 87, 88] Data comparing the effect of biologic material or prosthetic material on outcome in patients with PVE and NVE with periannular abscess are inadequate to draw definite conclusions concerning which material that should be used in this group of patients.[89, 90] These studies are small, not prospective or randomized, and the selection of either homograft or prosthetic replacement depends on surgeon's experience and preference.[89, 90]

Radical debridement of the prosthetic material and the infected tissue is an important surgical strategy, and is the key to success in the treatment of these patients.[91, 92] Our strategy has been to treat all cases with radical excision of infected and necrotic tissue, followed by reconstruction of the aortic root with a full freestanding biologic aortic root replacement. We have performed the Ross procedure, with resection of the aortic root and with autograft replacement, successfully in four patients with aortic valve endocarditis. As described above, the Ross operation is a complicated procedure and to use this procedure in a severely ill patient with advanced disease, when less demanding options are available, may be questioned.[86] There are several studies reporting AVR with a cryopreserved homograft to be a well-functioning alternative in patients with aortic NVE and periannular abscesses[43, 80, 93] and in aortic PVE.[43, 80, 85, 93]

We favour the use of a cryopreserved aortic homograft as our valve of choice for treatment of complicated aortic valve endocarditis. In our experience, the aortic homograft makes it possible to reconstruct and restore the aortic root after a radical

excision of all infective tissue. With this strategy, patients with a more complex situation may be treated with surgical resection, compared to the previous policy (prosthesis and reconstruction with patch).

In our study, 30-day mortality in the subset of patients with PVE was 19%, which is comparable or better than most reports[43, 80, 81, 84, 93] but markedly higher than in a report from the Cleveland Clinic, where Sabik et al reported an in-hospital mortality of only 3.9%.[85] Interestingly, survival at one year and five years was 90% and 73%, respectively in Sabik's material, which is comparable to the results in the present study (78% and 70%, respectively) (Study III). This indicates that mid-term mortality is highly dependent also of factors other than surgical success. Both early and mid-term mortality tended to be higher for PVE than for NVE in the present study (Study III), which is in accordance with previous studies.[43, 81] This may be caused by a more complex pathology and thus a more complicated operation in the PVE patients, as suggested by David et al.[43] This was confirmed by us in study III, where CPB time and aortic cross clamp time were longer and perioperative complications were more common in the PVE group. Differences in the preoperative risk profile may also contribute to the disparity in outcome, however, as our PVE patients were older, had higher Cleveland Clinic risk score, and a higher incidence of diabetes at the time of surgery.

Quality of life (QoL) is becoming more and more important in description and validation of the outcome of cardiac surgery. Instruments to validate QoL have been developed.[58] To the best of our knowledge, this is the first report of patient-perceived QoL after homograft implantation (Study III). Patients undergoing AVR without endocarditis have comparable QoL with matched healthy populations and without differences between bioprotheses and mechanical valves.[94, 95] Patients with pulmonary autografts have better QoL than patients with mechanical valve substitutes[96] and valve surgery patients have better self perceived postoperative QoL than CABG patients.[97] In the present study, QoL was investigated with the SF-36 instrument, which has been validated in cardiac surgery patients[58] and compared to an age and gender-matched general population. The combined SF-36 scales for physical health and mental health did not differ significantly between the surgery and non-surgery groups. There were significant differences between the groups in four of the eight subscales, however; role physical (RP), general health (GH), vitality (VT) and mental health (MH). One may thus conclude that patients operated with homograft for acute severe endocarditis most likely have an inferior mid-term QoL compared with a healthy matched control group, but the reduction in QoL is small or moderate.

Patients with aortic valve stenosis develop LV hypertrophy as an adaptive response to the increased LV pressure. Following AVR, most patients will improve their

functional status and the LV mass will decrease. One of the primary objectives of AVR apart from symptom reduction is to relieve the left ventricular outflow tract obstruction and thereby reduce, or ideally normalize, the LV mass. The LV mass is closely related to long-term mortality and the regression of LV mass is therefore an important issue. Importantly, left ventricular hypertrophy often remains after AVR at long-term follow-up.[47, 98-100] Patients with prosthetic valves are today routinely investigated with Doppler echocardiography. Many prosthetic valves with normal function, mechanical and biological, have relatively high Doppler gradients.[101, 102] It is an important issue to what extent the Doppler gradients describe the left ventricular pressure burden. Reports on the relation between Doppler and catheter gradients in prosthetic valves have been conflicting. Early in vitro reports[103-105] and one previous in vivo study[106] described good agreement between Doppler and catheter gradients. However, later in vitro studies have shown overestimation of pressure gradients in bileaflet mechanical valves using Doppler echocardiography.[51-53] The discrepancy between Doppler and catheter gradients in bileaflet valves has been explained by the pressure recovery phenomenon.[107] The total energy of flow consists of pressure and kinetic energy. When blood accelerates through a prosthetic valve the velocity increases and thereby the kinetic energy. The total energy is constant and thus the pressure must decrease. When the velocity decreases inside the prosthetic valve (bileaflet model) or in the aorta some of the kinetic energy is transformed back to pressure energy. This conversion from kinetic to pressure energy is called pressure recovery (PR).[51-53] Doppler measures the highest velocity across the stenosis corresponding to the highest pressure gradient, whereas catheters measure the recovered pressure at some distance from the stenosis. It is the pressure gradient between the left ventricle and the ascending aorta after PR that is the hemodynamically most relevant gradient, because it describes the energy loss and determines the LV pressure and wall tension.[108]

The present study is the first in vivo study that demonstrates the discrepancy between Doppler and catheter gradients. One previous in vivo study investigating the relation between Doppler and catheter findings in prosthetic valves claimed that Doppler correlated well with catheter gradients.[106] In this simultaneous catheter-Doppler study the investigators used fluid-filled catheters. We started our study using fluid-filled catheters but the quality of the pressure recordings was poor and therefore we changed to electronic high-fidelity catheters. Fluid-filled catheters are not optimal when recording the fast changing pressure in the LV and aorta. The use of fluid-filled catheters might explain the seemingly good catheter-Doppler agreement reported in the previous in vitro study.

Our findings in mechanical bileaflet valves agree with previous in vitro studies.[51-53] The Doppler gradient overestimate the net pressure gradient between the LV and the ascending aorta. On the other hand, previous in vitro data investigating stented

bioprostheses, were conflicting.[51, 52, 109] Baumgartner et al concluded that PR was of no importance in stented bioprostheses[51, 109] while an important discrepancy between Doppler and catheter gradients was described by us.[52] Our previous in vitro findings were supported by the present in vivo study, in which we demonstrate a Doppler–catheter discrepancy in most patients with a stented bioprosthesis. A stented bioprosthesis is equivalent to a mild to moderate aortic stenosis, and considering basic fluid mechanical theory[110, 111] PR therefore is an expected finding. Moreover, we observed a Doppler–catheter discrepancy of the same magnitude in mechanical prostheses and bioprostheses. From previous in vitro studies, we anticipated a more pronounced Doppler–catheter discrepancy in mechanical valves compared with biologic valves because of local high velocities and PR within the central tunnel- like orifice in a bileaflet valve.[52, 53] In our in vivo study, we could not position the catheter within the prosthetic valves and therefore the findings should be interpreted with caution regarding the in vivo importance of localized high velocities or within-prosthesis PR. However, the similarity between mechanical and biologic prosthetic valves suggested that the within-prosthesis part of the Doppler-catheter discrepancy was less pronounced in vivo compared with in vitro.

Study limitations

Study I

In this study the surgeon's learning curve for the operation is analysed. By changing technique results improved. One must bear in mind that failure rates decrease with experience of the surgeon and even without changing technique in this study results may had improved.

Study II

The comprehensive echocardiography part of this study was limited to the intermediate and follow-up investigations. The distal part of the native aorta including the aortic arch was not studied preoperatively or at the first baseline investigation. Therefore, it can be concluded that at the follow-up the distal native aorta was dilated compared with controls, but the progression of the distal ascending aorta or the arch is unclear. Furthermore, it is difficult to distinguish between the autograft and the native aorta on the proximal ascending aorta measurements. Therefore, the observed change in proximal ascending aorta diameter from baseline to the follow-up conceivably reflects both autograft and native aorta enlargement.

Study III

One limitation of our QoL measurements is that they are not recorded at the same time point after surgery. Another limitation is that comorbidity, such as stroke and heart failure, may influence the results. However, the size of the material in the present study does not allow any subgroup analysis.

Study IV

Assessment of Doppler and pressure recordings qualities was based on the visual impression of the ultrasound beam interrogation angle with expected flow direction, plus the quality of spectral Doppler and pressure recordings. Although quality criteria were strict, we cannot exclude the possibility of errors in both Doppler and pressure measurements. The most likely Doppler error was an angle 20° between the ultrasound beam and flow direction. This would underestimate the Doppler gradient and thereby falsely underestimate the degree of Doppler–catheter discrepancy. The aortic pressure curve had a greater tendency to be somewhat distorted, and this would falsely increase the net gradient and underestimate the discrepancy between Doppler and catheter gradients. The number of patients in the study was small and therefore the importance of prosthesis size and dimension of the ascending aorta on the Doppler–catheter discrepancy could not be investigated.

During pressure recordings, we did not know the exact position of the catheters but from the pulsed Doppler recordings in the left ventricular outflow tract, we know that velocity was not high (1.4 m/s) and this should therefore not influence results.

7. Conclusions

1. Patient selection, intraoperative correction of anatomical mismatch and improved surgical technique can reduce the aortic regurgitation after the Ross procedure.

2. Pulmonary autograft dilatation is common and progresses over time after the Ross procedure in adults and is often accompanied by dilatation also of the native aorta. The baseline dimension of the autograft was found to be a risk factor for dilatation. The bicuspid valve disease and the need to downsize the aortic root were not found to be risk factors for dilatation.

3. Severe aortic endocarditis treated with homograft replacement is still associated with a substantial early complication rate and mortality. Long-term survival and quality of life are satisfactory in patients surviving the immediate postoperative period.

4. Doppler overestimated catheter gradients in both mechanical and stented biologic valves.

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10. Summary in Swedish

Kirurgisk behandling av hjärtats aortaklaff

Bakgrund och syfte: Patienter med förträngning eller läckage i aortaklaffen (klaffen mellan hjärtat och stora kroppspulsådern) får med tiden förstorad vänsterkammare i hjärtat som leder till ökad dödlighet. Patienter med symtom av sin klaffsjukdom bör behandlas med ett kirurgiskt ingrepp vilket ger förbättrad överlevnad. Det finns flera alternativ: reparation, ersättning med konstgjord mekanisk eller biologisk klaffprotes, donerad mänsklig klaff (homograft) eller egen lungklaff (autograft) flyttad till aortaposition samt homograft i pulmonalposition (Ross operation). Vi har studerat olika klaffsubstituts egenskaper samt resultat efter klaffoperation. Syftet var att öka kunskapen och göra valet av klaffsubstitut mer välunderbyggt och därmed öka möjligheten att den enskilda patienten får optimal behandling.

Material och metoder: I *arbete I,* undersöktes en första serie (24 patienter) med ekokardiografi och jämfördes med 53 patienter i en andra serie där kirurgisk teknik och urvalsmetoder förändrats. I *arbete II,* studerades dimensionerna av lungklaffen och den kvarvarande aortan hos 91 patienter opererade med Ross operation med ekokardiografi upp till 14 år efter klaffoperationen. I *arbete III,* studerades 62 patienter som opererats med homograft för komplicerad endokardit. Överlevnad, komplikationer och livskvalitet studerades. I *arbete IV,* mäter vi tryckfallet mellan vänster kammare och stora kroppspulsådern (blodtrycksfall över aortaklaffen) med elektroniska katetrar simultant med ekokardiografi (tryckfall mätt med Doppler) på 27 patienter med mekanisk och biologisk aortaprotes.

Resultat: I *arbete I,* fann vi att moderat aortaläckage minskat från 8 av 24 patienter till 2 av 53 patienter (33% till 4%, p=0.001). I *arbete II,* fann vi att patienterna hade en vidgning av autograftet (43%) eller aorta (32%) vid sen efterundersökning. Hos patienter undersökta tre gånger ökade vidgningen signifikant med tiden. *Arbete III,* visade att 15% av patienterna dog inom 30 dagar. Ökad risk för död var högre risk score (p=0.014), tid i hjärt-lungmaskin (p=0.003), medicinsk hjärtstimulering (p=0.03), blödning (p=0.01) och hjärtinfarkt (p<0.001). Livskvalitet (mätt med SF-36) för fysisk och psykisk hälsa skilde sig inte signifikant från matchade friska kontrollpersoner. I *arbete IV,* förelåg ett starkt förhållande mellan kateter och Doppler gradienter (r = 0.85 till 0.92). Doppler överskattade gradienter både för mekanisk och biologisk klaffprotes.

Slutsatser: Läckage i den inopererade klaffen efter Ross operation kan minskas med förbättrad kirurgisk teknik och patienturval. På lång sikt kommer en del klaffar vidga sig och kan i vissa fall leda till en ny operation. Patienterna måste kontrolleras regelbundet med ultraljud efter operationen för att inte nyuppkomna förändringar skall missas. Komplicerad endokardit kan med fördel behandlas med homograft. Dödligheten på sjukhus är hög efter operationen, men överlever man denna period är överlevnad och livskvalitet tillfredställande. Doppler som används som klinisk undersökning av aortaklaff, överskattar tryckfallet både för mekanisk och biologisk klaffprotes.