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Aortic Valve Replacement with Stentless Bioprostheses

Prospective long-term studies of the Biocor and the Toronto SPV

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Fortitudo et Sapientia

To my wife Helen and our children

Victor, Emelie and Douglas

Abstract

Background. Aortic valve disease is increasing among the elderly and aortic valve replacement is the most common cardiac surgical valve procedure in adults. Aortic stenosis (AS) is often associated with left ventricular hypertrophy (LVH) in an unexplained pattern. Traditionally, younger patients receive mechanical valves and patients older than 70 years receive bioprostheses. Stentless bioprostheses have physiologically attractive hemodynamic properties. There is hope that stentless bioprostheses will improve long-term survival and that a reduced risk of valve-related complications will allow its use in younger patients than those receiving bioprostheses today.

Patients and methods. These studies comprise 367 patients operated with the Biocor stentless (BS, n=112) or the Toronto stentless porcine valve (T-SPV, n=255) bioprostheses in two different patient populations (mean age; 78.5 vs. 63.3 years and female; 66% vs. 29%, respectively). Early and late clinical results were evaluated for both patient populations. Long-term survival for the BS population was compared to expected survival for an age- and gender-matched comparison population and relative survival rates were calculated. Hemodynamic results were investigated by echocardiography for both valves at early and late follow-up, and in addition, the BS valve was evaluated during exercise. Regression of left ventricular mass index (LVMI) was studied in both populations after the use of stentless bioprostheses. The angiotensin-converting enzyme (ACE) gene insertion (I) / deletion (D) polymorphism was studied and subsequently related to LVMI in patients with AS operated with stentless valves.

Results. Early mortality was 7% (8/112) and 1% (2/255) for the BS and the T-SPV valve groups, respectively, and long-term actuarial survival at 7 years was 59%±6% and 90%±2%. There was no difference in survival between the BS valve patients and the expected survival for the age- and gender-matched comparison population supplied by Statistics Sweden, and the annual relative survival rates indicated a normalized survival pattern for those patients. Valve-related complications were few for both stentless valves under study. Early and late hemodynamic function was similar and at seven years the mean pressure difference was 5.4±2.0 and 3.6±2.0 mm Hg for the BS and the T-SPV valves, respectively. Coronary artery disease and hypertension were associated with a higher LVMI over time in patients with the T-SPV and most patients had a normal LVMI at five years of follow-up. Patients with the DD genotype of the ACE gene had a higher LVMI (197±47g/m^2) preoperatively than those with ID (175±41g/m^2) or II (155±43 g/m^2) genotypes (p=0.01). The LVMI decreased in DD (p<0.001) and ID (p<0.001) genotypes but not in the II genotype during follow-up. There was a significant difference in regression of LVMI over time between genotypes (p=0.0056) with no significant difference between genotypes at follow-up.

Conclusions Early and long-term hemodynamic function is excellent for both stentless bioprostheses and they both confer good long-term survival. The BS patient population could be regarded as “cured” from valve disease since the observed survival did not differ from the expected survival for an age- and gender-matched Swedish comparison population, a conclusion that is also supported by a constant relative survival after the first postoperative year. Coronary artery disease and hypertension influenced the degree of LVH and its regression over time and most patients with the T-SPV valve had no LVH at long-term follow-up. Furthermore, I/D polymorphism of the ACE gene is one determinant for the hypertrophic response in patients with severe AS.

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Submitted Eur J Cardiothorac Surg.

List of abbreviations

AS	Aortic stenosis
AR	Aortic regurgitation
LVOT	Left ventricular outflow tract
LVH	Left ventricular hypertrophy
NYHA	New York Heart Association
AVR	Aortic valve replacement
BS	Biocor stentless bioprosthesis
EBS	Extended Biocor stentless bioprosthesis
T-SPV	Toronto stentless porcine valve
ACE	Angiotensin-converting enzyme
I	Insertion allele
D	Deletion allele
bp	Base pair
CW	Continuous-wave
PW	Pulsed-wave
LVM	Left ventricular mass
LVMI	Left ventricular mass index
P_{max}	Transvalvular peak pressure difference
P_{mean}	Transvalvular mean pressure difference
EOA	Effective orifice area
CO	Cardiac output
VTI	Velocity time integral
CABG	Coronary artery bypass grafting
AV	Aortic valve
IVS	Interventricular septum
PWT	Posterior wall thickness
LVEDD	Left ventricular end diastolic dimension
ASE	American Society of Echocardiography
EF	Ejection fraction
AVA	Aortic valve area (Gorlin)
DNA	Deoxyribonucleic acid
PCR	Polymerase chain reaction
SVD	Structural valve degeneration
TIA	Transient ischemic attack
ANOVA	Analysis of variance
CV	Coefficient of variation
CAD	Coronary artery disease

Introduction

Aortic valve disease

Aortic stenosis

Aortic stenosis (AS) is characterized by an obstruction of the left ventricular outflow tract (LVOT). AS is the most common cause of valvular disease among adults, with an estimated prevalence of 3% (1). The stenosis is most commonly localized to the valve itself and may be congenital or acquired. Acquired AS can be further stratified into rheumatic and degenerative origin. Rheumatic fever is increasingly uncommon in the Western hemisphere but is still a common cause of AS in the developing countries. In contrast, the incidence of degenerative AS seems to be increasing with increasing age of the general population and more frequent in women among elderly (2, 3).

The natural history of AS in adults is characterized by a long asymptomatic period with gradually increasing obstruction of the aortic valve. Left ventricular output is often maintained by the development of left ventricular hypertrophy (LVH), which may sustain a large pressure difference across the aortic valve for many years without reduction in cardiac output, ventricular dilatation or the development of symptoms. The prognosis is good as long as the patient is asymptomatic but when symptoms occur, such as angina pectoris, syncope or congestive heart failure, the prognosis rapidly becomes poor. However, despite the good prognosis for asymptomatic patients the risk of sudden death was found to be 6% during a mean follow-up of 14 months in a prospective study (4). Approximately 50% of patients with symptomatic AS are dead within 2 years after the onset of symptoms and the risk appears to be even higher among elderly (50% die within 18 months) (5, 6). The occurrence of symptoms should be a strong incentive to consider surgical correction of moderate to severe AS.

Aortic regurgitation

Primary disease of the aortic valve leaflets or the wall of the aortic root (or both) may cause aortic regurgitation (AR). AR originating primarily from the valve leaflets is stratified according to etiology and the most common causes are rheumatic fever,

infective endocarditis, prolapsing bicuspid valves, an inflammatory disease process associated to the serotype HLA-B27 (7) and - increasingly common - structural valve deterioration of an aging bioprosthesis.

Moderate AR may be associated with a favorable prognosis for many years. Approximately 75% of patients survive for 5 years and 50% for 10 years after diagnosis. However, as in the case of AS, once symptoms occurs patients rapidly deteriorate. Even during the asymptomatic period there is often a gradual deterioration of left ventricular function and it is important to intervene surgically before these changes have become irreversible (8, 9). Both early and late mortality was lower among patients who were operated on when they had fewer symptoms (New York Heart Association (NYHA) class I and II) than among severely symptomatic patients (NYHA class III and IV) (9). The presence of left ventricular dilatation or of class II symptoms should be a strong incentive to consider immediate surgical correction of severe AR (8, 9, 10).

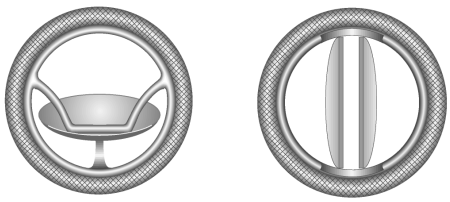
Aortic valve replacement

History of aortic valve surgery

The first surgical attempt to treat aortic stenosis was performed in 1913 by Tuffier who dilated the aortic valve by invaginating the aorta (11). Maybe that should be regarded as the first successful attempt to surgically treat aortic valve disease since the patient was still alive 12 years later. Valve surgery was subsequently performed under experimental conditions for many years but mainly in patients with mitral valve disease. In 1950, Bailey performed the first successful closed heart aortic commissurotomy for aortic stenosis in man (12). Two years later, Hufnagel performed the first successful implantation of an artificial valve placed in the descending aorta of a patient with aortic incompetence (13). When the heart-lung machine became available, a number of surgical methods were designed in order to repair the aortic valve in patients with AS and AR. Most of these methods were disappointments due to the fact that most valves were too severely damaged and not amenable to repair. In 1960, Harken implanted the first successful mechanical valve in a patient with severe AR, shortly followed by Starr, who performed the first successful intracardiac mechanical mitral valve replacement (14,

15). Subsequently a number of different mechanical valves were developed, and the Björk-Shiley tilting-disc (Figure 1) was introduced in 1969 at the Karolinska Hospital and became the standard prosthesis for aortic valve replacement (AVR) for more than two decades at our institution (16, 17, 18).

Figure 1.

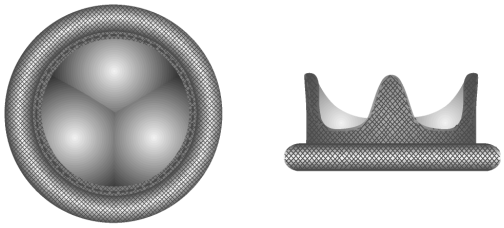


Examples of mechanical aortic prostheses. A monoleaflet (Björk-Shiley Monostrut) and a bileaflet mechanical valve.

History of stented and stentless bioprostheses

Ross described the clinical use of aortic homografts for AVR in 1962, in parallel to the development of mechanical valve prostheses, and established the concept of tissue valves as prostheses (19). One week after this first homograft implantation and independently from Ross, the second homograft implantation was performed by Barratt-Boyes (20). However, even though these valves had a good long-term outcome they never became widely used because of the complex logistics of sterilization, storage and availability. Binet and Duran described in 1965 the use of aortic valves from non-human sources, i.e. heterografts – valves from pig and calf (21). These valves were unstented valves treated with a mercurial solution in order to render them less antigenic and suitable for implantation in humans. Heterografts were readily available in all conceivable sizes but the extensive muscle bar at the base of the right coronary sinus of the pig valve raised technical concerns. Carpentier and coworkers reported in 1969 graft dysfunction in a number of patients with "direct suture" (i.e. stentless) of porcine aortic heterografts, and one of the problems was prolapse of the unsupported porcine right coronary cusp (22). Their conclusion was that the heterograft should be stent-mounted in order to prevent problems related to the muscle shelf and to prevent host tissue ingrowth, which at that time was considered detrimental to the graft function. They also suggested that the heterograft should be preserved with glutaraldehyde instead of formerly used formaldehyde or mercurial solutions, as they claimed glutaraldehyde would improve the structural integrity and durability of the heterograft. Subsequently, both heterografts and homografts were often stent-

Figure 2.



A stented aortic bioprosthesis from below and from the side clearly showing the large stent that surrounds the valve.

mounted although some surgeons continued to use a freehand technique, especially for the homografts. It soon became evident, however, that the stent-mounted homografts and heterografts had a significantly higher failure rate than the regular homograft valve replacement (23, 24). Glutaraldehyde was proven to be more effective than formaldehyde in providing cross-links between collagen molecules and the terminology was changed: these xenografts were now called bioprostheses (23, 25).

Carpentier and Hancock introduced the first commercially available glutaraldehyde fixed porcine stented bioprostheses (26, 27). Since then there have been a number of changes in valve design, and maybe the most important one is the change of pressure in the preservation technique. In order to improve integrity and durability of valve tissue the evolution has progressed from "high pressure" (first generation) to "low pressure" (second generation) with the most recent one being "zero pressure" (third generation) preservation technique. That third generation porcine bioprostheses have good long-term outcome has been shown in several studies (28, 29). Ionescu and colleagues introduced in 1971 the use of glutaraldehyde treated bovine pericardial valves for AVR (30). Those valves were at the time superior to porcine valves from a hemodynamic point of view (31) but showed signs of limited durability in fatigue tests; this was later confirmed clinically (32, 33). The Carpentier-Edwards Perimount aortic valve was introduced after several design changes which included improved tissue preservation, a more flexible stent, a modified shape of the cusps and in the tissue-mounting of the pericardium in the stent. Early and late clinical and hemodynamic studies have shown satisfactory results (34, 35). There is an ongoing debate whether pericardial or porcine stented bioprostheses are superior from a hemodynamic point of view. Currently the preferred valve for AVR in elderly patients (> 65 years) is a porcine or a pericardial stented bioprosthesis (Figure 2). The most thoroughly investigated third generation bioprostheses are the Carpentier-Edwards (pericardial) (35), Hancock II (porcine) (29) and the Biocor (porcine) (28) valves. Noninvasive hemodynamic

studies, however, have revealed that most stented bioprostheses as well as some mechanical valves have relatively high transvalvular obstruction to flow (36, 37).

In the search for the "ideal" prosthesis, David reintroduced in 1988 the concept of stentless bioprostheses with the Toronto stentless porcine valve (T-SPV) (38, 39). A stentless design offers theoretical advantages in hemodynamic performance as the obstruction caused by the rigid stent and sewing ring is eliminated. This advantage would particularly well benefit the elderly female patients, who often have a narrow aortic root. These patients are less suitable for a valve replacement resulting in significant residual obstruction, as is the case with many stented valves. One alternative for these patients is a patch widening of the aortic root in order to fit in an adequately sized valve prosthesis. However, these procedures are time consuming and prone to technical errors and are therefore associated with a greater risk for the patient. Experimental animal and in vitro studies have demonstrated promising performance of stentless bioprostheses (38). Studies in humans have also shown low pressure differences across currently available stentless prostheses and satisfactory early clinical results (39, 40). However, there is no information about long-term clinical and hemodynamic outcome with the stentless bioprostheses.

Left ventricular hypertrophy in AS

Left ventricular hypertrophy (LVH) in AS is concentric and is due to pressure overload. In contrast, LVH in AR is eccentric and is due to volume overload. Preoperative studies of patients with symptomatic AS have demonstrated a poor correlation between the degree of AS and the degree of LVH (41, 42). The absence of a clear relationship between the stenosis-dependent pressure load on the left ventricle and the degree of ventricular hypertrophy suggests that the left ventricular phenotype is dependent on many factors. Plausible contributing factors include gender, age and hypertension. Our study was designed to investigate the incidence of LVH in patients with symptomatic AS undergoing AVR and the relation between LVH and preoperative transvalvular pressure differences. In addition, we monitored the regression of left ventricular mass after AVR with stentless bioprostheses and intended to correlate these changes to clinical parameters.

Angiotensin converting enzyme gene polymorphism

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase, anchored to the cell membrane by a carboxy-terminal hydrophobic peptide, with the active site exposed extracellularly. The importance of this enzyme in cardiovascular physiology is based on its vasoactive properties, as it cleaves angiotensin I into angiotensin II, which is a potent vasoconstrictor. However, its physiologic role is not limited to vasoactive peptide metabolism in the hormonal renin angiotensin system. There is strong evidence for a local renin-angiotensin system in the heart (43, 44), supported by the fact that angiotensin-converting enzyme inhibitors can prevent or reverse cardiac hypertrophy (45). These effects seem to be caused by angiotensin II, which has direct inotropic and chronotropic effects on myocardial cells (44) and also increase protein synthesis and connective tissue deposition of the heart (46).

When the ACE gene had been cloned, it was shown to be characterized by an insertion (I) / deletion (D) polymorphism based on the presence (I) or absence (D) of a 287-basepair (bp) "*alu"* repeat sequence within intron 16 (47). The I/D polymorphism results in three genotypes, one heterozygote (ID) and two homozygotes (DD and II). The ACE gene polymorphism at locus 17q23 of a non-coding region (intron 16) has been suggested to influence cardiovascular morbidity (48, 49, 50, 51, 52, 53). Although data from different investigations are to some extent contradictory, the DD genotype appears to be related to adverse effects in regard to ischemic or idiopathic dilated cardiomyopathy (54), hypertrophic cardiomyopathy (55, 56) and cardiac hypertrophy and remodeling (57, 58). In patients with idiopathic chronic heart failure, the DD genotype was found to be related not only to increased left ventricular mass but also to be an independent risk factor for mortality (59). Therefore, ACE gene polymorphism was postulated to be an important genetic factor contributing to the development of LVH in patients with AS.

Clinical evaluation of aortic valve prostheses

Clinical examination of patients with prosthetic heart valves is important not only to detect new or increased systolic or diastolic murmurs but also for classifying patients according to the NYHA classification system (60). However, there is a poor correlation between cardiac murmurs and echocardiographic findings of valvular obstruc-

tion and/or incompetence. It is very common that elderly patients have a systolic murmur after AVR with a normally functioning bioprosthesis. In many cases systolic murmurs are related to stiff atherosclerotic main arteries but could also be related to a relative obstruction seen in some valve prostheses. Furthermore, mild to moderate aortic regurgitation is difficult to detect either clinically or by auscultation. Heart valve studies should ideally be performed as prospectively designed studies in order to detect complications that should be reported according to the current guidelines for valve studies (61). A retrospectively designed valve study runs the obvious risk of missing valve related events such as thromboembolic episodes or endocarditis.

Hemodynamic evaluation of prosthetic function

Cardiac catheterization

Cardiac catheterization was also in our institution for many years the gold standard for evaluation of the hemodynamic function of prosthetic aortic valves (62, 63, 64, 65). However, severe complications occurred in more than 1% of procedures and nowadays, due to its invasiveness, cardiac catheterization has been abandoned for serial evaluation of heart valves (66).

Echocardiography

Transthoracic echocardiography is now considered the gold standard for serial monitoring of valve function after AVR. The main advantage is that necessary information about hemodynamics and anatomy can be obtained noninvasively.

A complete echocardiogram includes M-mode and 2-D measurements as well as continuous-wave (CW), pulsed-wave (PW) and color Doppler ultrasound. M-mode and 2-D measurements are important to determine left ventricle dimensions, wall thickness and systolic function. Moreover, M-mode and 2-D measurements allow calculations of left ventricular mass (LVM). When LVM is indexed for body mass (LVMI) it is possible to assess whether patients have LVH. Some 2-D measurements are also essential in order to calculate certain hemodynamic variables. CW and color Doppler are useful tools in determining aortic valve regurgitation (67, 68, 69). However, CW and color Doppler estimation of AR have so far been based on qualitative or semi-quantitative criteria as angiography.

The Doppler ultrasound technique allows blood flow measurements and calculations of transvalvular pressure differences. Transvalvular maximum (ΔP_{max}) and mean pressure (ΔP_{mean}) differences, based on the modified Bernoulli equation ($\Delta P = 4 \times V^2$), are the most frequently used Doppler derived variable in reporting on AS and heart valve prostheses (70). However, some authors claim that since the transvalvular aortic pressure difference is relatively low, the velocity in the LVOT should be considered, as in the longer form of the modified Bernoulli equation ($\Delta P = 4 \times [(V_{AO}^2) - (V_{LVOT})^2]$) (71). Furthermore, using data from 2-D echocardiography and Doppler ultrasound allows calculations of hemodynamic data such as effective orifice area (EOA) and cardiac output (CO) (72, 73). Since pressure differences are flow dependent, the area through which the flow must pass is generally considered a better measure of obstruction. A velocity or a velocity time integral (VTI) can be used to estimate the EOA according to the continuity equation ($VTI_{LVOT} \times Area_{LVOT} / VTI_{aorta}$). CW Doppler across the aortic valve prosthesis and PW Doppler in the LVOT are used to obtain the velocity or the VTI.

Aims

- To describe early and late clinical outcome after implantation of two different stentless porcine aortic bioprostheses.

- To evaluate early hemodynamic valve function at rest and during exercise after implantation of the BS stentless bioprosthesis.

- To evaluate late hemodynamic valve function at rest in two different aortic stentless bioprostheses.

- To study the change in left ventricular mass postoperatively after implantation of two different stentless valves.

- To study the relation between transvalvular pressure difference and left ventricular mass in patients with symptomatic AS operated with stentless valves.

- To study the relation between left ventricular mass and angiotensin-converting enzyme gene polymorphism in patients operated on for AS.

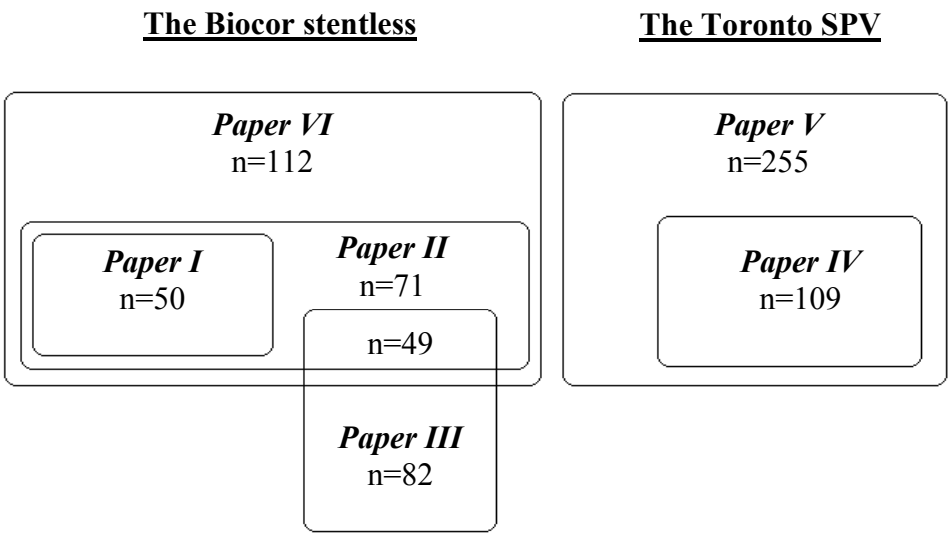
Methods

Patients and study design

Patients included in the present studies were operated with AVR at the Department of Thoracic Surgery, Karolinska Hospital, Stockholm, Sweden and at the Department of Cardiovascular Surgery, Toronto General Hospital, Toronto, Ontario, Canada. Between October 1990 and November 2000, 112 patients underwent AVR with either a Biocor stentless (BS) or an "extended" Biocor stentless (EBS) bioprosthesis at the Karolinska Hospital. The first consecutive 91 patients had the EBS valve implanted and the following patients received the regular BS bioprosthesis. From July 1991 to December 1998 the Toronto SPV (T-SPV) bioprosthesis was used for AVR in 255 patients at the Toronto General Hospital.

Altogether, this study includes 400 patients (Figure 3) with different stentless valves. Table 1 outlines the preoperative characteristics in two patient cohorts with two different stentless valves. All patients gave their informed consent to participate in this study.

Figure 3.



Distribution of patients between studies I –VI. Studies with the Biocor (studies I – III and VI) and the Toronto SPV (studies IV – V) stentless porcine aortic bioprostheses.

Table 1. Clinical characteristics

	Biocor No. and (%), or Mean ± SD	Toronto SPV No. and (%), or Mean ± SD
No. of patients	112	255
Age (years)	78.5 ± 5.0	63.3±10.6
Age range (years)	60-88	22-83
Sex		
Male	38 (34)	182 (71)
Female	74 (66)	73 (29)
Electrocardiogram		
Sinus	97 (87)	239 (89)
Atrial Fibrillation	14 (12)	13 (7)
NYHA functional classification		
Class I	3 (3)	15 (6)
Class II	27 (24)	114 (45)
Class III	74 (66)	102 (40)
Class IV	8 (7)	24 (9)
Aortic valve lesion		
Stenosis	96 (86)	155 (61)
Regurgitation	2 (2)	35 (14)
Mixed lesion	12 (12)	64 (25)
Coronary artery disease		
None	65 (58)	174 (50)
One-vessel	27 (24)	31 (16)
Two-vessel	16 (14)	30 (14)
Three-vessel	4 (4)	20 (20)
Preoperative endocarditis	1 (1)	6 (2)
Reoperation	2 (2)	13 (5)
Previous aortic valve replacement	2 (2)	7 (3)
Previous aortic valve repair		1 (0.4)
Previous coronary artery bypass surgery		5 (2)

NYHA – New York Heart Association

The ethics committee of the Karolinska Hospital approved the Swedish protocols. Canadian regulatory authorities and the Food and Drug Administration (FDA) in the USA closely followed patients operated with the T-SPV bioprosthesis. Toronto General Hospital participated in a multi-center observational trial sponsored by St. Jude Medical to obtain FDA approval for the T-SPV, which was achieved in late 1997.

Paper I – Early hemodynamic results with the Extended Biocor stentless bio-prosthesis

Seventy-one patients underwent AVR with the EBS bioprosthesis between October 1990 and June 1995. There were five early deaths, 4 late deaths and 11 patients with less than 3 echocardiographic examinations postoperatively. The remaining 50 patients underwent Doppler echocardiographic ex-aminations on three occasions: the first within one week after operation before

being discharged from hospital, the second at 6 months postoperatively and the third at a mean follow-up time of 15 months. Their mean age was 77 years (range 60-87 years) with a majority of patients being women (28/50, 56%). The indication for surgery was predominantly AS in 43 patients, AR in 1 patient and mixed lesion in 6 patients. All patients were prospectively followed with clinical examinations and echocardiography. In addition, 30 patients (60%) were able to perform a symptom-limited bicycle exercise test in the supine position at late follow-up.

Paper II – Early clinical results with the Extended Biocor stentless bioprosthesis

Early clinical results are outlined in detail for the first consecutive 71 patients operated between October 1990 and June 1995 with the EBS bioprosthesis. All patients were prospectively followed on an annual basis with a clinical examination as well as an echocardiographic investigation. The follow-up was 100% complete. The mean follow-up was 15 ± 3 months and 76 patient years of follow-up were available for analysis. The mean age at operation was 77.5 years (median age 78 years, range 60-87 years). Forty-three patients were women (60%, mean age 78.8 years) and 28 were men (mean age 75.7 years). Preoperative aortic valve pathology was stenosis in 86% (61/71), regurgitation in 1% (1/71), mixed in 10% (7/71) and a failing bioprosthesis in 3% (2/71). Concomitant coronary artery bypass grafting (CABG) was performed in 39%. In this paper, operative techniques, and early morbidity and mortality were described in detail, as were mortality and valve related complications that occurred during the follow-up period. Echocardiography at rest was performed at latest follow-up in 60 of the 62 surviving patients.

Paper III – ACE-gene polymorphism and LVH in patients operated for AS

Eighty-two patients (40 women and 42 men) with AS underwent AVR between 1990 and 1995 with either a stentless bioprosthesis or an aortic allograft. Indication for aortic valve replacement was in all cases symptomatic AS verified by echocardiography (aortic valve area less than 1 cm^2 and/or a mean transvalvular gradient of more than 30 mm Hg). A Biocor stentless bioprosthesis (n = 49), a Baxter (Baxter Inc., Irvine, CA) stentless bioprosthesis (n = 4) or an aortic allograft (n = 29) was used. We included only patients with stentless bioprostheses or allografts since these valves are considered to be less obstructive than other valve alternatives, thereby

minimizing the postoperative pressure overload of the left ventricle. All surviving patients who received any of these valve prostheses were investigated in a prospective study employing Doppler echocardiography before AVR and approximately one year (mean 15 months) postoperatively. Hemodynamic parameters and left ventricular measurements, before surgery and at late follow-up, were investigated and LVM was calculated and indexed for body surface area. The degree of AS, measured as the preoperative transvalvular gradient, was correlated to preoperative LVMI. ACE genotypes were correlated to pre- and post-operative LVMI.

Paper IV – Late hemodynamic results with the Toronto SPV bioprosthesis

Late hemodynamic results were investigated in the first 109 consecutive patients that underwent AVR with the T-SPV bioprosthesis between July 1991 and February 1994 at the Toronto General Hospital. All patients had been followed for at least 5 years, and for most of them, six postoperative echocardiographic examinations performed during this time interval were available for analysis. Mean age was 62.7 years and most patients were men (74%). Preoperatively 52% of patients were in NYHA class III or IV. Indications for surgery were AS in 80%, AR in 8% and a mixed lesion in 12%. Long-term hemodynamic valve function was evaluated in terms of transvalvular pressure differences and EOA. Calculations of LVM were correlated to clinical parameters likely to affect LVM, such as preoperative hypertension, sex, aortic valve pathology and coronary artery disease.

Paper V – Late clinical results with the Toronto SPV bioprosthesis

Late clinical and hemodynamic results were investigated in 255 patients (mean age 63 years, median age 66, range 22-83 years) that underwent AVR with the T-SPV bioprosthesis between July 1991 and December 1998 at the Toronto General Hospital. The characteristics of these patients are summarized in Table 1. Operative survivors were followed prospectively and the closing interval was between February 1999 and February 2000. The follow-up was 100% complete. The mean follow-up was 53 ± 24 months (range, 2-101 months) and 1097 patient-years of follow-up were available for analysis. Late clinical results were examined in detail. In addition, hemodynamic data were presented for the first 173 consecutive patients included in the echocardiographic follow-up study.

The remaining patients were not followed at regular intervals with echocardiography.

Paper VI – Late clinical and hemodynamic results with the Biocor stentless bioprosthesis

Between October 1990 and November 2000, 112 patients (mean age 78 years, median age 79 years, range 60-88 years) underwent 113 procedures for AVR with either a BS or an EBS bioprosthesis at the Karolinska Hospital. Patient selection criteria were primarily aortic valve disease and age >70 years. Detailed patient data are shown in Table 1. We deliberately sought to include patients with a narrow aortic root, which explains the high percentage of older women. Patients were prospectively seen on an annual basis for clinical examination and echocardiography. Those not able to come were contacted by phone. The closing interval for this study was between October 1st and December 31st 2001. Mean follow-up was 66 ± 33 months and was 100% complete. Total follow-up was 562 patient years. Late clinical outcome was studied in detail as were longitudinal hemodynamic data from serial echocardiographic examinations. Late survival of patients was compared to an age- and gender-matched comparison group derived by Statistics Sweden and relative survival rates were calculated for the patient population.

Stentless bioprostheses

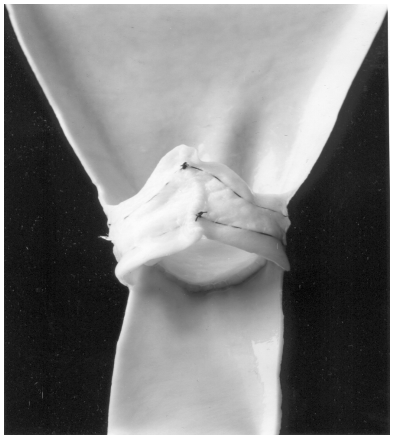
The Biocor stentless valve (I – III, VI)

The Biocor stentless (BS) aortic valve prosthesis (originally from Biocor Industria e Pesquisas Ltda., Belo Horizonte, Brazil; as of September 1996, from St. Jude Medical, St. Paul, Minnesota, USA) consists of three separate porcine aortic valve cusps mounted in a ring of bovine pericardium and treated with glutaraldehyde under minimal pressure fixation (Figure 4). Valve size is determined by external diameter and available from 19 to 29 mm. Three marking sutures are placed on the inflow aspect of the pericardial tube to indicate the bottom of each sinus and at equidistant length from the two closest commissures. The pericardial tube of the regular BS prosthesis has scalloped inflow and outflow borders. The ”Extended” Biocor stentless (EBS) bioprosthesis is a BS bioprosthesis with added pericardial extensions corresponding to one third of

Figure 4.

The regular Biocor stentless (BS).

Figure 5.



The extended Biocor stentless (EBS).

the circumference, extending both superiorly and inferiorly from the bovine pericardial ring (Figure 5). The superior and inferior extensions are referred to as the "collar" and the "skirt", respectively. The BS and the EBS bioprostheses are thus identical except for the pericardial extensions. The EBS bioprosthesis allows optional enlargement of the aortic root down to or into the mitral valve as well as up into the aortotomy. When not needed, the extensions can be cut away and the valve used as a regular stentless valve. In the following text when we refer to the BS valve population it includes patients with both the regular BS and the EBS valves unless specifically stated.

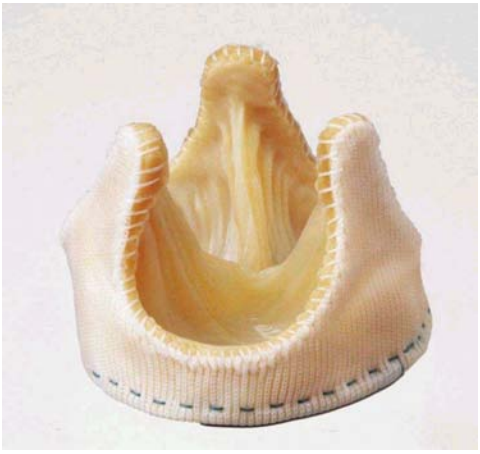
The Toronto SPV (IV – V)

The Toronto SPV (T-SPV) bioprosthesis (St. Jude, St. Paul, Minnesota, USA) is an excised complete porcine aortic valve with scalloped sinuses and fixed in glutaraldehyde under low pressure. The whole exterior of the valve is covered with a single layer of fine Dacron polyester fabric in order to prevent septal muscle bar resorption, thereby reducing the risk of paravalvular leakage (Figure 6). Three colored sutures at the inflow edge indicate where the commissures are located. Valve size is determined by external diameter and available sizes are from 19 to 29 mm.

Operative technique

At the Karolinska Hospital (I-III, VI), midline sternotomy and cardiopulmonary bypass were used in all patients implanted with the BS or the EBS valves. After aortic crossclamping, antegrade and retrograde cold crystalloid (11%) or blood (89%) cardioplegia was administered through a large

Figure 6.



The Toronto SPV bioprosthesis.

bore needle and a coronary sinus catheter. Table 2 shows the operative data for the whole cohort of patients. An oblique aortotomy into the noncoronary sinus was used in most of the patients for the EBS valve. The incision was prolonged down to or into the aortic-mitral curtain if the aortic root was considered very narrow. A transverse aortotomy was usually used for the BS valve. After excision of the aortic valve, the annulus was sized with Biocor sizers. The selected prosthesis was implanted into the aortic root with a technique similar to the "freehand" technique used in allograft surgery (74, 75). A tendency towards limited oversizing of the bioprosthesis compared to the aortic annulus was accomplished (23.3 ± 1.6 mm vs. 22.8 ± 2.2 mm). When deemed desirable the lower pericardial extension of an EBS valve was used to widen the aortic annulus and the upper extension was patched into the aortotomy. The proximal valve suture line was performed with either isolated 4-0 braided polyester sutures or three running 3-0 polypropylene sutures. The distal suture line was done with continuous 4-0 polypropylene sutures, starting under the right and left coronary ostiae, respectively.

***At the Toronto General Hospital (IV-V)*,** all patients with the T-SPV valve were operated with midline sternotomy and cardiopulmonary bypass. After aortic cross-clamping, antegrade cold blood cardioplegia was administered through a large bore needle and/or by separate direct cannulation of the coronary ostiae. Table 2 shows the operative data for the T-SPV patient population. The manufacturer warns against using the valve if there is a discrepancy between the aortic annulus and the sinotubular junction of more than one valve size (2 mm). The size of the selected prosthesis was based on the diameter of the aortic annulus and the sinotubular junction. If the sinotubular junction was larger than the aortic annulus, a valve size was chosen corresponding to the diameter of the sinotubular junction. However, in most patients these two diameters were similar and a T-SPV of the same diameter as the sinotubular junction was selected and prepared for implantation

Table 2. Operative data

	Biocor		Toronto SPV	
	No. or Mean ± SD	% or range	No. or Mean ± SD	% or range
Patients	112		255	
Extended Biocor stentless (EBS)	91	81		
"Collar" used	77	85		
"Skirt" used	12	13		
Both used in the same patient	11	12		
Standard Biocor stentless (BS)	21	19		
Valve sizes implanted (mm)	23.3 ± 1.6	19-25	26.5 ± 1.6	19-29
19 mm	1	1	2	1
20 mm			1	0.5
21 mm	27	24	3	1
22 mm			2	1
23 mm	37	33	21	8
25 mm	47	42	65	26
27 mm			93	36
29 mm			68	27
Associated procedures				
Coronary artery bypass surgery	35	31	86	34
Mitral valve repair	1	1	10	4
Mitral valve replacement			11	4
Tricuspid valve repair			4	1
Miscellaneous	2	2	11	4
Aortic cross-clamp time (min)	107 ± 25	61-172	86 ± 23	46-195
AVR alone (min)	96 ± 19	61-153	80 ± 22	46-195
AVR combined procedures (min)	124 ± 23	84-172	97 ± 20	56-151
Cardiopulmonary bypass time (min)	156 ± 52	85-409	106 ± 29	58-259
AVR alone (min)	132 ± 24	85-227	99 ± 28	58-259
AVR combined procedures (min)	196 ± 59	120-409	120 ± 25	74-194

AVR = aortic valve replacement

Some patients received a valve size larger than the aortic annulus and corresponding to the sinotubular junction. This method of sizing was called "limited oversizing". Limited oversizing is thought to prevent AR, secondary to an outward movement at the top of the commissures if the valve is wrongly sized. A greater discrepancy, more than one valve size (2 mm), requires tailoring of the sinotubular junction after the implantation of the T-SPV valve. The T-SPV was implanted with a subcoronary technique. The valve was secured in the LVOT with multiple (20-25) interrupted 4-0 polyester sutures. The proximal suture line was aligned to a horizontal plane corresponding to the bottom of all three sinuses of the aortic annulus and was not allowed to follow the scalloped natural shape created by the commissures. The distal suture line was performed with three continuous double armed 4-0 polypropylene sutures. The alignment of the three commissures in the aorta is very important to achieve normally coapting valve leaflets.

When the T-SPV and the BS valves were in place, and patients weaned from cardiopulmonary bypass, intraoperative echocardiography was used at both the Karolinska Hospital and the Toronto General Hospital to determine valve function, and only trivial AR was accepted.

Doppler Echocardiography

All patients with the BS valve were included in a prospective study with echocardiograms performed before discharge, after 6 months and annually thereafter. The first 173 patients with the T-SPV valve were also included in a prospective study with examinations performed at the same time intervals. Examinations of the BS valves were performed at the Karolinska Hospital and patients with the T-SPV had their echocardiograms done at the Toronto General Hospital. Transthoracic Doppler echocardiography was performed at the Karolinska Hospital using Acuson 128 XP/10 ultrasound equipment with 2-MHz imaging transducer. At the Toronto General Hospital, transthoracic echocardiography was performed using a Hewlett Packard 1000, 1500 or 2500 Ultrascope equipped with a 2.5 MHz transducer.

Rest studies (I-VI)

On each occasion complete color, PW and CW Doppler echocardiography were carried out including two-dimensional and M-mode measurements (76). Color flow Doppler was used to assess AR in the parasternal long- and short-axis views and in the 5-chamber apical views. Two-dimensional-guided and stand-alone CW Doppler was used to determine flow through the aortic valve from multiple positions. PW Doppler was used to assess flow in the LVOT.

The peak (V_{max}, m/s) and mean (V_{mean}, m/s) systolic blood velocity across the aortic valve (AV) was recorded with CW Doppler, and proximal to the aortic valve using PW Doppler in the LVOT. The average of 3 consecutive cardiac cycles in sinus rhythm or of 5 (at Karolinska Hospital) to 10 (at Toronto General Hospital) cardiac cycles in atrial fibrillation was used to calculate transaortic velocities and velocity time integral (VTI, cm). Peak (ΔP_{max}) and mean (ΔP_{mean}) pressure differences were calculated using the modified and simplified Bernoulli equation (77). The LVOT diameter (D, cm) was determined in midsystole from the parasternal long-axis view. The EOA was calculated with the continuity equation (77).

The modified and simplified Bernoulli equation (77)

ΔP_{max} (mm Hg) = 4 x $[(V_{max}AV)^2]$, (used in paper I-III and VI)

ΔP_{max} (mm Hg) = 4 x $[(V_{max}AV)^2 - (V_{max}LVOT)^2]$, (Used in paper IV-V)

ΔP_{mean} (mm Hg) = $P_{mean}AV - P_{mean}LVOT$ = 4 x $[(V_{mean}AV)^2 - (V_{mean}LVOT)^2]$

The continuity equation (77)

EOA (cm^2) = $[(\pi \times (D/2)^2) \times (VTI_{LVOT}/VTI_{AV})]$

Cardiac output (77)

CO (L/min) = HR x $[(\pi \times (D/2)^2) \times VTI_{LVOT}]/1000$

The ASE cube method (78)

LVM (g) = 1.04 x $[(IVS + PWT + LVEDD)^3 - (LVEDD)^3]$

(Original ASE cube used in paper I and III)

LVM (g) = 0.8 x $\{1.04 \times [(IVS + PWT + LVEDD)^3 - (LVEDD)^3]\}$ + 0.6

(Corrected ASE cube used in paper IV)

CO was calculated as the product of stroke volume and heart rate (HR, min^{-1}) (77).

Measurements of interventricular septum (IVS, cm), posterior wall thickness (PWT, cm) and left ventricular end diastolic dimension (LVEDD, cm) were obtained with two-dimensional echocardiography in a standard fashion. Left ventricular mass (LVM) was calculated from IVS, PWT and the LVEDD based on the American Society of Echocardiography (ASE) cube method (78). The LVMI was calculated by dividing LVM by body surface area. LVH was defined as a LVMI higher than 150 g/m^2 and 120 g/m^2 for men and women, respectively, with the original cube function formula, and higher than 131 g/m^2 and 100 g/m^2 for men and women, respectively, with the anatomically corrected modified formula (78, 79).

AR was assessed using color flow Doppler, CW and PW Doppler in any view (68). AR was quantified using color flow Doppler and based on either percent diameter or percent area of the jet relative to that of the LVOT in the long-axis or short-axis views, respectively (68). AR was classified as absent, trivial, mild, moderate or severe. The relative jet-to-LVOT diameter in the long-axis view was < 24%, 24 to <45%, 45 to <65% or > 65% for trivial, mild, moderate and severe AR, respectively. Similarly, AR was defined as trivial, mild, moderate or severe if the jet-to-LVOT area in the short-axis view was < 4%, 4 to <25%, 25 to <60% or >60%, respectively. The ejec-

tion fraction (EF) was determined according to the Simpson rule and left ventricular function was classified as grade 1 (EF>60%), grade 2 (EF 40-60%), grade 3 (EF 20-40%) or grade 4 (EF<20%) (80).

Exercise studies (I)

A symptom-limited bicycle exercise test in the supine position, with a left tilt to facilitate ultrasound measurements, was performed to evaluate early hemodynamic function of the EBS bioprosthesis. The bicycle ergometer was mounted on the examination table with the pedal fulcrum 45 cm above the table. The initial workload was 20 or 30 Watts depending on age, sex and fitness. The workload was then increased in steps of 10 or 20 Watts every three minutes. The exercise test was interrupted when severe symptoms occurred, i.e. grade 7/10 according to the Borg scale (81). Heart rate was measured, Doppler recordings across the aortic prosthesis and in the left ventricular outflow tract were obtained at rest and during the last minute at each level of work. Ten good-quality Doppler curves were traced at each load and the measurements were averaged. CO, stroke volume, aortic valve volume flow, ΔP_{max}, ΔP_{mean} and EOA were calculated. Diameter of the LVOT at rest was used to calculate stroke volume and EOA during exercise. In addition, the aortic valve area (AVA) was calculated from non-invasive measurements, according to the Gorlin equation (AVA = Stroke volume x (systolic ejection period x 44.5 x $P_{mean}^{1/2}$)$^{-1}$) (82). The same acoustic windows were used at rest and during exercise. Calculations from exercise studies were made off-line from videotapes using the same equipment and the same software as for resting studies.

Polymerase chain reaction (PCR)

ACE genotyping

Peripheral blood was separated in plasma and blood cells and stored in a freezer at -70° C until further analysis. Deoxyribonucleic acid (DNA) was extracted from frozen ethylenediamine-tetraacetic acid whole blood using the QIAamp® blood kit (QIAGEN Inc.). In brief, the polymerase chain reaction (PCR) amplification of the insertion / deletion polymorphism of the human ACE gene was performed with primers that flank the polymorphism (47).

Sense primer:

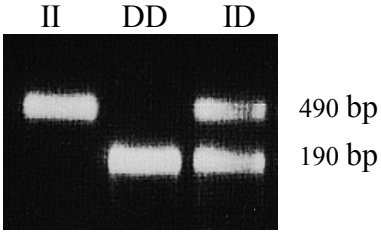
5′ CTG GAG ACC ACT CCC ATC CTT TCT 3′

Anti-sense primer:

5′ GAT GTG GCC ATC ACA TTC GTC AGA T3′

The PCR reaction contained 100 ng DNA template, 0.125 μmol/L of each primer, 1 unit of Taq DNA polymerase, 200 μmol/L 4dNTPs, 3 mmol/L $MgCl_2$ and 5% of dimethylsulphoxide (DMSO). DMSO was added to enhance amplification of the I allele (83). DNA was amplified for 30 cycles, each cycle composed of denaturation at 94°C for 1 minute, annealing at 58°C for 1 minute and extension at 72°C for 1 minute with a final extension time of 3 minutes.

Figure 7.



Polymerase chain reaction. ACE D/I genotyping on 2% agarose gel stained with ethidium bromide. The first lane shows a single 490-bp band, indicating homozygosity for allele I (II genotype). The second lane shows the presence of a 190-bp band, indicating homozygosity for allele D (DD genotype). The last lane shows a 490-bp and 190-bp product, indicating heterozygosity for ACE alleles (ID genotype).

After the samples had been separated by electrophoresis on a 2 % agarose gel and stained with ethidium bromide (0.5 mg/ml), genotyping was undertaken in a blinded manner (Figure 7).

Data collection and clinical follow-up

Patients with the Biocor stentless valves were followed in a prospective study with an annual clinical examination. In a few cases, patients were not able to come a specific year for the annual investigation; however, most of them were then able to come at the next scheduled visit. Patients not able to attend were contacted by phone to answer questions regarding clinical status and clinical events that had occurred since last visit. Patients with the Toronto-SPV were also followed in a prospective study with annual clinical examinations in a similar fashion and were also contacted by phone if not able to attend. At annual follow-ups we enquired about or investigated the following: symptoms of heart failure such as dyspnea on exertion and leg edemas, thromboembolic episodes such as stroke, transient ischemic attack (TIA), myocardial infarction and peripheral emboli; infections, especially endocarditis; and episodes of hospitalization after previous outpatient visit. Patients underwent clinical examination including blood pressure measurement and an auscultation of the heart and the chest. The clinical information available constituted the basis of

how patients were assessed according to the NYHA classification.

The follow-up was 100% complete for both patient cohorts and covered 1659 patient years (V and VI). Autopsies were performed in 36% (19/51) of deaths in the BS valve group.

Censoring

The end-points reported in the clinical studies are death, reoperation or completed follow-up. Patients undergoing reoperation in paper V and VI were withdrawn alive from the analysis at the date of reoperation if they survived 30 days after the valve reoperation. In all, 5 patients (1%) were withdrawn alive according to these criteria. All patients undergoing reoperation survived uneventfully.

Definitions

Definitions were applied according to the "Guidelines for reporting morbidity and mortality after cardiac valvular operations" (61) and were as follows:

Early or operative mortality: Death within 30 days of operation, or death within any time interval after operation if the patient was not discharged from the hospital. Hospital to hospital transfer was not considered discharge; transfer to a nursing home or rehabilitation unit was considered hospital discharge unless the patient subsequently died of complications related to the operation.

Valve-related mortality: Death caused by structural valvular deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, valvular endocarditis, or death related to reoperation of an operated valve. Sudden, unexplained, unexpected deaths of patients with an operated valve are included as valve-related mortality. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not included. Patients that died of myocardial infarction were classified as valvular deaths when they had a normal preoperative coronary angiogram. Specific causes of valve-related deaths were reported.

Cardiac death: All deaths resulting from cardiac causes. This category includes valve-related deaths (including sudden unexplained deaths) and non-valve-related cardiac deaths (e.g., congestive heart failure, acute myocardial infarction, documented fatal arrhythmias).

Total deaths: All deaths resulting from any cause after a valve operation.

Reoperation: Any operation that repairs, alters, or replaces a previously operated valve. The reasons for reoperation were reported.

Structural valvular deterioration (SVD): SVD includes operated valve dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy, or clinical investigation.

Thromboembolism: Any embolic event that occurs in the absence of infection after the immediate perioperative period. A neurologic event includes any new, temporary or permanent, focal or global neurologic deficit. A TIA is a fully reversible neurologic event that lasts less than 24 hours. A reversible ischemic neurologic deficit is a fully reversible neurologic deficit that lasts more than 24 hours and less than 3 weeks. A stroke or permanent neurologic event lasts more than 3 weeks or causes death.

Bleeding event: Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion.

Valvular endocarditis: Any infection involving an operated valve. The diagnosis of valvular endocarditis is based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs, and histologic confirmation of endocarditis at reoperation or autopsy.

NYHA functional classification: New York Heart Association (NYHA) developed a classification for patients with heart disease based on the relation between clinical symptoms and the amount of effort required to provoke these symptoms (84).

- Class I – No limitations. Ordinary physical activity does not cause fatigue, dyspnea or palpitation.

- Class II – Slight limitation of physical activity. Ordinary physical activity results in fatigue, dyspnea or angina.

- Class III – Marked limitations of physical activity though patients are comfortable at rest.

- Class IV- Inability to carry out any physical activity without discomfort, and patients have symptoms of heart failure even at rest.

Statistics

Continuous data are presented as mean ± SD. For statistical evaluation ordinary or repeated measures of analysis of variance (ANOVA) were used. Two-way ANOVA was used to test the influence of clinical parameters and time on hemodynamic outcome (I, IV). When the F-test revealed a significant difference, each pair of means was compared with Scheffe´s test (85). The null hypothesis was rejected when a p value was < 0.05 and consequently considered statistically significant.

Regression analysis (V, VI)

Univariate and multivariate stepwise linear regression was undertaken to identify predictors of hemodynamic outcome (I, III-IV). Multivariable regression analysis performed according to Cox proportional hazard model (backwards selection) was used to analyze risk factors for late death (VI) (86). The multivariable analyses were performed in SAS (version 8.0, SAS Institute, Inc., Cary, NC).

Life table analysis and Kaplan-Meier (IV-VI)

Life table technique and Kaplan-Meier curves were used to provide actuarial estimates of observed survival and time related events (87). The log rank test was used to test significance of differences between independent groups.

Linearized incidence (II, VI)

The linearized incidence was used to report the incidence of thromboembolic events since only the first event for each patient can be considered in the Kaplan-Meier actuarial method. The linearized incidence more accurately illustrates thromboembolic complication rates since multiple events frequently occur in the same patient. The linearized incidence was calculated as the number of events (n) divided by the total number of patient years available in the group of patients under study (n / Σ yr.). The standard error, based on the Poisson distribution, was calculated as $\sqrt{n} / \Sigma$ yr. (88, 89).

Expected survival (VI)

The expected survival was calculated in collaboration with Statistics Sweden (the Swedish population bureau) in an “exact” way from Swedish life tables with a specially designed software program (90, 91). An assigned comparison group, consisting of all Swedish inhabitants of the same sex and age who were alive at the time (same

month) of operation, was individually constructed for each patient with the BS bioprosthesis. All the individually based expected survival curves were then used to construct a composite survival curve and subsequently compared to the survival curve of the patients. The expected survival is based on calculations from the entire Swedish population and therefore errors of sampling do not apply and no standard errors are provided.

Relative survival rate (VI)

Relative survival rates have previously been used for describing long-term survival after heart valve replacement (91). Briefly, the relative survival rate corrects the observed survival of the patient group in relation to that of a comparison group from the general population, matched for age, sex and month of operation (91, 92). We have calculated the relative survival rates only taking yearly intervals into consideration with an annual adjustment of life tables, which start at the time of operation. A normalized survival pattern for the study group is represented by a constant relative survival from that time on. Therefore, the fraction of surviving patients has only the normal risk of dying and could be considered "cured" from a statistical point of view. When the annual relative survival rate stabilizes around 1.0 the fraction of surviving patients will represent the "cured" fraction. In contrast, an increased risk of death in the study group would be represented by a continuously decreasing relative annual survival rate.

Methodological considerations

Clinical studies

Clinical studies were performed in a prospective manner in order to properly monitor valve related complications. Considering that follow-up for both stentless valves under study also were 100% there is a little likelihood that we have missed any of these events. However, the incidence of complications that neither caused death nor reoperation or hospitalization can to some extent be underreported if patients do not remember those events when asked for. Furthermore, none of these studies were designed for a comparison between the studied valves.

Selection of measurements and methods of calculation

Two physicians assessed all Doppler echocardiographic recordings and M-mode registrations at the Karolinska Hospital. At the Toronto General Hospital, one physician

performed the corresponding assessments. M-mode registrations and off-line measurements were guided by the two-dimensional image to avoid incorrect measurements. Two different equations normally used at the two different echocardiographic laboratories were used to calculate the LVM, which makes comparisons inappropriate between studies. However, both equations have been found to be valid methods for calculation of LVM, although with different reference intervals (78). However, the anatomically corrected modified formula is now regarded as the more appropriate, since it correlates more accurately with necropsy and echocardiographic findings without the tendency to overestimate LVM, which is the case with the original cube function formula. Both formulas were at the time when they were used, regarded as the preferred method by the respective laboratories.

Inter- and intra-variability data

The variability of Doppler-derived measures is expressed with coefficient of variation (CV) for duplicate measurements. The standard error (s) of a single determination was estimated from duplicate measurements and calculated as: $s = SD_{diff} / \sqrt{2}$ (93). CV, which describes variation as a percentage of the pooled mean values (x), was calculated according to the formula $CV\ (\%) = (s/x) \times 100$. When the same operator measured flow velocities twice from the same video recording, CV was 2-2.5% for velocities at rest. The intra-observer measurement variability at rest expressed as CV for the calculated parameters ΔP_{max}, stroke volume and EOA was 3.9%, 5.3% and 5.3%, respectively. The CV for measurement variability of LVOT diameter was 2.0%. The intra-observer measurement variability of Doppler and M-mode data, including wall thickness, LVEDD and LVM, for our laboratory is shown in Table 3. The coefficient of variation for inter-observer variability was 2.0% for aortic velocity measurements at rest and 2.0% for measurements during exercise. Inter-observer measurement variability for the diameter of the left ventricular outflow tract at rest was 3.9%

Temporal variability, defined as the variability between two Doppler echocardiographic examinations of the same patient, was described in 26 patients at rest with unchanged ejection fraction and non-progressive AR (Table 4). The mean time interval between the two tests was 7.2 ± 1.9 months. The first examination was performed at 6.5 ± 1.5 months postoperatively.

Table 3. Intra-observer measurement variability for Doppler- and M-mode data

Variable	Coefficient of variation (CV) %
VTI_{AO}	3.6%
VTI_{LVOT}	2.2%
IVS	9.7%
PWT	13.8%
LVEDD	4.8%
LVM	13.9%
LVMI	13.8%

Table 4. Temporal variability of measurements for Doppler-data and calculations

Variable	Mean of absolute difference	Coefficient of variation (CV) %
V_{AO} (m/s)	0.16	8.2%
V_{LVOT} (m/s)	0.08	8.0%
VTI_{AO} (cm)	4.7	12.2%
VTI_{LVOT} (cm)	1.8	7.8%
△Pmax (mm Hg)	2.4	16.0%
△Pmean (mm Hg)	1.0	14.1%
EOA (cm^2)	0.24	10.2%

Results

Early clinical results (II, V-VI)

Surgical considerations

The EBS bioprosthesis allowed functional widening of the aortic annulus. The subvalvular extension was used for this purpose in 15% of the patients. It is worth noting, that surgeon's conception of the need of widening of the aortic annulus changed over time. Towards the end of the study patients rarely received a functional widening of the aortic annulus with the subvalvular extension (9/47 vs. 3/46 in the first and second halves of the EBS population, respectively). However, the supravalvular extension was used frequently throughout the study (in 86% of the patients who received an EBS prosthesis), facilitating aortic closure in patients with severe calcifications of the ascending aorta. Furthermore, implanted valves were on average somewhat larger than measured aortic annulus, which implies a limited oversizing. The T-SPV valve requires accurate sizing of the aortic annulus and the sinotubular junction to prevent development of early AR postoperatively.

Early mortality and morbidity (I, V-VI)

There were 8 (7%) and 2 (0.8%) early deaths in the BS and the T-SPV valve groups, respectively. As is clear from Table 1, these two patient series are very different in terms of characteristics such as age, gender and aortic valve pathology. Causes of early morbidity and total deaths are listed in Table 5.

Early follow-up (II)

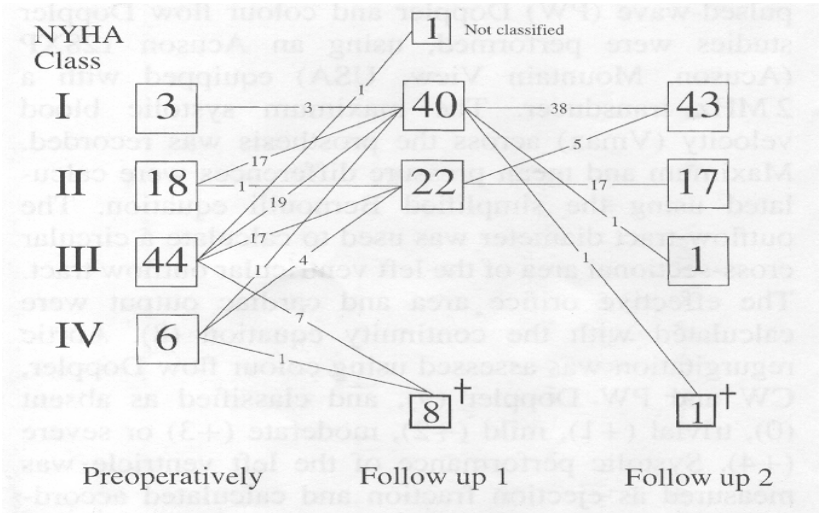
Early follow-up of the EBS valve was 100% complete at a mean follow-up of 15 months. 60/61 patients were in NYHA class I or II at follow-up (Figure 8). While there were four late deaths none was valve-related. In this small group of patients mortality seemed to be higher among patients with preoperative NYHA class III and IV and in patients that underwent combined AVR and CABG. Linearized incidence of thromboembolism was 5.2% / patient year (5.2 ± 2.6 events / 100 patient years) in these elderly patients. In addition, two pacemaker implantations due to heart block had occurred during the follow-up period

Table 5. Early morbidity and mortality and late mortality

	Biocor		Toronto SPV	
	No.	(%)	No.	(%)
Early morbidity				
Reexploration for bleeding	7	(6)	5	(2.0)
Reexploration for cardiac arrest			1	(0.4)
Perioperative myocardial infarction	2	(2)	5	(2.0)
Perioperative stroke or TIA	9	(8)	3	(1.2)
Mediastinitis	4	(3)	2	(0.8)
Permanent pacemaker implantation	10	(9)	13	(4.7)
Early mortality	8	(7)	2	(0.8)
Valve related				
Stroke	1			
Endocarditis			1	
Cardiac related				
Low cardiac output syndrome	4			
Expired post MVR	1			
Myocardial infarction			1	
Noncardiac				
Pneumonia	1			
Multiorgan failure	1			
Late mortality	43	(38)	21	(8)
Valve related				
Stroke	2		1	
Myocardial infarction *	2			
Cardiac related				
Congestive heart failure	13		2	
Myocardial infarction #	7		1	
Noncardiac	18		12	
Unknown	1		3	
Total No. (early and late) of deaths	**51**	**(46)**	**23**	**(9)**

TIA = transient ischemic attack. MVR = mitral valve replacement. * Patients with normal preoperative coronary angiogram who died of myocardial infarction were classified as valvular deaths. # Patients with coronary artery disease on preoperative coronary angiogram who died of myocardial infarction were classified as cardiac deaths.

Figure 8.



NYHA functional classification in EBS operated patients during a mean follow-up of 15 months.

Early hemodynamic results (I-II)

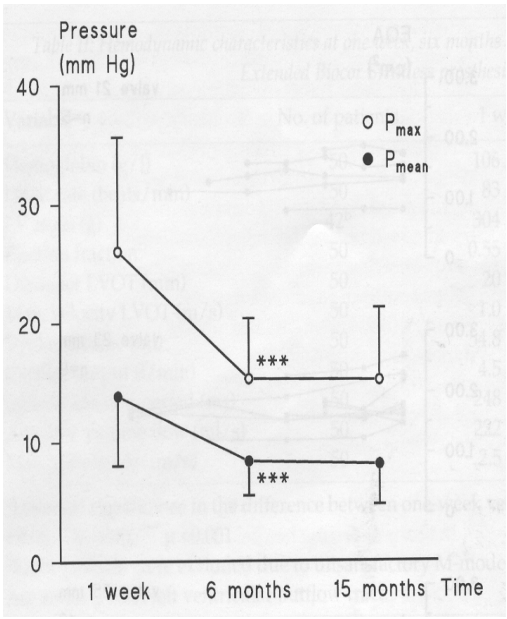
Rest studies (I-II)

Transvalvular peak (ΔP_{max}) and mean (ΔP_{mean}) pressure differences decreased significantly and on average by 40%, during the first six months following surgery ($p < 0.001$). No further significant changes were demonstrated between the six-month and 15-month visits (Figure 9). All valve sizes demonstrated a similar degree of pressure decrease. There was a significant increase in EOA for the whole group, from 1.3 ± 0.3 cm^2 at one week postoperatively to 1.6 ± 0.3 cm^2 at the six-month examination ($p < 0.05$). ΔP_{max} and ΔP_{mean} across the prostheses seemed to be inversely related to valve size but no statistically significant differences between the groups were achieved, possibly due to the small number of patients for each valve size. EOA was significantly larger in 23 and 25-mm valves than in the smaller valve sizes. Doppler-derived pressure differences, effective orifice areas and cardiac index according to valve size for 60 patients at a mean follow-up of 15 months are summarized in Table 6. Stroke volume increased significantly during the same time interval from 54.8 ± 12.5 ml to 61.9 ± 13.7 ml without any further changes ($p < 0.001$).

To examine the relationship between the decrease in ΔP_{max} and other variables, a stepwise multiple regression was used. Changes in hemoglobin, ejection fraction, LVM and aortic valve volume flow were entered into the model. The decrease in ΔP_{max} correlated only with the decrease in aortic valve volume flow ($r = 0.34$, $p < 0.05$).

Trivial AR was detected in one patient one week after surgery, in three patients at first follow-up and in six at second follow-up. No patient had AR greater than grade 1+ on any occasion.

Figure 9.



Doppler-derived ΔP_{max} and ΔP_{mean} with the EBS bioprosthesis. ΔP_{max} and ΔP_{mean} values at discharge were significantly different from these at 6 months, without any further change up to 15 months of follow-up.
*** = $p < 0.001$.

Table 6. Doppler echocardiographic results according to valve size of the EBS bioprosthesis at 15 months of follow-up

Valve size	No. of patients	ΔP_{max} (mm Hg)	ΔP_{mean} (mm Hg)	EOA (cm^2)	CI ($L\ min^{-1}\ m^{-2}$)
19 mm	1	16.2	8.1	1.6	3.0
21 mm	14	18.2 ± 7.4	9.9 ± 4.0	1.4 ± 0.4	2.5 ± 0.6
23 mm	22	14.7 ± 6.7	7.7 ± 3.5	1.7 ± 0.4[a]	2.5 ± 0.5
25 mm	23	13.5 ± 4.6	7.0 ± 2.6	1.8 ± 0.4[b]	2.4 ± 0.4

All values are expressed as mean ± SD. ΔP_{max} = maximum pressure difference, ΔP_{mean} = mean pressure difference, EOA = effective orifice area, CI = cardiac index.
[a] $p < 0.05$ size 23 versus size 21 mm and [b] $p < 0.05$ size 25 versus size 21 mm

Exercise studies (I)

The achieved workload during the symptom-limited supine exercise test ranged from 30 to 100 Watts (median 60 Watts) in 26 patients with technically adequate Doppler echocardiogram at a mean follow-up of 15 months. The workload achieved corresponded to approximately 60% of age-related reference values for exercise capacity during sitting bicycle test (94). There was no significant difference in workload between different patients grouped by valve size. In 11 patients, exercise capacity was limited by fatigue, in 11 by leg discomfort and in four by shortness of breath. None of the patients stopped due to chest pain.

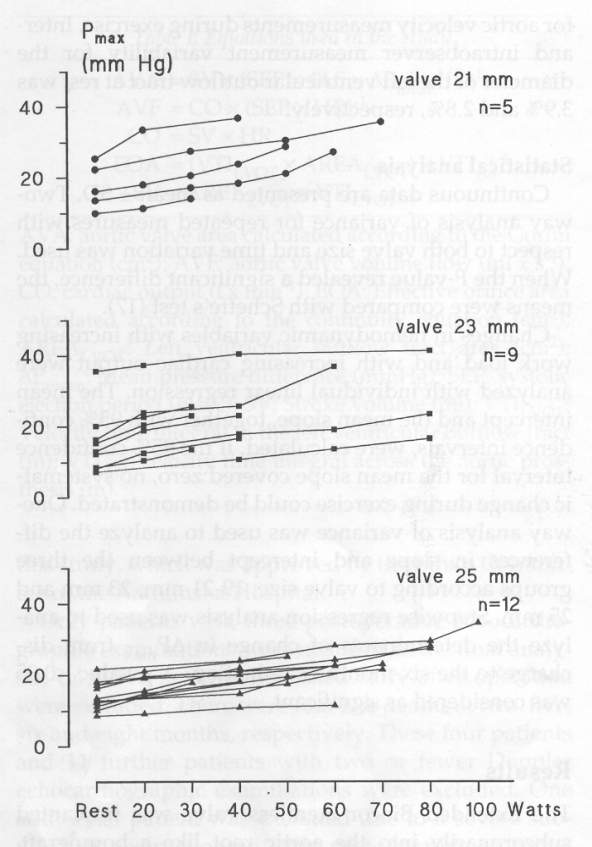
Heart rate and systolic arterial blood pressure increased with exercise from 67 ± 9 to 108 ± 30 beats/min ($p < 0.001$) and from 143 ± 24 to 188 ± 30 mm Hg ($p < 0.001$), respectively. Cardiac output increased from 4.6 ± 0.9 to 7.6 ± 1.2 l/min ($p < 0.001$). However, stroke volume remained unchanged (68.7 ± 11.7 vs. 71.6 ± 14.7, p = ns) by exercise and, therefore, the increase in cardiac output was mainly due to an increased heart rate. The ΔP_{max} and ΔP_{mean} calculated with the short form of the modified Bernoulli equation increased during exercise from on average 15.2 ± 6.2 to 24.4 ± 7.7 mm Hg and from 8.1 ± 3.2 to 11.9 ± 3.6 mm Hg, respectively (Figure 10). For comparison, the ΔP_{max} and ΔP_{mean} were also calculated with the long form of the modified Bernoulli equation and numbers then increased from 11.9 ± 5.9 to 19.9 ± 7.3 mm Hg and from 6.2 ± 3.1 to 9.3 ± 3.4 mm Hg, respectively. All groups of patients with different valve sizes showed a similar response to exercise regarding transvalvular pressure differences calculated with both equations. Regression analysis revealed a significant increase in

ΔP_{max} and ΔP_{mean} with increasing workload and cardiac output in all individuals.

EOA did not change during exercise in any of the valve size groups (Figure 11). The valve areas calculated with the Gorlin equation (AVA) were approximately 4% larger than those calculated by the continuity equation (EOA) (mean difference 0.07 ± 0.09 cm^2, $p < 0.001$), both at rest and at different levels of exercise. There was no significant change in AVA with moderately increased cardiac output or workload during exercise.

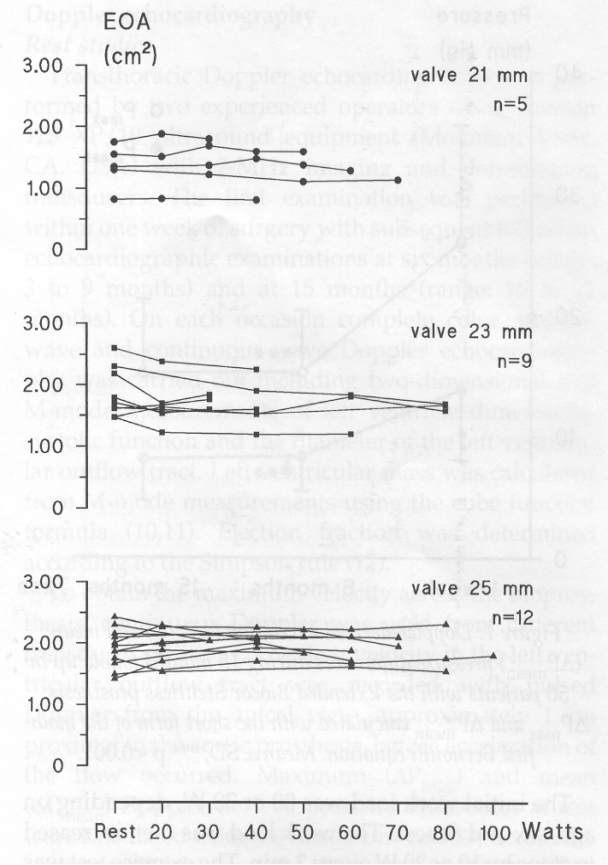
AR grade 1 was seen in 1/50 (2%) of patients postoperatively before discharge and in 6 patients (12%) at follow-up at 15 months.

Figure 10.



Doppler-derived ΔP_{max} during supine exercise as a function of workload in 26 patients with the EBS bioprosthesis.

Figure 11.



EOA during supine exercise as a function of workload in 26 patients with the EBS bioprosthesis.

Late hemodynamic valve function (IV-VI)

Ejection fraction was well preserved postoperatively, indicating a satisfactory intraoperative myocardial protection. There were no signs by echocardiography of dilatation of the superior pericardial extension used for patch closure of the aortotomy in patients with the EBS valve.

Transvalvular pressure differences

Peak and mean systolic gradients across the aortic valve were for both the BS and the T-SPV valves significantly decreased at one year compared to at discharge. There was no further significant change over time in these hemodynamic parameters (Table 7). Doppler-derived data at seven years showed peak and mean pressure differences across the aortic valve to be: 11.0 ± 3.4 mm Hg and 5.4 ± 2.0 mm Hg for the BS valve; 9.6 ± 5.1 mm Hg and 3.6 ± 2.0 mm Hg for the T-SPV valve. The pressure differences of these two valves are very similar despite the fact that the pressure differences for the BS valves were calculated with the short form of the modified Bernoulli equation and the T-SPV valves with the long form of the equation. ANOVA revealed that peak and mean pressure differences of the T-SPV were significantly higher in smaller valve sizes compared to larger valve sizes during follow-up (Table 8). These findings correlate well to what we have shown for the EBS valve at early follow-up. A multivariate stepwise linear regression for peak and mean pressure differences showed significantly lower mean gradients with increased valve size ($p = 0.001$), lower pressure differences for female sex ($p = 0.001$) and increased pressure differences for preoperative atrial fibrillation ($p = 0.001$) (model RR 0.124, $p = 0.002$).

Effective orifice area

The EOA of the T-SPV valve had increased significantly during the follow-up period. ANOVA showed significantly larger EOA in larger valves, which also was consistent throughout the follow-up period (Table 8). EOA with the BS valve had increased significantly between discharge and one year and remained unchanged up to nine years of follow-up. Aortic valve cusps appeared thin and pliable in all cases without apparent signs of increasing obstruction or calcification.

Table 7. Echocardiographic data at long-term follow-up

	Biocor		T-SPV	
ΔP_{max} (mm Hg)				
Discharge	25.9±10.9	(n=98)	12±5.5	(n=173)
1 year	15.6±6.7	(n=83)	7.5±4.8	(n=166)
5 years	17.1±8.2	(n=35)	8.5±6.8	(n=86)
7 years	10.7±3.4	(n=14)	9.6±5.1	(n=12)
ΔP_{mean} (mm Hg)				
Discharge	13.7±6.4	(n=98)	5.4±2.8	(n=173)
1 year	8.2±3.8	(n=83)	4.0±2.4	(n=166)
5 years	8.1±4.1	(n=35)	4.1±3.3	(n=86)
7 years	5.2 ±2.0	(n=14)	3.6±2.0	(n=12)
Effective orifice area (cm^2)				
Discharge	1.4±0.4	(n=98)	2.0±0.5	(n=173)
1 year	1.7±0.4	(n=83)	2.1±0.6	(n=166)
5 years	1.6±0.6	(n=35)	2.3±0.7	(n=86)
7 years	1.6±0.4	(n=14)	2.3±0.4	(n=12)
Cardiac output (l/min)				
Discharge	4.5±1.1	(n=98)	4.9±1.4	(n=173)
1 year	4.3±0.8	(n=83)	4.6±1.0	(n=166)
5 years	4.2±1.5	(n=35)	5.3±1.3	(n=86)
7 years	3.5±0.9	(n=14)	5.6±1.2	(n=12)

ΔP_{max} = maximum pressure difference, ΔP_{mean} = mean pressure difference.

Aortic valve regurgitation

When they were discharged from hospital, all but a few patients with stentless bioprostheses, both the BS and the T-SPV, had competent valves, and the exceptions had only grade 1 insufficiency (BS: 1 patient and T-SPV: 12 patients). In a few patients AR progressed and in the rare case necessitated a reoperation (BS: 2 patients and T-SPV: 2 patients).

At five years the majority of patients had competent valves without significant AR (none or trivial) in 74% (23/35) of the BS valves and in 92% (79/86) of the T-SPV valves. Mild AR (grade 2) was found in another 20% (7/35) of the BS valves and in 8% (7/86) of the T-SPV. No patient with the T-SPV had more than AR grade 2 at five years. However, 2 patients with BS valves had at five years developed significant AR, 1 patient had grade 3 and the other one had grade 4 AR. The latter patient was subsequently reoperated and given a new valve and the other one is being managed medically. The other three patients reoperated for AR, due to structural valve degeneration, developed significant AR abruptly between two sched-

uled follow-ups and were not registered as severe AR in the annual charts. AR in the two BS valve patients that were reoperated was caused by commissural tears and was regarded as structural valve degeneration. AR in the T-SPV patients that were reoperated was related to dilatation of the sinotubular junction but the valve was also found to have cusp tears on reoperation and was classified as structural valve dysfunction. At 7 to 9 years of follow-up there seem to be relatively more patients with trivial to mild AR than earlier during follow-up. This might be an early sign of degeneration but the small number of patients reaching this length of follow-up could also hamper interpretation of the results.

Table 8. Hemodynamic data by valve size for the Toronto SPV

Variable	Whole group	Valve size (mm) 22-23 (n=7)	25 (n=28)	27 (n=37)	29 (n=37)	ANOVA p-value
BSA (m^2)	1.87±0.20	1.78±0.17	1.76±0.22	1.90±0.18	1.96±0.15	
ΔP_{max} (mm Hg)						
Postop (n=109)	12.3±5.6	14.5±6.6	15.0±6.5	12.2±4.6	10.0±4.8	Size: 0.0001
1 Year (n= 104)	7.2±4.8	9.2±3.6	9.9±6.5	6.6±3.7	5.1±2.9	Time: 0.0001
5 Years (n=86)	8.6±6.8	12.2±5.6	11.1±9.1	9.2±6.8	5.4±3.5	Size/time: 0.557
ΔP_{mean} (mm Hg)						
Postop (n=109)	5.5±3.1	4.8±3.4	6.2±3.4	6.0±3.0	4.6±2.3	Size: 0.0090
1 Year (n=104)	3.9±2.4	4.3±2.4	5.2±3.4	3.4±1.8	3.1±1.6	Time: 0.0015
5 Years (n=86)	4.1±3.3	6.3±2.7	5.3±4.8	4.4±3.0	2.6±1.7	Size/time: 0.048
EOA (cm^2)						
Postop (n=109)	2.0±0.5	1.8±0.4	1.7±0.5	2.0±0.4	2.2±0.5	Size: 0.0001
1 Year (n=104)	2.2±0.6	2.0±1.0	1.8±0.4	2.3±0.4	2.5±0.6	Time: 0.0156
5 Years (n=86)	2.3±0.7	1.6±0.4	1.9±0.3	2.2±0.4	2.8±0.8	Size/time: 0.019
CI ($l/min/m^2$)						
Postop (n=109)	2.7±0.8	2.5±0.8	2.8±1.0	2.7±0.6	2.6±0.7	Size: 0.3431
1 Year (n=104)	2.5±0.6	2.2±0.5	2.5±0.5	2.6±0.7	2.4±0.5	Time: 0.0095
5 Years (n=86)	2.8±0.7	2.4±0.3	2.9±0.8	2.8±0.6	3.0±0.8	Size/time: 0.828
LVMI (g/m^2)						
Postop (n=109)	130±41	113±29	123±32	123±41	143±45	Size: 0.0001
1 Year (n=104)	104±31	99±30	98±26	101±29	114±26	Time: 0.0001
5 Years (n=86)	97±24	69±12	95±28	98±21	103±25	Size/time: 0.051

BSA – body surface area, ΔP_{max} and ΔP_{mean} – transvalvular peak and mean pressure differences, EOA – effective orifice area, CI – cardiac index, LVMI - left ventricular mass index, Postop - postoperatively. Data expressed as mean ± SD. P values indicate statistically differences for valve size, time and valve size/time as tested by two-way ANOVA.

Left ventricular hypertrophy (I, III-IV)

Relation between aortic valve disease and LVH (III-IV)

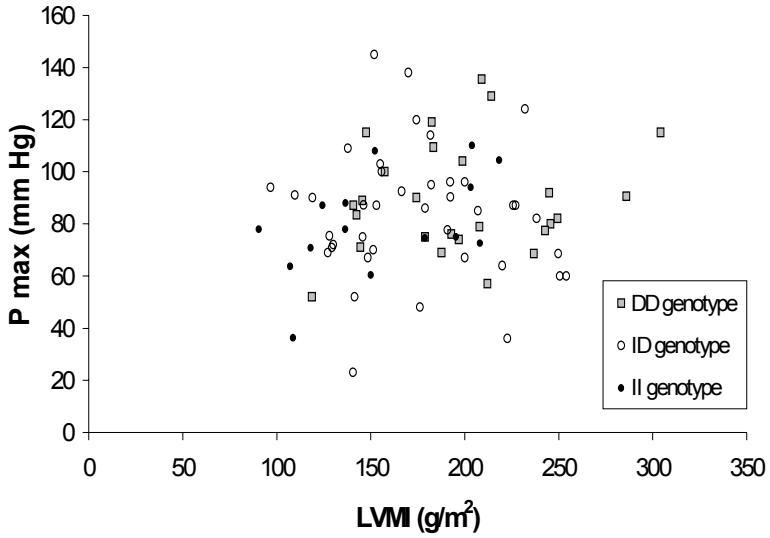
Preoperatively, 80% with symptomatic AS had LVH whereas 49% of patients operated with the T-SPV valve were found to have LVH early postoperatively. Correspondingly, 20% of patients with symptomatic AS did not have LVH preoperatively, while a majority of patients receiving the T-SPV valve did not have LVH early postoperatively. Unfortunately the T-SPV patients did not have preoperative echocardiograms performed that enabled calculation of the left ventricular mass. There was no apparent hemodynamic correlation found between preoperative degree of AS, measured as transvalvular pressure difference, and preoperative LVMI ($r = 0.12$, $p = 0.29$) (Figure 12). Clearly – and this was seen in both the BS and the T-SPV patient cohorts - many patients undergoing AVR had LVH, but apparently in an inconsistent pattern not related to pressure differences across the aortic valve.

ACE gene polymorphism and LVH in symptomatic AS (III)

The genotype frequency of the ACE gene was 32% (26/82) for the DD, 50% (41/82) for the ID and 18% (15/82) for the II genotype among patients operated for symptomatic AS. The frequencies of the I and D alleles in our study, only including Caucasians, were 43% and 57%, respectively. There was no significant difference in age, gender, body surface area or preoperative hypertension between the patients with different genotypes. Maximum and mean pressure differences across the aortic valve and left ventricular measurements, as determined by echocardiography, are given in Table 9. ANOVA revealed no significant difference in maximum and mean pressure differences, ejection fraction, E/A quotient or left ventricular dimensions between DD, ID, and II genotypes preoperatively.

Preoperatively, the DD genotype had a significantly larger left ventricular mass ($p = 0.02$) and a higher LVMI than the other genotypes ($p = 0.01$). The preoperative LVMI and maximum pressure difference across the aortic valve were not related as determined by a linear regression analysis ($r = 0.12$, $p = 0.29$) (Figure 12) and did not

Figure 12.



Relation between preoperative left ventricular mass index (LVMI) and maximum pressure difference (P_{max}) across the aortic valve. LVMI and P_{max} were not related as determined by linear regression analysis (r = 0.12, P = 0.29).

significantly improve after genotype stratification. Maximum pressure difference, gender and ACE genotype were analyzed together in a multiple regression analysis versus preoperative LVMI. The LVMI showed significant correlation in a multiple regression analysis (multiple r = 0.46, r^2 = 0.21, p = 0.0014) with gender (p = 0.004) and DD genotype (p = 0.009).

Regression of LVH with stentless bioprostheses (I and IV)

Regression of LVM occurred in a consistent manner in patients operated with both valves investigated. At follow-up of the BS valve, analysis showed that a significant decrease in LVM occurred between discharge (304 ± 100 g) and 6 months (259 ± 72 g) (p < 0.01), followed by a gradual but not significant further decrease up to 15 months (244 ± 80 g).

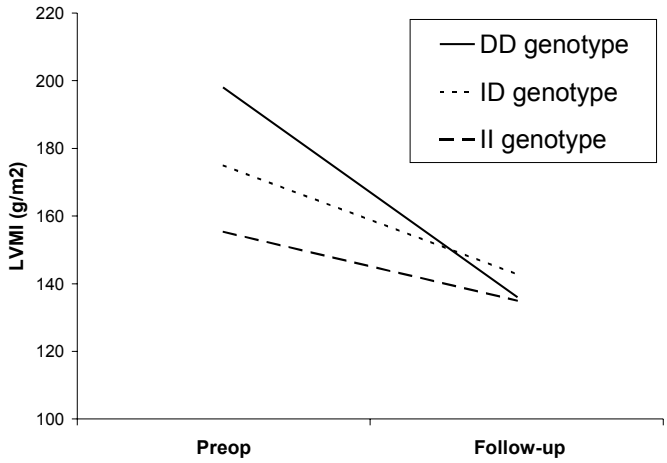
At five years of follow-up with the T-SPV valve, the wall thickness was normalized in both the PWT (10.0 ± 1.4 mm) and in the IVS (11.0 ± 1.4 mm). IVS, PWT and LVEDD measurements had all decreased significantly over time (p < 0.01). At 5 years, ANOVA revealed that the IVS had decreased more in smaller valve sizes (p = 0.04). There was no significant difference in the decrease over time in the PWT, when stratified for valve size. LVMI de-

creased significantly between discharge (130 ± 41 g/m^2) and one year (104 ± 31 g/m^2) ($p < 0.001$) and between one and three years (94 ± 22 g/m^2) ($p < 0.001$), without any further significant change between three and five years (97 ± 24 g/m^2) ($p = 0.12$). ANOVA revealed that the relative decrease in LVMI at five years was significantly larger in patients with a small valve size ($p = 0.04$). At five years, LVH was only present in 9% (2/22) of the women and 8 % (5/62) of the men.

ACE-gene polymorphism and its influence on LVH postoperatively (III)

At follow up, the LVMI had decreased significantly in DD and ID genotypes ($p < 0.001$) compared to preoperative values and, interestingly, no differences between genotypes were seen any longer in patients operated for severe AS (Figure 13, Table 9). The absolute difference in LVMI was significantly larger in the DD genotype compared to the ID or II genotypes. The decrease in the LVMI in the different genotype groups was 31% (DD), 19% (ID) and 13% (II), respectively. There was a difference ($p = 0.0056$) in regression of LVMI over time between genotypes (Figure 13). In the studied population as a whole, the decrease in the LVMI was 22% (from 179 ± 45 to 139 ± 34 g/m^2) ($p < 0.001$). There were no significant differences in postoperative transvalvular pressure difference or in the relative decrease of LVMI between used valve types. The left ventricular dimension decreased ($p = 0.05$) during follow-up only

Figure 13.



Mean values of LVMI preoperatively and at follow-up according to genotype (DD, ID and II). There was a significant difference over time between genotypes (ANOVA, $p = 0.0056$).

in the DD genotype and, 1 year postoperatively, the left ventricular dimension was similar in all 3 genotypes. Although tendencies were observed, there were no significant differences preoperatively between the genotypes regarding IVS or PWT. One year postoperatively there was a decrease in both septal and posterior wall thickness in the DD (IVS -22%, $p < 0.001$; PWT -9%, $p < 0.001$), ID (IVS -14%, $p < 0.001$; PWT -11%, $p < 0.01$) and II (IVS -12%, $p < 0.05$; PWT -12%, $p < 0.05$) genotypes. At follow-up, there were no differences between genotypes regarding interventricular septum or left ventricular posterior wall thickness, as shown in Table 9.

Clinical factors influencing the regression of LVH postoperatively (IV)

T-SPV patients with hypertension had no difference in LVMI at discharge or after 6 months follow-up compared to patients without hypertension. However, patients with hypertension had a higher LVMI after one year (116 ± 34 versus 99 ± 28 g/m^2, $p = 0.01$) and five years than patients without hypertension (106 ± 27 versus 93 ± 23 g/m^2, $p = 0.02$). Two-way ANOVA showed a higher LVMI over time in patients with hypertension than those without ($p = 0.01$).

There was no difference in LVMI between men and women at the time of discharge (130 ± 40 versus 127 ± 45 g/m^2, $p = 0.70$). A significant difference was observed in LVMI between males and females at three years (99 ± 21 versus 83 ± 21 g/m^2, $p = 0.01$) but this was no longer observed at five years (100 ± 23 versus 89 ± 27 g/m^2, $p = 0.06$). Two-way ANOVA showed no difference in LVMI over time between men and women ($p = 0.28$).

T-SPV patients with concomitant coronary artery disease (CAD) had increased LVMI compared to those without at discharge (140 ± 42 versus 124 ± 39 g/m^2, $p = 0.05$) and at one (113 ± 32 versus 99 ± 29 g/m^2, $p = 0.02$) year follow-up. Thereafter, this effect was abolished and at five years no difference between those with and without CAD was seen any longer (Figure 14). Two-way ANOVA showed a higher LVMI over time in patients with CAD compared to those without ($p = 0.02$).

ANOVA showed that preoperative AR was associated with a larger LVEDD at discharge, and therefore also an increased LVMI, than in patients with AS. Interestingly, there was no longer any difference between patients who were operated on for

AS and AI at five years, with both groups having a normal LVMI and LVEDD.

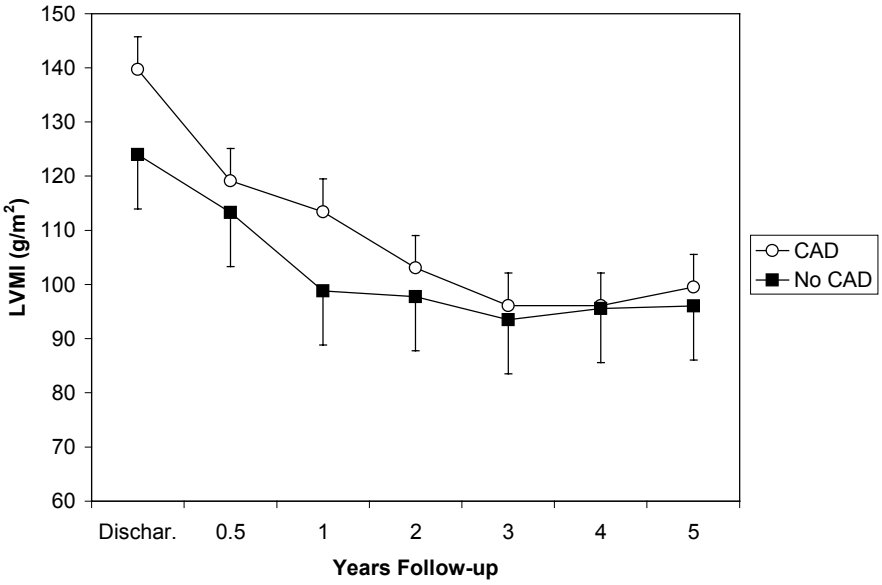
A multivariate stepwise linear regression showed significantly decreased LVMI over time, higher LVMI with larger valve sizes, higher LVMI in patients with CAD and higher LVMI in patients with hypertension (p = 0.01) (model RR 0.178, p = 0.01). Preoperative aortic valve lesion had no effect on LVMI in this model. Gender came out as a significant predictor of LVM in a similar stepwise linear regression analysis but failed to be a predictor of LVM when indexed for body mass.

Table 9. Clinical and echocardiographic data before and after AVR according to genotype.

		ACE Genotype			
		DD (n=26)	**ID** (n=41)	**II** (n=15)	P-value
Gender	(Male/Female)	15/11	20/21	7/8	NS
Age	(Years)	76 ± 5	76 ± 5	72 ± 11	NS
ΔP_{max} (mm Hg)					
	preoperatively	89 ± 22	84 ± 26	80 ± 20	NS
	postoperatively	15 ± 6***	13 ± 5***	13 ± 5***	NS
ΔP_{mean} (mm Hg)					
	preoperatively	56 ± 16	53 ± 17	51 ± 15	NS
	postoperatively	8 ± 3***	7 ± 3***	6 ± 3***	NS
Left ventricular mass (g)					
	preoperatively	354 ± 100	310 ± 79	277 ± 84	0.02
	postoperatively	243 ± 65***	254 ± 76***	238 ± 55	NS
Left ventricular mass index (g/m^2)					
	preoperatively	197 ± 47	175 ± 41	155 ± 43	0.01
	postoperatively	136 ± 30***	142 ± 38***	135 ± 33	NS
Left ventricular wall thickness (mm)					
IVS	preoperatively	15.1 ± 3.2	14.5 ± 2.9	13.6 ± 2.2	NS
	postoperatively	11.7 ± 2.6***	12.5 ± 2.0***	11.9 ± 2.4*	NS
PWT	preoperatively	12.6 ± 1.7	12.3 ± 2.0	12.0 ± 2.1	NS
	postoperatively	11.4± 1.6***	11.0 ± 1.6**	10.5 ± 1.1*	NS
LVEDD (mm)					
	preoperatively	49.2 ± 7.9	46.8± 6.0	44.8 ± 4.6	NS
	postoperatively	45.8 ± 5.5*	46.5 ± 6.2	46.0 ± 4.0	NS
LVEF					
	preoperatively	0.60 ± 0.11	0.57± 0.11	0.62± 0.13	NS
	postoperatively	0.60 ± 0.09	0.60 ± 0.10	0.59 ± 0.10	NS
E/A quotient					
	preoperatively	1.06 ± 0.49	0.91± 0.39	1.08 ± 0.60	NS
	postoperatively	1.00 ± 0.34	0.95 ± 0.34	0.98 ± 0.23	NS

ΔP_{max} and ΔP_{mean} – transvalvular peak and mean pressure differences, LVEDD – left ventricular end diastolic dimension, LVEF - left ventricular ejection fraction, IVS - interventricular septum, PWT - left ventricular posterior wall thickness, E/A quotient - ratio between early (E) and late (A) peak mitral velocity. P values indicate statistically significant differences between the three genotypes as tested by ANOVA. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ for differences between preoperative and follow-up values.

Figure 14.



Mean values and standard error of left ventricular mass index (LVMI) in patients with or without coronary artery disease (CAD). Two-way ANOVA for repeated measurements showed significantly higher LVMI over time in patients with CAD compared to those without. (p = 0.02).

Late clinical results (V-VI)

Survival (V-VI)

Mean age (78.5 vs. 63.3 years) differed significantly between the BS and the T-SPV patient populations and naturally this has impact on long-term outcome. Furthermore, long-term survival was determined at different mean follow-ups (66 ± 33 vs. 53 ± 24 months) making direct comparisons inadequate. However, results from these two populations are of importance to determine long-term outcome in two different populations of patients often seen in the clinical practice.

Actuarial survival at 5 and 7 years was 74% ± 5% and 59% ± 6% for the BS valve (Figure 15); and 92% ± 2% and 90% ± 2% for the T-SPV valve (Figure 16). The BS valve patients were followed longer, and survival had decreased at nine years to 38% ± 7% in this elderly population. Total deaths at late follow-up for the two patient cohorts numbered 51 (46%) in the BS group and 23 (9%) in the T-SPV group. Causes of all deaths are listed in Table 3. Late functional classification according to NYHA was determined for survivors in both groups of patients at late follow-up. 195 (87%) patients with the T-SPV valve were in NYHA class I, 29 (12.5%) were in class II, 1 (0.5%) in class III and no patient was in class IV at a mean follow-up of 4.4

± 2.0 years. Corresponding numbers for the BS valve at a mean follow-up of 5.5 ± 2.8 years was; 39 (66%) patients were in NYHA functional class I, 16 (27%) in class II, 4 (7%) in class III and none in class IV.

A multivariate analysis was conducted to determine preoperative risk factors for late mortality in the BS valve group. Multivariate analysis identified female gender (Hazard ratio 1.99 [CI 1.03-3.83], $p < 0.039$) and preoperative myocardial infarction (Hazard ratio 4.24 [CI 1.63-11.0], $p < 0.003$) as independent risk factors for late death.

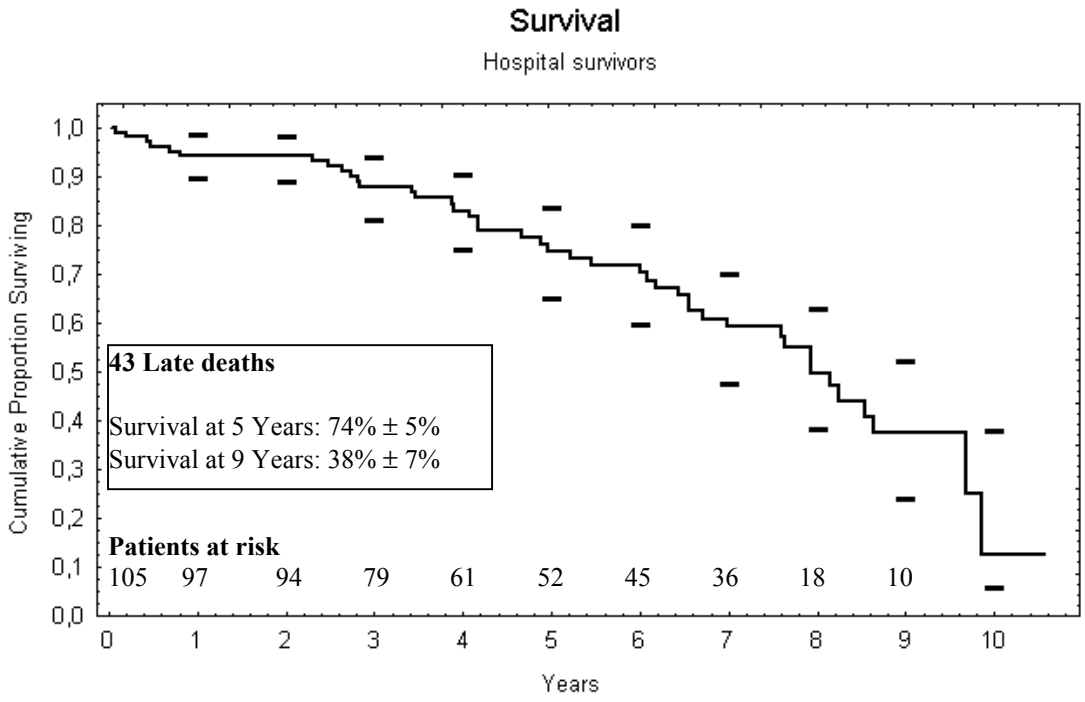
Expected survival and relative survival rate (VI)

There was no significant difference in survival between the BS valve patients and the expected survival for the age- and gender-matched comparison population supplied by Statistics Sweden (Log rank $p = 0.58$) (Figure 17). The annual relative survival rate indicates a normalized survival pattern for patients operated with the Biocor stentless bioprosthesis (Figure 18). During the first postoperative year there was a higher mortality among operated patients as indicated by the 95% confidence interval being below 1.0. After the first postoperative year patients seem to have a survival advantage for several years in relation to the comparison population. Towards the end of the study period, at nine years of follow-up and thereafter, the relative survival rate dropped significantly, which most likely is explained by the small number of patients at risk.

Valve-related mortality (V-VI)

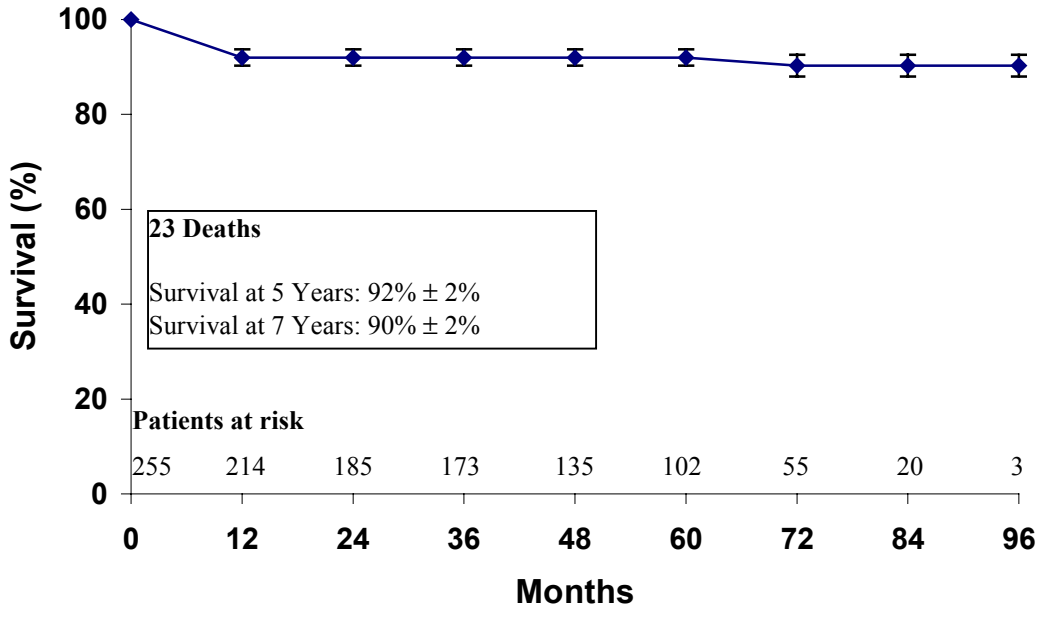
Seven patients fitted with one of the two valves under study died of valve-related causes: 4 died of stroke (3 BS and 1 T-SPV), 1 died of endocarditis (T-SPV) and 2 died of myocardial infarction (BS). Deaths of patients who died of myocardial infarction were classified as valvular deaths if the patient had had a normal preoperative coronary angiogram (Table 5). The actuarial freedom from valve-related mortality at 5 and 7 years was: 94% ± 3% and 91% ± 4% for the BS valve (Figure 19); and: 99% ± 1% and 99% ± 1% for the T-SPV valve, respectively. No deaths were caused by SVD, nonstructural dysfunction, valve thrombosis, bleeding events, operated valvular endocarditis or death related to reoperation of the operated valve. Sudden but not unexpected deaths occurred in 2 patients with a T-SPV valve due to congestive heart failure and were therefore classified as cardiac deaths.

Figure 15.



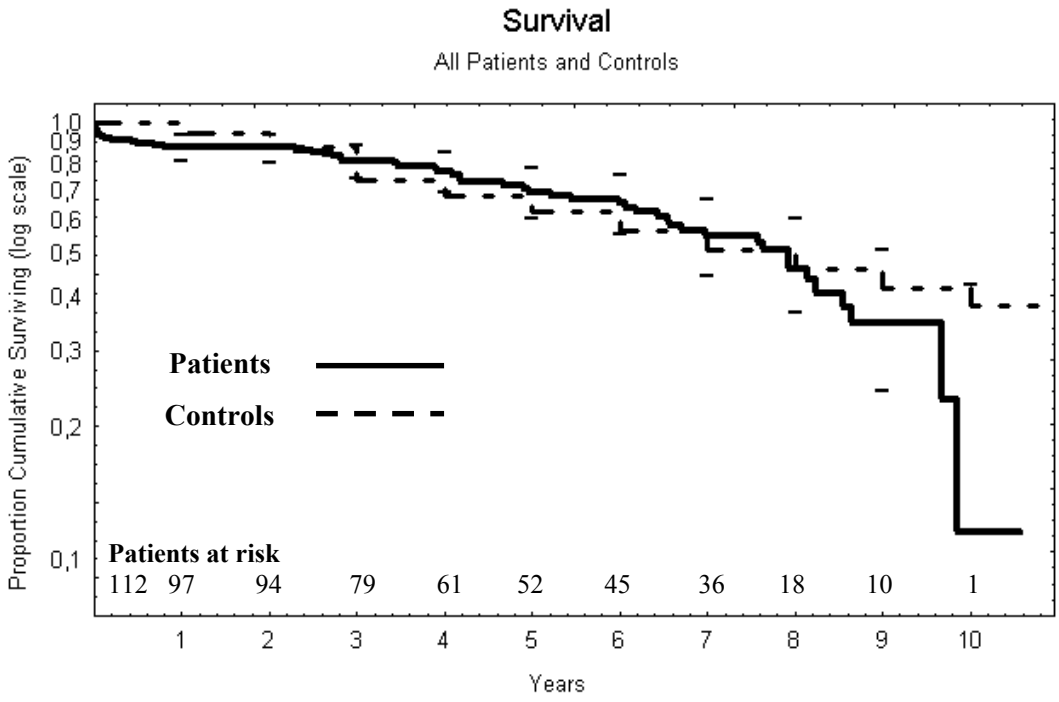
Actuarial survival for hospital survivors operated with the Biocor bioprosthesis. Horizontal bars indicate 95% confidence interval.

Figure 16.



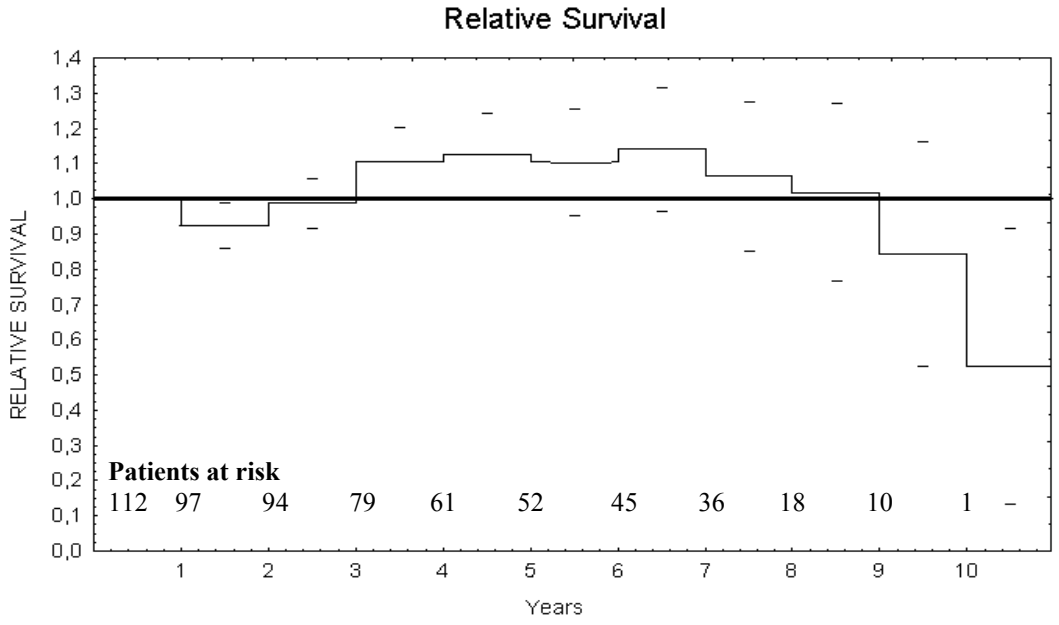
Actuarial survival rates for the Toronto SPV. Horizontal bars indicating 95% confidence interval.

Figure 17.



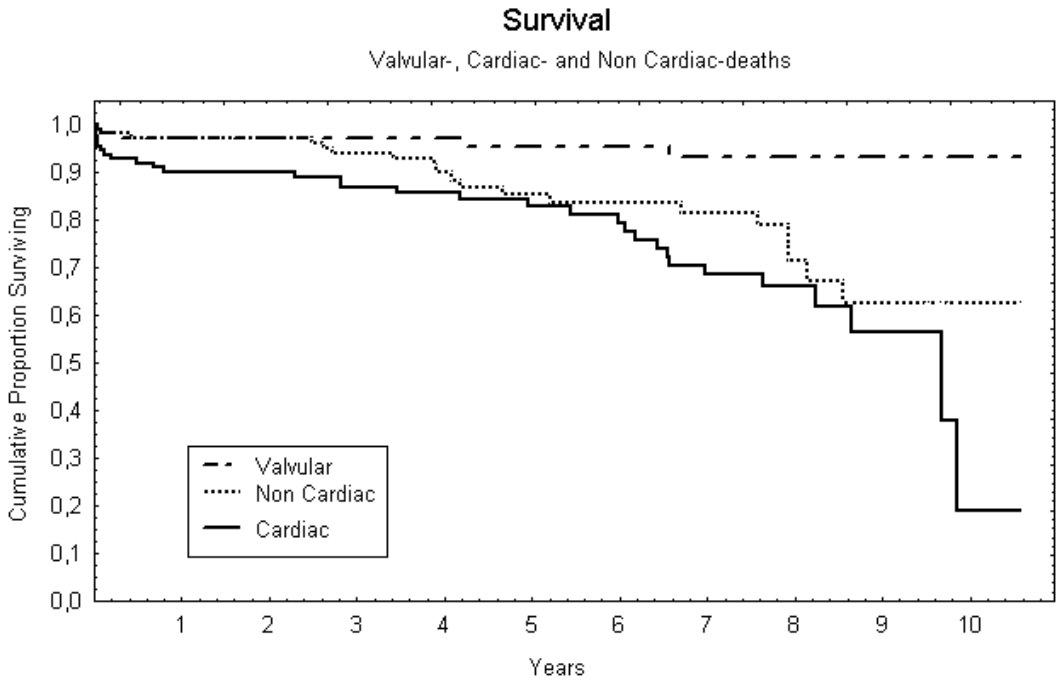
Actuarial survival for all patients (including early and late deaths) operated with the BS bioprosthesis (——) and for the age and gender matched control group (– –) derived from Statistics Sweden. Horizontal bars indicate 95% confidence interval for the patient population. Graphically presented with a logarithmic y-axis because this facilitates a correct visual comparison between different survival curves.

Figure 18.



Annual relative survival rates for patients operated with the BS bioprosthesis. Annual relative survival rates are calculated on yearly intervals as a ratio between survival for patients and for the age and gender matched Swedish comparison group. Horizontal bars indicate 95% confidence interval for relative survival.

Figure 19.



The actuarial freedom from valve-, cardiac- and non-cardiac-related deaths in the BS population.

Cardiac-related deaths (V-VI)

Cardiac-related deaths occurred in 25 patients (49% of all deaths) and in 4 patients (18% of all deaths) for the BS and T-SPV valves, respectively. The actuarial freedom from cardiac deaths at 5 and 7 years was: 82% ± 4% and 68% ± 6% for the BS valve (Figure 19); and 98% ± 1% and 98% ± 1% for the T-SPV valve, respectively.

Valve-related morbidity (V-VI)

Valve-related morbidity reported for these two valve series included structural valve deterioration (SVD), thromboembolism, valvular endocarditis and reoperation. There has been no bleeding event (requiring hospitalization or transfusion) or valve thrombosis.

SVD occurred in 4 patients (2 with the BS and 2 with the T-SPV). Both patients with the BS valve had commissural tears without signs of calcification and were reoperated on because of progressive AR. The two patients with the T-SPV had progressive AR due to dilatation of the sinotubular junction, however cusp tears were also found at reoperation. The actuarial freedom from SVD at 5 and 7 years was: 96% ± 2% and 94% ± 3% for the BS valve; and 100% and 97% ± 2% for the T-SPV valve, respectively.

Reoperation, due to SVD in two and early endocarditis in 1, was undertaken in 3 patients with the BS valve. Two patients in the T-SPV population were reoperated because of SVD. These five patients were reoperated after 1 week, 47, 74, 86 and 94 months of follow-up, respectively. All patients survived the reoperation. The actuarial freedom from reoperation at 5 and 7 years was: 96% ± 2% and 94% ± 3% for the BS valve; and 100% and 97% ± 2% for the T-SPV valve, respectively.

Late thromboembolic events were observed in 12 patients (13 strokes, 3 TIA) with the BS valve. The linearized incidence of thromboembolism was 2.8 ± 0.7 events/100 patient years. In the T-SPV group there were 14 patients with thromboembolic events (7 strokes, 7 TIA). The linearized incidence of thromboembolism in this group of patients was 1.3 ± 0.3 events/100 patient years. The actuarial freedom from thromboembolism at 5 and 7 years was: 89% ± 4% and 80% ± 5% for the BS valve; and 93% ± 2% and 92% ± 2% for the T-SPV valve, respectively. Multivariate analysis performed on preoperative characteristics could not identify any independent risk factors for late thromboembolism among the BS patients.

One patient with an EBS valve had an early bioprosthetic endocarditis assessed as secondary to postoperative mediastinitis. This stentless valve was replaced with another EBS valve in the early postoperative period. Two patients with the T-SPV valve had early bioprosthetic valvular endocarditis after 1 and 3 months, respectively. Both were treated medically and one patient died. No patient experienced late endocarditis in any of the two patient cohorts. The actuarial freedom from bioprosthetic valve endocarditis at 5 and 7 years was: 96% ± 2% and 94% ± 3% for the BS valve; and 99% ± 1% and 99% ± 1% for the T-SPV valve, respectively

Discussion

Nowadays, 40 years after the pioneering efforts of Harken and others, aortic valves can be replaced with a wide variety of mechanical, bioprosthetic and human tissue prostheses. Mechanical valves are more durable and have lower reoperation rates than other valve alternatives. However, they are associated with thromboembolism, which necessities anticoagulation and therefore those patients have a concomitant risk of hemorrhage (18). In contrast, bioprostheses have a low thrombogenicity and there is no need for anticoagulation in most patients. The main limitation, though, is the structural degeneration that occurs in the valve over time and the subsequent need for reoperation (28, 29, 35). Aortic homografts are mainly limited by a scarce supply of grafts even if these valves to a lesser extent also are subject to structural valve degeneration. Stentless bioprostheses provide hemodynamics similar to the native aortic valve and are a more physiologically attractive concept than stented bioprostheses and mechanical valves. There is hope that stentless bioprostheses will be associated with improved survival and fewer valve related complications than available alternatives.

Surgical implications

Calcified degenerative AS – particularly in elderly women with a narrow aortic root - poses a difficult problem. Valve replacement surgery in these patients has been a great challenge for the surgeon and has entailed a substantial risk of complications for the patient. In our opinion, we have shown that these patients can be satisfactorily dealt with using stentless valves. The EBS valve was used mainly in elderly female patients, who often had a narrow aortic root. In the early years it was believed that those patients with the narrowest aortic roots, in analogy with patients receiving stented valves, would benefit from aortic root widening using the subvalvular extension. However, experience showed that the hemodynamic outcome was excellent even for small valve sizes of the stentless valve. Use of stentless valves for AVR therefore implies that patients do not have to undergo any additional surgical procedures to improve hemodynamics at small valve sizes, as is sometimes the case with stented valves (95). The superior pericardial extension of the EBS valve was frequently used and facilitated aortic closure in patients

with heavily calcified ascending aortas. The well-preserved ejection fraction after aortic valve replacement with stentless valves may indicate that even though most of these patients had severe LVH, the intraoperative myocardial protection was satisfactory.

Clinical experience with stentless bioprostheses

Long-term survival has not earlier been determined for any of the commercially available stentless bioprostheses. We have shown, for two different brands of stentless valves, that survival is excellent for two different populations of patients frequently seen in the regular cardiac surgical practice.

Early results

Stentless valves are technically more challenging to implant than stented valves. Despite the fact that implantation of stentless valves requires longer cross clamp time, it has not in any of our series been associated with a higher operative mortality or morbidity rate than what previously has been published for stented alternatives (28, 35, 96). The early mortality was 7% for the BS valve group and 1% for the T-SPV valve group. However, these two patient populations were very different mainly in terms of the mean age (78.5 versus 63.3 years) and the distribution of gender. Patients with characteristics traditionally considered to entail high intraoperative risk, such as elderly females with a narrow aortic root (97), were actually recruited to receive the BS valve. It has previously been shown that independent predictors of mortality were advanced age, female gender, advanced left ventricular dysfunction, coronary artery disease and advanced NYHA functional class in patients older than seventy years of age that underwent AVR (98). Furthermore, AVR in patients 80 years of age and older has been shown to be associated with a distinctly increased early mortality (14%) and morbidity (96). Another study reported an early mortality of 14% in a population similar to the BS valve population but with a somewhat higher mean age (99). Early mortality, in patients older than 70 years of age that undergo AVR with stented valves, seems to be between 3% and 14% in most studies even if age distribution varies somewhat between these studies (96-100). Westaby et al reported an early mortality of 8% for the Freestyle stentless valve in a consecutive, unselected but somewhat younger patient population (101). Early mortality, although in younger patient populations, has been

reported to be 1 and 3% with the Cryolife-O´Brien stentless porcine valve and with the Biocor stentless valve, respectively (102, 103). Against this background, the early mortality is acceptable and comparable to other studies both for our elderly patients with the BS valve as well as for the T-SPV population. In fact, early mortality and morbidity among the T-SPV valve patients is exceptionally low and compares favorably with most other series of stented valves (28, 29, 35, 104). However, the T-SPV population was selected to a certain extent, since patients with an expected survival of less than 2 years as well as those with renal insufficiency were excluded from having this valve implanted. Also worth considering is the fact that surgeons who are comfortable with stentless valves tend to do many valve operations and the excellent early results of our two valve series may in part simply be a reflection of their experience. Our studies suggest that stentless valves can be used successfully, without a negative impact on early mortality or morbidity, also among elderly patients needing a combined procedure.

Late survival

Late survival after aortic valve replacement with the Biocor stentless and the Toronto SPV aortic bioprostheses was very different but obviously related to dissimilarities between the patient populations. Therefore, direct comparison of results for these two valves is impossible not only due to above-mentioned disparities but also because long-term survival was determined at different times, in different countries, at different institutions, in different health care systems and with different duration of follow-up. However, our results can be used to guide us in the treatment of different individual patients. Long-term survival after the use of a stented bioprosthesis has previously been found to be highly dependent on age, coronary artery disease and functional class, although bioprosthetic durability seemed mostly dependent on age (105). Regression analysis revealed that age > 65 years, presence of coronary artery disease and advanced NYHA functional classification were associated with a higher risk for late death. The late survival with the BS valve was lower than with the T-SPV stentless valve, but it should be born in mind that the patients who received the BS valve were considerably older. The T-SPV group had an excellent long-term survival and the valve compares favorably at a corresponding follow-up interval to most other series of stented bioprostheses in patients with a similar age distribution (28, 29). The T-SPV and the BS valve patient

populations do not seem to be very different from what is generally seen in a clinical practice, with varying degrees of coronary artery disease in about 40 % of the cases. The long-term survival of the BS valve population is well in line with what others have reported for a similar population of elderly patients undergoing aortic valve replacement with a stented bioprosthesis (99). Another study has reported a long-term survival of 82% at seven years for the regular Biocor stentless valve, which compares better than the BS valve but worse than the T-SPV population (102). Mean age though, was 70 years of age, which is a mean age in between our two series of stentless valves. Altogether, long-term results from these series indirectly support the evidence that age is one of the most important determinants of long-term outcome. A retrospective case-match study comparing stentless and stented porcine valves has previously showed a significantly better survival for the stentless group (101, 106). The difference in survival seen for these two valve series was mainly constituted by a reduction of cardiac mortality rates among patients fitted with a stentless valve. Furthermore, Westaby et al also showed an enhanced survival in patients receiving the Freestyle stentless valve when compared to a stented pericardial bioprosthesis (101). However, there were also unexplained differences in noncardiac deaths in both studies to advantage for the stentless valves, which may be explained by different patient populations (101, 106). Although it is possible that confounding factors may have influenced the outcome of these case-control studies, it suggested that stentless porcine valves enhance survival. Even if long-term survival so far is excellent for our series of stentless bioprostheses, patients need to be closely followed in the future to determine whether stentless valves will be associated with enhanced survival rates or not, when compared to stented bioprostheses.

Expected- and relative survival

Survival of the elderly BS valve population was not different from an age- and gender-matched Swedish control group supplied by Statistics Sweden. Patient survival is the ultimate criterion for measuring the effectiveness of treatment in heart valve disease as for most other chronic diseases. The interpretation of survival curves, though, is complicated by deaths due to causes other than the disease under study. The relative survival rate has been used to adjust for "normal mortality risk" and could thus be regarded as the probability of escaping the extra risk of dying from the disease under study (92). A previous study using relative

survival rates from our institution has shown that patients older than 65 years of age with pure aortic stenosis achieved a normalized survival pattern after isolated mechanical valve replacement (91). We have used the relative survival rates to evaluate whether valve disease affected long-term mortality for our elderly patients that underwent AVR with the BS valve. It seemed that those elderly patients experienced a normalized survival as also illustrated by a constant relative survival from at least the second postoperative year. Relative survival rate during the first postoperative year was lower than later on during the study and this seems mainly related to the early in-hospital mortality. Patients seemed to have a survival advantage, although not statistically significant, in relation to the comparison population after the first postoperative year. However, this may be due to a selection bias, towards a generally healthy patient population with few concomitant diseases at the time of operation. At nine years of follow-up and thereafter, the relative survival rate dropped significantly, which most likely is related to the small number of patients at risk. The BS patient population may thus be regarded as "cured" from their valve disease even considering that approximately 30% had concomitant coronary artery disease. In our opinion, relative survival rates are a useful complementary tool for analyzing long-term survival in patients with operated valvular disease, particularly in elderly populations that have a high "normal mortality risk". Traditionally it has been argued that elderly patients mainly undergo AVR for symptomatic relief rather than for prognostic reasons. Our results indicate that elderly patients who undergo AVR with a stentless valve not only find relief from symptoms, but also benefit in terms of increased survival, an effect that was earlier thought to be reserved mainly for younger patients.

Valve-related mortality and survival

Valve-related mortality and morbidity was very low with both stentless valves under study. Valve-related mortality has so far also been shown to be low in general for other stentless valves (101, 102, 103). Previously mentioned case-match studies between stentless porcine valves and stented bioprostheses showed that both valve-related and cardiac-related mortality seemed to be lower for stentless valves. However, valve-related mortality has already been shown to be very low with some of the third generation stented bioprostheses (107). Improvements in manufacturing techniques or in how the valve is processed could perhaps contribute to the

proposed enhanced survival in previously mentioned studies of stentless valves. However, the window of improvement in valve related-mortality is too small, at least for the first 10-year interval, to extrapolate to an overall enhanced survival benefit for stentless valves compared to the third generation bioprostheses. If differences in survival were mainly constituted by a difference in noncardiac deaths this would rather suggest non-comparable patient populations, difficult to adjust for in any form of retrospective study (101, 106). Therefore, if the stentless design offers a survival advantage over stented bioprostheses as proposed, it should translate into not only fewer valve-related deaths but also fewer cardiac-related deaths. Hypothetically, a more complete regression of LVH may facilitate the reduction of late cardiac deaths for stentless valves. The cardiac-related mortality among patients receiving the BS valve was considerably higher compared to the T-SPV population. The difference in cardiac-related deaths indicates that there might be other differences than age between these two populations. There was no apparent difference in the incidence of coronary artery disease or hypertension among these patient populations. There may be some other difference between populations that causes the observed difference in cardiac-related mortality, possibly related to LVH. Patients with the T-SPV valve might have been accepted for surgery at an earlier stage in their disease, a possibility supported by the lower LVM at the early postoperative echocardiogram, or maybe age itself is a stronger predictor of cardiac mortality than thought. Alternatively, patients receiving the BS valve might have been operated late in their course of the disease. It has previously been shown that interstitial fibrosis develops in parallel to LVH in patients with aortic valve disease without having a negative impact on systolic left ventricular function at least in the early phase (108, 109). However, these histological changes have been found to have a negative impact mainly on the diastolic function of the heart (110). Patients operated late in their disease probably have a greater degree of interstitial fibrosis, in addition to LVH. One might speculate that these histological findings are more pronounced and irreversible among elderly and that they are associated with cardiac deaths. This would then suggest that these patients would benefit from having their valve operation earlier, before these changes occur or become irreversible. Most patients with AS are today followed for several years before intervention is decided upon. Maybe long-term outcome for these patients would improve if they were operated upon earlier.

Whether stentless valves confer a survival advantage cannot be determined on the basis of current knowledge and the possibility needs to be evaluated in a prospective randomized study.

Valve-related morbidity

Thromboembolic events were more common in the elderly BS valve population than the T-SPV population and were also the most common cause of valve-related morbidity observed in our studies. Thromboembolic events are traditionally considered to be valve-related complications (61). However, the older the study population is, the more likely it is that the thromboembolic events are associated with vascular disease rather than with the valve itself. Since thromboembolism becomes more common with increasing age in the general population there is a growing likelihood to overestimate valve-related complications, particularly in elderly valve recipient populations. Our opinion is therefore, even if we acknowledge the current definitions of valve-related complications to be used for valve studies, that valve-related morbidity is likely overestimated, since most of the observed thromboembolic events are not associated with the valve itself. Late endocarditis did not occur at all in our experience when stentless valves were used. However, we saw a few cases of early endocarditis, which most certainly were caused by intraoperative contamination. Reoperation occurred in a few cases and was closely related to structural degeneration of the valve, which occurred rarely. Actuarial freedom from structural valve degeneration, reoperation and operated valvular endocarditis seems lower for stentless valves than for some stented bioprostheses (107, 111). There are, however, examples of series with stented bioprostheses with results comparable to what has so far been reported for stentless valves regarding structural valve degeneration and reoperation (29, 35). Furthermore, structural degeneration of implanted valves has been described to be an age related phenomenon with a higher incidence among younger patients, which makes comparisons between different valve substitutes even more difficult (107, 111). However, longer follow-up is needed to conclude whether or not there is a difference in valve related morbidity between stented and stentless bioprostheses. We also acknowledge that actuarial analysis, as pointed out by Grunkemeier, is probably not the most accurate way to measure non-fatal events (112). In order to answer the question, “what is the chance the valve will fail before the patient dies”, the actual survival is regarded a better estimate. The actual fail-

ure is the percentage of valves that will actually fail before patients die. This risk is always less than the actuarial risk and the difference increases with age of the patient population. However, our actuarial freedom from valve-related complications, such as structural valve degeneration, was already low by the actuarial method and would have been even lower if calculated with the actual method. Since we observed very few valve related complications, it was not deemed necessary to calculate according to the actual method. If our studies had consisted of larger patient populations and there had been more events due to valve related complications, the actual method would have been useful to distinguish between patients who will actually suffer from a valve failure during life and those who actually will die prior to valve failure.

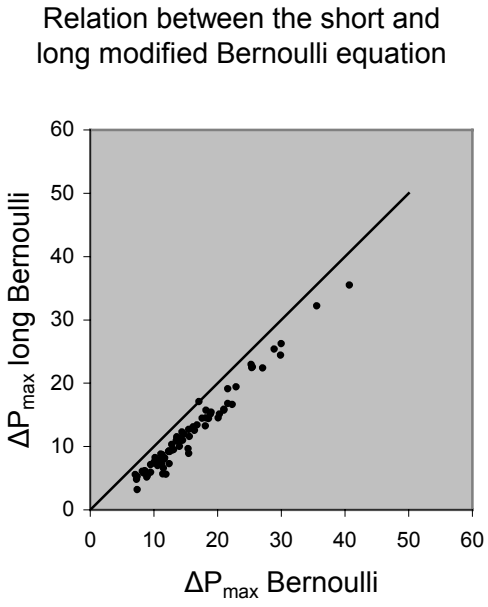
Hemodynamic experience with stentless bioprostheses

At rest

Optimal prosthetic valve function provides a non-obstructive valve with low flow resistance and low incidence of valvular regurgitation. For the stentless porcine valves used in our studies, transvalvular pressure differences decreased during the first postoperative year and remained unchanged up until 9 years of follow-up. A similar development was seen for EOA, which increased during the first postoperative year and remained unchanged up until 9 years of follow-up with the BS valve. However, the T-SPV seemed to have a slight increase in EOA during the first 5 postoperative years. Previous studies of different stentless valves have shown similar results, with a decrease in transvalvular pressure differences and an increase in EOA, with most of the changes occurring during the first year (113, 114, 115). Furthermore, others have demonstrated that the hemodynamic performance of stentless valves at early follow-up is superior to that of stented bioprostheses and essentially similar to that of homografts (116, 117, 118, 119). When several mechanical and bioprosthetic valves were compared with each other at follow-up, the Toronto SPV showed a larger orifice area and lower transvalvular pressure differences and was regarded to have the best hemodynamic performance (117, 120). Another study from our institution has shown that transvalvular pressure differences were smaller and EOA was larger for similar valve sizes for stentless valves compared to stented bioprostheses and mechanical valves, only exceeded by homografts (37). Whether the

long or short form of the modified Bernoulli equation should be used is a matter of choice as long as the reader always bears in mind that the calculated results are not equal. Pressure differences calculated with the longer form were approximately 4 mm Hg smaller, for the present range of pressures, than with the short form of the Bernoulli equation (Figure 20). However, the longer form of the equation will more accurately estimate the obstruction of the valve itself, taking the pressures in the LVOT into account. The reason for the observed differences with the gradual increase in EOA and the decrease of gradients over time is not clear, and no such changes are observed in mechanical valves. It has been speculated whether these changes are related to the resolution of tissue edema and hematoma, or maybe to the decrease in left ventricular mass with altered geometry in the aortic root, despite an unchanged LVOT diameter. When tested in a stepwise regression analysis the decrease in ΔP_{max} during follow-up correlated only with the decrease in aortic valve volume flow. Another hypothesis is that the early increase in blood flow acceleration might be related to postoperative anemia, which is reversed by time (120). However, in our opinion, the changes in transvalvular pressure differences and EOA over time are likely to be due to many different factors, with all reasons mentioned above contributing. The superior hemodynamic performance of stentless valves is not just the result of not having a stent in the left ventricular outflow tract but also because a valve with a larger effective orifice area can be implanted (119).

Figure 20.



The relation between ΔP_{max} calculated with the long and short form of the modified Bernoulli equation at one-year follow-up in 83 BS patients.

At long-term follow-up the majority of patients did not have any significant AR. At five years of follow-up two patients with the BS valve and none with the T-SPV valve had AR more than grade two. At seven years of follow-up, one patient in each valve population had AR more than grade two. However, four patients, two in each valve population, were also reoper-

ated for AR during follow-up. All these patients had cusp tears on reoperation. The T-SPV valves that failed have been associated with dilatation of the sinotubular junction during follow-up (121). AR remains uncommon at long-term follow-up although there is a minor concern that, as time goes by, more valves seem to be subject to trivial to mild leakage. Whether this is an early sign of degeneration or not remains to be determined and therefore patients should be evaluated with echocardiography at regular intervals to discover the rare case of progressive AR.

At exercise

A flow dependent increase in ΔP_{max} was observed for all valve sizes in patients performing a symptom-limited supine exercise test. The increase was, however, smaller than that seen for other mechanical and bioprosthetic valves according to another study from our institution (37). We did not detect any signs of valve mismatch among patients with stentless valves undergoing exercise test. Valve mismatch would show up as a step increase in pressure difference during exercise and is associated with less symptomatic improvement and impaired hemodynamics (122). The EOA calculated with the continuity equation remained unchanged by exercise, suggesting that maximal EOA is already in use at rest. The aortic valve area calculated with the Gorlin formula was slightly larger than the area calculated with the continuity equation, which is in accordance with what others have reported (123).

Left ventricular hypertrophy

In aortic stenosis

The preoperative evaluation of patients with AS often shows that some have developed severe LVH while others have only mild LVH, despite a similar degree of AS. However, LVH is far more common among patients with AS than in a general population, in which 16% of men and 19% of women were reported to have LVH in a cohort study (79). Others have shown that severe preoperative LVH increases mortality and morbidity after aortic valve surgery (124, 125). It has previously been shown that the aortic valve area or transvalvular pressure difference were poorly correlated with left ventricular mass or left ventricular function in patients with AS (41). Furthermore, left ventricular wall thickness was not found to be an indicator of the severity of AS (42). In line with these previous reports, we found no correlation between the preoperative pressure difference across the

aortic valve, regarded as an estimate of the severity of AS, and LVMI.

In stentless valves

The LVMI decreased significantly among T-SPV patients during the first postoperative year and continued to decrease up to 3 years, where after it remained unchanged up until 5 years of follow-up. Most patients normalized their LVMI within 3 years after implantation of a T-SPV valve. Also the BS valve patients showed a significant reduction in LVM during the first postoperative year. A significant reduction in LVMI has also been reported to occur after AVR with stented valves (126). However, even after 8 years of follow-up, LVMI had not normalized. Furthermore, incomplete regression of LVMI at three years of follow-up has been reported in an age group similar to the T-SPV population, for all valve sizes after mechanical AVR (127). In a previous report, a higher LVMI was associated with stented bioprostheses when compared with mechanical valves of similar sizes, with a 27% overall reduction in LVMI postoperatively that seemed to be smaller for stented bioprostheses (128). It has also been shown that stentless porcine valves have similar hemodynamics and effect on LVM as aortic valve homografts (118). Furthermore, a prospectively randomized study comparing a stentless valve with a stented bioprosthesis showed a more pronounced regression of left ventricular mass, investigated by magnetic resonance imaging (119). It should be emphasized that in all these studies the transvalvular pressure differences were higher in stented than in stentless valves. Transvalvular pressure differences are lower and EOA is larger, and therefore left ventricular wall stress is further diminished in stentless valves compared to stented ones. This results in a significant decrease in LVMI after implantation of a stentless valve, lately also shown for several other stentless valves (118, 129). Hopefully this will translate into a lower risk of sudden death and congestive heart failure in long-term studies. Previously, it has been shown that smaller prosthetic valve sizes were a risk factor for long-term mortality after AVR (130). Furthermore, a narrow aortic root and increased relative wall thickness have been found to be risk factors for early mortality (131). In the T-SPV group we showed that LVMI decreased more in patients with smaller valve sizes, usually women with massive LVH, than in patients fitted with larger valves.

Clinical factors influencing LVH

We have also shown that the amount of LVH and the pattern of regression are different depending on factors such as gender, hypertension, coronary artery disease and aortic valve pathology. Interestingly, at discharge no difference was seen in LVMI when stratified for gender or hypertension in the T-SPV group. In contrast, a previous study has reported that men with AS had a higher LVMI than women with AS (132). This may suggest that male patients with the T-SPV valve were operated on early after the onset of symptoms without development of severe LVH. Furthermore, a higher LVMI was found preoperatively in patients with coronary artery disease and AR. There was no difference in LVMI between patients with AS and AR at five years of follow-up: both groups had a normal LVMI. The only predictors of higher LVMI over time were coronary artery disease and hypertension. However, there was no difference in LVMI at 5 years between patients with or without coronary artery disease, indicating a successful revascularization. Altogether, the decrease in LVMI after AVR seems to be multifactorial, dependent on several clinical factors other than the valve type itself, which complicates use of LVMI for comparison of different valves.

ACE-gene polymorphism and LVH

Polymerase chain reaction revealed that the genotype frequency for the ACE gene in patients operated on for AS does not deviate from what has been reported for the normal Caucasian population (DD: 29%, ID: 50%, II: 22%) (53). Also, the frequencies of the I and D alleles in patients operated on for AS were similar to previously published data from control subjects, being 44% and 56%, respectively (59). We have shown that the DD genotype of the ACE gene and male gender were preoperatively associated with a higher LVMI in patients operated on for AS. Others have also reported that male gender is associated with a higher LVMI in patients with AS (132). Interestingly, at 15 months follow-up, patients with the DD and ID genotypes had a significantly decreased LVMI, which was most pronounced in the DD genotype group. Furthermore, at follow-up, no significant difference was seen between the three genotypes regarding the LVMI. This observation suggests that the influence of the ACE D/I polymorphism on the development of LVH in these patients is mainly related to a reversible component and that when the precipitating factor - the pressure overload - is eliminated, the D/I polymorphism no longer contributes to the propensity to develop or maintain LVH. However,

according to reference values (79), LVH was still present at follow-up in about 50 % of the subjects with preoperative AS, equally distributed among men and women. Surprisingly, we found that despite severe preoperative AS in most cases, only 48 % of the T-SPV patients had LVH at discharge. It has been shown in another study, however, that LVMI had decreased significantly within one week after AVR (133). This may explain our findings of an unexpectedly low proportion of LVH early after surgery in the T-SPV population. Therefore it is likely that differences in LVMI over time would have been even more significant in the T-SPV population if we had recorded a preoperative baseline echocardiogram for comparison. Regression of the LVMI in patients with AS and an implanted stented aortic valve has been reported to be 28% after a mean follow-up of 19 months (126). The regression of the LVMI among patients with significant AS in our study was 22%, but the follow-up was somewhat shorter. Our patients were also much older, perhaps indicating a slower normalization of the LVMI in older patients. An increased regression of the LVMI after aortic valve replacement has been observed in an age and gender-matched population when using stentless valves compared to stented mechanical valves (117). Hypothetically, the reversible hypertrophy might be due to the decrease in cardiomyocyte hypertrophy and the irreversible hypertrophy to less reactive components, e.g. connective tissue. However, time should also be considered as an important factor for regression of LVH, which might continue even after the first postoperative year, as earlier demonstrated (126). Our T-SPV patients, who experienced an ongoing decrease in LVMI over time, further support time as an important factor for regression of LVH.

Increased left ventricular wall stress due to pressure overload (AS) or increased afterload induces myocardial growth and LVH (134). Nonetheless, ten percent of patients with severe AS never develop LVH despite long-standing disease (125), suggesting that factors other than increased left ventricular wall stress modulate the transformation of the phenotype (57). We found that 20% of our patients had not developed LVH preoperatively despite severe AS. Although our measurements of the pressure overload did not reveal any correlation with LVMI, pressure overload is probably necessary to trigger myocardial growth in AS. Our findings further indicate that the hypertrophic response has a polygenic background where gender and ACE gene D/I polymorphism explains only some of the variability in LVMI. In a previous study

there was no association between ACE genotype and echocardiographically determined left ventricular mass in a cohort study (135), indicating that the D/I polymorphism is a modulating factor rather than a trigger of LVH by itself. We have shown that the decrease of LVMI over time was significantly different between genotypes after aortic valve replacement, with no significant differences between genotypes at follow-up, again indicating a modulating effect of the D/I polymorphism. Experimentally, the renin-angiotensin system is known to modulate the hypertrophic response to pressure overload in the development of LVH. Angiotensin II is a potent growth factor acting on cardiomyocytes (136). Our study indicates that ACE gene D/I polymorphism is one significant determinant for the hypertrophic response.

LVH and prognosis after valve replacement

Severe LVH is associated with arrhythmias and sudden death, a common cause of death in the natural history of valvular AS (137). Patients with mechanical aortic valve replacements still have an increased risk of sudden death (18). The reason for this might be incomplete regression of LVH or irreversible changes in the myocardium. Therefore, treatment of patients with AS and LVH should probably be focused on achieving rapid regression of LVH. This might include valve replacement with stentless valves and also perhaps pre- and/or post-operative low-dose ACE inhibitors or angiotensin II receptor antagonists. If patients with massive LVH have the DD genotype of the ACE gene in a higher proportion than others, as indicated by our study, this might be considered when evaluating patients preoperatively, as the genotype may have prognostic and therapeutic implications (55, 59). Despite increasing age of patients undergoing AVR the results continue to improve over time. However, it is important that patients are referred for surgery without delay when symptoms start to occur. Furthermore, there is some evidence that patients with AS have an increased risk of dying even before symptoms develop (4). The question raised should be whether it is preferable to undergo AVR with a hospital mortality risk between 1-7% or to wait for symptoms and in the mean time experience a 6% risk of sudden death during a 14 month interval (4), and in addition run the risk that irreversible myocardial damage will develop before the operation is eventually decided upon. There are some fears that some of these elderly patients are referred for surgery too late or not at all.

Studies of death certificates in Stockholm County have previously shown that approximately 35% of patients with AS died, without being assessed for surgery (138). The referring general practitioners probably thought the patients were inoperable due to age. Even worse - perhaps they were unaware that most of these patients can be treated successfully with surgery, regardless of age.

Conclusions

- The clinical use of stentless bioprostheses, despite being technically more challenging, is safe and not associated with increased early morbidity or mortality.

- The long-term survival with stentless valves is excellent, with few valve related complications.

- Implantation of a stentless valve in elderly patients results in normalized survival compared to an age- and gender-matched general population.

- Relative survival rates among elderly operated with a stentless valve indicate that these patients are "cured" from their valve disease.

- Our results indicate that elderly patients who undergo AVR with a stentless valve benefit both in terms of improved prognosis and alleviated symptoms, as traditionally only the younger patient population is believed to benefit from.

- Early hemodynamic performance of stentless porcine valves is excellent, with small pressure differences at rest and during exercise.

- Long-term hemodynamic performance with stentless porcine valves is excellent, with small transvalvular pressure difference, a low incidence of AR and a normalization of LVMI.

- There is no correlation between preoperative transvalvular pressure difference and LVMI in patients with severe AS.

- I/D polymorphism of the ACE-gene is one significant determinant – but not the only determinant - of the hypertrophic response in patients with severe AS

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