CONSERVATIVE AORTIC VALVE SURGERY IN ADULTS

Aortaklepsparende chirurgie bij volwassenen

Casselman, Filip Paul Angele
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(met een samenvatting in het Nederlands)

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Filip Paul Angele Casselman

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Promotor
Prof. dr. A. Brutel de la Rivière (Universiteit Utrecht)

Promotiecommissie
Prof. dr. W. Daenen (Katholieke Universiteit Leuven)
A. Marc Gillinov M.D. (The Cleveland Clinic Foundation, U.S.A.)
Prof. dr. D.E. Grobbee (Universiteit Utrecht)
Dr. W.J. Morshuis (St. Antonius Ziekenhuis Nieuwegein)
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Le coeur a des raisons que la raison ne connait pas.
Blaise Pascal

Aan mijn lieve vrouw Rebecca
en onze 3 (b)engeltjes:
Amaury, Paul-Henry en Nicolas

CONTENTS

CHAPTER 1

The failing aortic valve in adults: where do we stand?

Filip P.A. Casselman M.D.

Introduction

In order to understand the physiology and pathophysiology of the aortic valve, one needs to be aware of the normal anatomy of the aortic valve and the most commonly seen structural deviations. This review will therefore first focus on the anatomy of the aortic valve and its most frequent abnormalities. Subsequently, the possible pathological conditions of the aortic valve will be discussed. Finally, the various treatment modalities for correction of the failing aortic valve will be presented. As this thesis focuses on reconstructive surgery of the adult aortic valve, this chapter will accordingly be limited to adults.

Anatomy and function of the normal aortic valve

The normal aortic valve is a structure consisting of three freely mobile cusps, located between the left ventricular outflow tract and the tubular portion of the aorta [1]. These three cusps together form a thin, mobile layer of tissue which, by opening, allows free flow of blood from the left ventricle into the aorta during systole, and which prevents, by closing during diastole, regurgitation of blood from the aorta back into the ventricle. The three aortic valve cusps are designated right, left and non-coronary cusp according to the respective coronary artery or the absence of an originating coronary artery from the sinus which they face. The size of the three cusps is usually unequal with the non-coronary cusp commonly being the largest and the right coronary cusp being the smallest [1-4]. In 16% of cases, the three aortic valve cusps are equal in size [1].

The aortic valve cusps are not attached in a circular horizontal plane to the aortic wall but in a semilunar fashion. This line of attachment, also called the annulus fibrosus, constitutes the physiologic ventriculo-arterial junction and is in fact a coupled sequence of three paraboloids [5] (Fig. 1). This physiologic ventriculo-arterial junction is different from the anatomical ventriculo-arterial junction being the straight horizontal circle where the fibro-elastic aortic wall joins the supporting structures of the left ventricle (Fig. 1) [6-7] or, beneath the non-coronary cusp, the aortic-mitral fibrous continuity. The area between the physiological and the anatomical ventriculo-arterial junction is made of fibrous tissue and forms three interleaflet triangles between the longitudinal limbs of the annulus fibrosus. These interleaflet triangles are thus situated underneath the line of attachment of the valve cusps and are therefore exposed to ventricular hemodynamics.

Each aortic valve cusp contains a hinge point, a body and a coapting surface (lunula) with a thickened central nodule, the nodule of Arantius. The hinge point is the area where the leaflet is attached to the aortic root in the earlier mentioned semilunar fashion. The top of these attachments is called the ‘commissure’ and is situated at the level of the sinotubular junction whereas the bottom (the so-called nadir) is situated below the anatomical ventriculo-arterial junction.

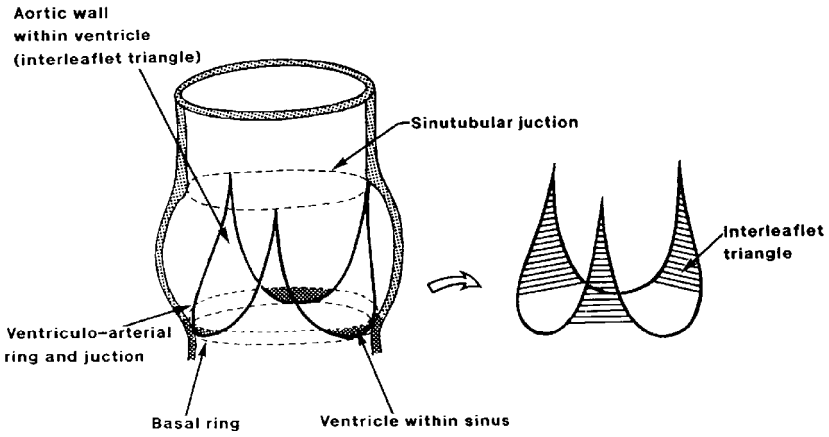

Figure 1: *Diagram of the aortic root. The coronetlike arrangement of the valvar attachments. (From: Sutton III JP, et al. The forgotten interleaflet triangles: a review of the surgical anatomy of the aortic valve. Ann Thorac Surg 1995;59:419-27. Reprinted with permission from The Society of Thoracic Surgeons).*

The function of the aortic valve cannot be separated from the more complex setting of the aortic root. The aortic root comprises the initial portion of the ascending aorta and is limited inferiorly by the anatomical ventriculo-arterial junction and superiorly by the sinotubular ridge or sinotubular junction which delineates the beginning of the proper ascending aorta. The components of the aortic root are thus the three sinuses of Valsalva, the interleaflet triangles and the valve cusps [6-9]. The three sinuses of Valsalva are designated left, right and non-coronary according to the aortic valve cusp they face and they are limited superiorly by the sinotubular ridge. The sinuses of Valsalva were already recognized by Leonardo da Vinci who realized their importance in correct aortic valve functioning [10]. Indeed, the aortic valve/root is a dynamic structure in which most geometric parts are continuously changing during a cardiac cycle in response to aortic pressure (which is also determined by the peripheral resistance), ventricular pressure and ventricular geometry [2, 11]. More precisely, due to the global left ventricular contraction during systole, there is an inward movement of the physiologic ventriculo-aortic junction, resulting in a reduction of its diameter. In addition there is an outward movement of the commissures. This change is supposed to facilitate systolic blood expulsion from the left ventricle [3, 9, 11]. During diastole, the opposite movement takes place and the aortic valve closes. The diastolic aortic pressure provides blood flow into the coronary arteries. The correct functioning of the aortic valve complex is an interaction of all of its components including the ventriculo-aortic junction, the aortic valve leaflets, the sinuses of Valsalva and the commissures with their apex reaching the sinotubular ridge. The importance of the diameter

of the sinotubular ridge was already recognized in 1832 by Corrigan who suggested that a dilatation of the sinotubular junction, frequently a result of ascending aortic aneurysm, was probably the cause of aortic regurgitation [12]. This pathophysiologic mechanism has been accepted since several years by cardiac surgeons and has recently been confirmed experimentally [13].

Anatomical variations

Congenital bicuspid aortic valve is the most frequent structural anomaly of the aortic valve. Its frequency in the general population however is not exceeding 0.4 to 2% [14]. There are two types of congenital bicuspid aortic valve: the cusps are either located right and left with the commissures being anterior and posterior or the cusps can be located anteriorly and posteriorly with the commissures being right and left [14-15] (Fig. 2).

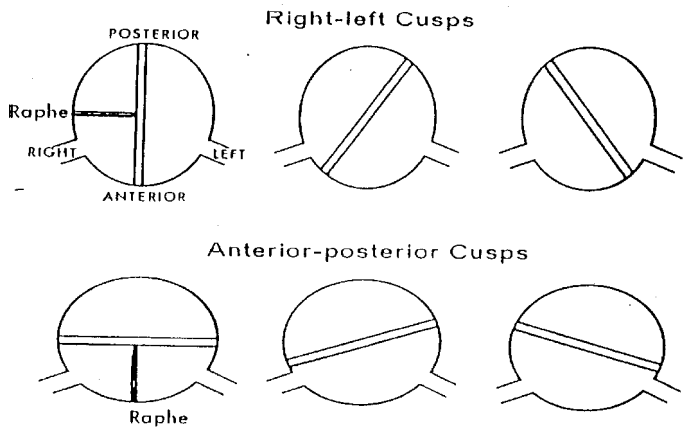

Figure 2: *Diagram showing the two basic types of congenitally bicuspid aortic valves. (From: Roberts WC. The congenitally bicuspid aortic valve: a study of 85 autopsy cases. Am J Cardiol 1970;26:72-83. Reprinted with permission from Exerpta Medica Inc.).*

Approximately 50% of congenital bicuspid valves have so-called false raphes [16]. A raphe is a ridge of tissue which partially divides one of the cusps of the bicuspid valve and which lies vertically in the wall of the aortic sinus. Although congenital bicuspid aortic valve is generally not considered to be inherited, there is a high incidence of familial clustering [17]. Besides the congenital bicuspid aortic valve, most authors also distinguish the so-called acquired bicuspid aortic valve. This type of valve originates from a trileaflet aortic valve in which fusion of two adjacent cusps occurred. This fusion constitutes a ‘new’ raphe,

and it is sometimes difficult to differentiate these two types of bicuspid aortic valves [14, 16, 18]. The majority of the bicuspid aortic valves belong to the acquired type of bicuspid valve as evidenced by the presence of three interleaflet triangles [7, 18].

Other anatomical variations are the unicuspid or quadricuspid aortic valve [16]. Unicuspid or quadricuspid valves occur very rarely but frequently develop stenosis or regurgitation throughout life.

Histology of the aortic valve and root wall

The aortic valve leaflet consists of three distinctive connective tissue layers covered by an endothelial cell layer on both the aortic and the ventricular side of the leaflet [19-20]. These three layers are the lamina fibrosa which is on the aortic side of the leaflet, the lamina spongiosa which is the middle layer and the lamina ventricularis which is on the ventricular side of the leaflet [21].

The lamina fibrosa is a dense layer of collagenous chords starting at the level of the commissures and running in circumferential direction towards the middle of the leaflet where the chords divide in smaller fibers forming a meshwork. The free edge of the leaflet is especially dense in collagenous fibers. The lamina fibrosa supports most of the diastolic pressure.

The lamina spongiosa is the middle layer which serves as a shock-absorber layer [21-22]. To fulfil this role, this layer contains only very few fibers but is composed of loose connective tissue mainly consisting of proteoglycans. The lamina spongiosa is relatively thick in the center of the leaflet but thins out towards the free edge.

The lamina ventricularis is a very thin layer consisting mainly of elastin fibers which are oriented in radial direction. Additionally, this layer contains smooth muscle cells. The lamina ventricularis is connected to the ventricular outflow tract [21].

The valve leaflet tissue is in constant tissue renewal and this tissue turn-over is maximal in the regions where stress is highest e.g. along the hinge point. This tissue turn-over is probably important to resist tissue wear [16].

A recent study demonstrated the vascularization of the aortic valve [23]. Vessels were found predominantly in the basal third of the cusps and extended in from the commissures almost to the level of the free edge. There was a significant difference between the presence of vessels in the basal part and the mid and free edge regions of the valve. There was no difference among the three cusps.

Innervation of the aortic valve arises from the ventricular endocardial plexus and is located in the lamina ventricularis [24]. The entire cusp contains nerve fibers with the exception of the coapting edge. The non-coronary cusp, which has no underlying ventricular endocardium, receives its innervation from the adjacent valve leaflets. Its innervation however is less dense than that of the two other cusps. The overall density of innervation decreases with age. It is unclear whether the innervation of the cusps plays a role in proper valve functioning [24].

The histology of the aortic root is characterized by a gradual shift from the muscular ventricle to the primarily elastic aorta [6]. The ascending aortic wall itself contains 3 layers which are, from intraluminal to extraluminal, the intima, the media and the adventitia. The media has a predominant circular 'lamellar' elastic architecture which is immediately proximal from the sinotubular ridge and further towards the aortic annulus, progressively interrupted by increasing amounts of collagenous tissue. The layers of elastic tissue eventually become thinner and subsequently disappear. It is at this level that the dense collagen bundles form the aortic annulus [6].

Pathological conditions of the aortic valve

These can either be aortic stenosis, aortic regurgitation or a combination of both, the so-called combined or mixed aortic valve disease. This paragraph will focus on the pathogenesis of aortic stenosis and aortic regurgitation. Mixed disease will not be discussed as this is a combination of both pathological conditions in a variable degree.

Aortic stenosis

Although aortic valves can become stenotic from several different causes, the large majority of them becomes stenotic because of congenital malformation or degenerative calcification [25-26]. Isolated aortic stenosis, in the absence of mitral valve disease, is uncommon in rheumatic heart disease [14, 16, 25-26]. The pathogenesis of rheumatic aortic valve disease is further explained in the section on aortic regurgitation.

Degenerative changes in the human body also affect the aortic valve and root. Aging causes a thickening of the collagen fibers in the aortic valve leaflets. These fibers also seem to lose their predominantly circumferential orientation [27]. In addition, aging aortic valves have an increased number of elastic fibers but this is most likely due to fragmentation rather than to an increase in the number of fibers present [28]. Other age-related changes include an accumulation of cellular degradation products such as lipids and calcium. This is probably due to an insufficient microvascular scavenging mechanism in the valve leaflets [29]. The presence of these cellular degradation products will increase the rate of calcification [29-30] and this phenomenon occurs initially at the sites of the highest mechanical stress in the aortic valve leaflets [31-32]. These areas are the hinge point of the aortic valve leaflet and the commissural area [31]. Once calcification is initiated at the leaflet attachment line, stress distribution on the remaining parts of the aortic valve leaflet is changed and the calcification then usually progresses along the line of coaptation [16].

These aging changes in the aortic valve leaflet result in an increasing valve thickening, stiffness and a decrease in extensibility of the valve leaflet [27, 29, 33-34].

Although up to 64% of patients with a bicuspid aortic valve have a normal life span without ever developing aortic valve pathology, about 50% of patients with aortic stenosis have a bicuspid aortic valve [25, 35-37]. The presence of a raphe might change the stress

distribution characteristics of the leaflet and therefore lead to calcification. However, the exact mechanism of calcification in bicuspid aortic valves is unknown. Edwards [38] suggested a mechanical trauma in the pathogenesis of bicuspid aortic valve stenosis. Indeed, the length of the free edge of the two valve leaflets is usually unequal. This unequal length creates abnormal contact between the two leaflets which in turn produces tension or mechanical trauma to the leaflet. This will result in focal fibrous thickening leading to dystrophic calcification. This hypothesis explains stenosis as a result of leaflet trauma but does not explain why other bicuspid aortic valves perform satisfactorily throughout a normal life span.

Aortic stenosis is considered the most frequent complication of a bicuspid aortic valve. Its clinical manifestation at a mean age of 56 to 59 years is earlier than in degenerative aortic stenosis (mean age of 62 to 72 years) whereas aortic stenosis in unicuspid valves occurs at an average age of 48 years [25].

Some other rare causes of aortic stenosis include Paget's disease, and end stage renal disease which both result in calcific aortic stenosis [39-40]. This subtype of aortic stenosis is an extreme form where the whole leaflet surface is calcified. Another rare cause of aortic stenosis is ochronosis, an inherited metabolic disorder [41].

The natural history of aortic stenosis in the adult is characterized by a prolonged latent period in which morbidity and mortality are very low [42-44]. Medical therapy during this time interval mainly consists of afterload reduction. The rate of progression of aortic stenosis is impossible to predict for a specific patient but the decrease in valve area is usually around 0.12 cm^2 per year or an increase in pressure gradient across the valve of about 15 mm Hg per year [42]. The development of symptoms such as angina, syncope or heart failure identifies a critical point in the natural history of aortic stenosis [42-44]. After the onset of symptoms, survival averages two to three years. Patients in heart failure due to a deteriorating left ventricular function are dead within one to two years. Sudden death is also possible in patients with aortic stenosis but has hardly ever been documented in patients without prior symptoms. Deteriorating left ventricular function or the onset of symptoms are therefore strong indicators for operative management of aortic stenosis.

The diagnosis of aortic stenosis is usually confirmed by echocardiography and/or angiography. Stress tests have proved to be unreliable, especially with coexisting coronary artery disease. The severity of aortic stenosis is expressed as a pressure gradient between the left ventricle and the aorta as wel as a measurement of the (reduced) aortic valve orifice area. Currently, an aortic valve area < 1 cm^2 and/or a ventricular-aortic gradient of > 50 mm HG, are considered an operative indication in asymptomatic patients with normal left ventricular function. Symptomatic patients or patients with a deteriorating left ventricular function due to aortic stenosis should be operated within a short time frame, even though the above criteria might not be matched. Accordingly, patients with milder disease may undergo concomitant aortic valve surgery when other indications for heart surgery necessitate earlier intervention [42-44].

Aortic regurgitation

Aortic regurgitation may result from diseases from either the aortic valve, the ascending aorta or both [45]. The most common causes of aortic regurgitation in this study were aortic root dilatation (37%), postinflammatory or rheumatic disease (29%), incomplete closure of a congenitally bicuspid aortic valve (24%), and infective endocarditis (6%).

In rheumatic fever, the aortic valve cusps become infiltrated with fibrous tissue, and retract. This causes failure of cusp coaptation during diastole and consequently, central aortic regurgitation will result [46]. The associated fusion of the commissures may also restrict aortic valve opening, resulting in combined aortic valve stenosis and regurgitation. As stated earlier, associated mitral valve disease is the rule in rheumatic heart disease.

Other primary valvular causes of aortic regurgitation include incomplete closure and/or leaflet prolapse of a bicuspid aortic valve. It is true that the most frequent complication of a bicuspid aortic valve is stenosis [16, 25, 44] but nevertheless, bicuspid aortic valve is the major cause of isolated aortic regurgitation, especially in the absence of ascending aortic or aortic root dilatation [47]. Moreover, regurgitant bicuspid aortic valves tend to occur at a younger age than stenosis [35]. The cusp prolapse usually affects the leaflet containing the raphe since the free edge of this leaflet is longer. Although much less frequent, cusp prolapse may also occur in tricuspid aortic valves [48].

Infective endocarditis may destroy, or cause perforation of a leaflet; alternatively, vegetations on the valve leaflets may interfere with proper cusp coaptation. All of these will lead to massive aortic regurgitation [44].

Less common causes of aortic valve regurgitation include trauma, rupture of a congenitally fenestrated valve and aortic regurgitation associated with systemic diseases like lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Syphilis and Takayasu's disease or associated with Whipple's and Crohn's disease [44]. Aortic regurgitation associated with prosthetic valve replacement will not be discussed here.

The incidence of patients undergoing surgery for pure aortic regurgitation secondary to aortic root disease with subsequent dilatation has steadily increased over the years and now accounts for about 50% of the cases [26]. Various conditions affecting the aortic wall produce dilatation of the sinotubular junction with secondary central aortic regurgitation [13]. Age-related changes affecting the aortic root and the ascending aorta include accumulation of ground substance, fragmentation of elastic fibers, gradual replacement of smooth muscle cells with collagen and focal medial necrosis [49]. The overall result is an increasing stiffness of the aortic root which also tends to dilate with age [50].

Other pathological conditions associated with dilatation of the aortic root include aortitis [51-54], Marfan syndrome [55], aortic dissection [56], hypertension [57], or other diseases associated with connective tissue abnormalities such as cystic medial necrosis [58], Ehlers-Danlos syndrome [59] or osteogenesis imperfecta [60]. All of these conditions do not primarily affect the aortic valve but the dilatation of the root and the resulting central aortic regurgitation may secondarily affect the valve leaflets which may thicken and retract,

thereby increasing the existing degree of regurgitation [44]. Interestingly, isolated dilatation of one or more of the sinuses of Valsalva without dilatation of the sinotubular junction does not cause aortic regurgitation [13]. Aortic regurgitation in association with a peri-membranous ventricular septal defect is an almost exclusively pediatric entity and will therefore not be discussed here.

The natural history of aortic regurgitation in patients with acute aortic regurgitation is different from patients with a gradual progressive 'chronic' aortic regurgitation [42-44]. Even a normal ventricle cannot sustain an acute severe volume overload. The risk of acute aortic regurgitation is therefore much higher than that of chronic aortic regurgitation and patients with acute regurgitation should promptly be referred for surgery since they will rapidly develop pulmonary edema and cardiogenic shock.

In contrast, chronic aortic regurgitation, even when severe, may be well tolerated for several years. Medical therapy in patients with normal left ventricular function should, besides diuretic therapy, also consist of afterload reduction since this diminishes the regurgitant volume and has been proven to delay the need for aortic valve replacement [43]. Patients with chronic aortic regurgitation should be followed echocardiographically at regular intervals to detect any progression of the disease, which is generally unpredictable. The onset of left ventricular dysfunction is an early marker of subsequent symptoms such as angina, dyspnea and heart failure. As in aortic stenosis, once the patient becomes symptomatic, the condition often deteriorates rapidly and survival in patients with heart failure generally does not exceed two years. Sudden death may occur but is not frequent and usually does so in previously symptomatic patients [42-44].

Aortic regurgitation is usually confirmed echocardiographically [61] and angio-graphically. Current indications for surgery include acute aortic regurgitation, severe regurgitation, whether or not in association with symptoms or a dilated left ventricle, left ventricular dysfunction and symptomatic patients [42-44, 62].

Surgical options for the failing aortic valve

Aortic stenosis

- Repair procedures

Although the majority of stenotic aortic valves will require valve replacement, there are some indications for 'alternative' techniques. Balloon aortic valvuloplasty initially relieves obstruction in most patients but restenosis due to scarring occurs in about half of the patients within 6 months [63]. Its role is currently limited to the management of severe aortic stenosis in non-surgical candidates such as patients requiring an urgent non-cardiac operation, in pregnant women, in patients refusing surgical treatment or as 'bridge' to aortic valve replacement in patients with severe heart failure, and an otherwise high operative risk [64-65].

Initial attempts for the repair of calcific aortic valve stenosis were carried out in the late fifties and early sixties [66]. Cusp perforation and postoperative aortic regurgitation were frequent problems and the technique was abandoned when mechanical valve prostheses became available. However, with the increasing experience and improving results of mitral valve repair [67], renewed interest in aortic valve repair became apparent. This mainly included aortic valve repair for regurgitation of different origins (see further). Some authors also attempted aortic valve repair in calcific or degenerative aortic valve stenosis, either by manual debridement [68-69] or with the aid of electrohydraulic shock waves or ultrasonic therapy [70-73]. Although decalcification as such is technically feasible and has the benefit of avoiding oral anticoagulation, early recalcification is not prevented [74]. Restenosis after manual debridement may lead to reoperation in up to 25% of the patients at 5 years [69]. These unacceptable results currently exclude widespread use of manual aortic valve debridement. Aortic valve debridement with the aid of electrohydraulic shock waves or ultrasonic therapy equally leads to unacceptable results since restenosis or aortic regurgitation occur in the majority of patients at short-term follow-up [71-72].

Duran has been the proponent of aortic valve repair in a predominantly rheumatic patient population. Since most of his reports deal with valve repair for rheumatic aortic regurgitation, some with associated aortic stenosis, but not for pure aortic stenosis, this topic will be discussed in the section on valve repair for aortic regurgitation.

In summary, aortic valve repair for predominantly aortic stenosis has been disappointing, and largely abandoned in favour of valve replacement.

- Valve replacement options

The present paragraph aims to give a brief overview of the currently available valve substitutes while focussing on the main issues for each category rather than going into detail on all available types of valve substitutes for each category.

1) Mechanical aortic valve replacement. Since the first successful mechanical aortic valve replacement by Harken et al. in 1960 [75], a whole scala on mechanical valve prostheses has been developed and tested clinically. From all pioneering devices, only the Starr-Edwards® valve stood the test of time, and its Silastic ball valve model 1200 and 1260 is currently still implanted. The long-term performance (up to 31 years) of this valve was recently documented by Lund et al. [76]. No structural failures were seen in their series, and the incidence of valve related complications was as follows: thrombo-embolism 2%/patient-year (pt-year), valve thrombosis 0.06%/pt-year, anticoagulation related bleeding 2.08%/pt-year, endocarditis 0.38%/pt-year, paravalvular leak 0.26%/pt-year, hemolysis 0.1%/pt-year for a total of any valve related complication of 4.89%/pt-year. When only major complications were considered, the incidence was 2%/pt-year.

In order to further improve the clinical performance of mechanical heart valves, first the tilting disk [77-78], and later the bileaflet valve design was proposed which ultimately resulted in the St Jude Medical heart valve, clinically introduced in 1977 [79]. Intermediate and longer term follow-up of this model established its clinical domination [80-82], and

provoked competitors to design other bileaflet prostheses aiming to offer the patient a better and safer valve prosthesis [83-89]. Reported figures of valve related complications depend of course on the size and characteristics of the patient cohort and the duration of follow-up. Overall, the clinical performance of the currently available bileaflet aortic valve prostheses is rather good: structural failure is hardly ever reported; thrombo-embolic and anti-coagulation related bleeding events are both in the range of 1 to 1.5%/pt-year; valve thrombosis is rare and its incidence is around 0.06%/pt-year; endocarditis is less then 0.5%/pt-year; hemolysis accounts for approximately 0.1%/pt-year and paravalvular leak for approximately 0.25%/pt-year; finally, the aortic valve reoperation incidence is slightly less than 1%/pt-year.

In summary, the currently available mechanical aortic valve prostheses perform satisfactory but are not free from valve related complications. Patients need life-long anticoagulation and to date, it remains uncertain what the clinical impact will be on the very long-term.

2) Bioprosthetic valve replacement. Bioprostheses do not require permanent anticoagulation and therefore minimize the risk of trombo-embolism and anticoagulant related bleeding that is inherent to all mechanical prosthetic valves. Besides, they also obviate the practical inconveniences associated with permanent anticoagulation.

Numerous stented bioprostheses have been introduced in clinical practice during the past three decades. The second generation bioprostheses of the early eighties (Hancock II® porcine bioprosthesis, and the Carpentier-Edwards Perimount® pericardial bioprosthesis) have better hemodynamic features and appear to be more durable than the first generation bioprostheses of the seventies (Standard Hancock®, Hancock MO® and Carpentier-Edwards® porcine bioprostheses)[90]. Whether this can be solely attributed to the lower pressure fixation in the more recent series is beyond the scope of this review.

Myken et al. demonstrated a substantial reduction of valve related complications in bioprostheses when compared to bileaflet mechanical valve prostheses. The 10-year freedom from valve related complications in the bioprosthesis group was 74% versus 59% in the mechanical valve group [91].

The major problem with stented bioprostheses however is their limited durability. Cuspal tears, degeneration, perforation, fibrosis and calcification are possible complications which seem to occur more frequently in the younger patient population as opposed to a more elderly patient group [92-93]. This is probably due to the increased calcium metabolism in the younger patient group.

Currently, the Carpentier-Edwards® bovine pericardial valve is the most frequently used aortic valve bioprosthesis. Its low incidence of valve related complications, associated with a freedom of structural valve deterioration of 93% at 12 years in patients older than 65 years of age, makes this prosthesis the valve substitute of choice in this age group [94].

In order to improve the available stented bioprostheses, much attention and effort has been spent during the past decade in the development of stentless (mostly porcine) bioprostheses. These valves have better hemodynamic properties than stented bioprostheses,

and they also seem to have a more substantial beneficial effect on restoring left ventricular mass and function [90]. Besides, they may have a reduced medium-term mortality rate as compared to stented bioprostheses [95]. Whether the long-term durability will also be enhanced remains to be proven.

Stimulated by the favourable results with the Carpentier-Edwards® bovine pericardial valve, efforts have been undertaken to design a stented bioprosthesis made intra-operatively of autologous gluteraldehyde fixed pericardium. Results with this technique however have been disappointing and the idea was abandoned [96].

In summary, bioprosthetic valves obviate permanent anticoagulation, have a low incidence of trombo-embolic and bleeding complications but are limited by a substantial incidence of structural failure in patients of less than 65 years of age.

3) Homograft valve replacement. Homografts share the advantage of bioprostheses in avoiding the need of anticoagulation. Consequently, they have a very low thrombogenicity rate. Their hemodynamics are superior to those of stented bioprostheses and their clinical performance is excellent [97-99]. The incidence of valve related complications was given in the study by Lund et al. [99]: anticoagulant-related bleeding 0.09%/pt-year; embolism 1.4%/pt-year; endocarditis 0.6%/pt-year and tissue failure 4.5%/pt-year.

Limited availability and tissue failure restrict the use of homografts. Indeed, the overall freedom from tissue failure in the study from Lund et al. was 62 and 18% at 10 and 20 years respectively. This was however highly dependent on donor and recipient age with the best freedom of tissue failure obtained in a 70 year old recipient and a 30 year old donor. In this case, freedom from tissue failure was 91 and 64%, also at 10 and 20 years. Also, the technique of homograft insertion seems an important predictor. Basically, two techniques are used for homograft implantation: the subcoronary and the root replacement technique. In the paper by Lund et al. the root replacement group did significantly better with regard to tissue failure and subsequent aortic valve reoperation incidence. Freedom from tissue failure at 15 years in the root replacement group was 56% versus 33% with the subcoronary technique. The fact that their patient population mainly consisted of subcoronary implants may have adversely influenced the overall results of this study. Homografts are currently mainly indicated as root replacement in the treatment of native, or prosthetic valve endocarditis with excellent clinical results and a freedom from recurrent endocarditis of 98% at 5 years [100].

4) Pulmonary autograft for aortic valve replacement (Ross procedure).The use of the autologous pulmonary valve to replace the aortic valve was first described by Ross in 1967 [101]. A homograft is then used in the pulmonary position to replace the patients' own pulmonary valve. The initial technique employed a subcoronary implantation, and long-term follow-up of the initial series showed a 23% reoperation rate for severe regurgitation of the autograft [102]. Currently, most authors use the root replacement technique while some favor the inclusion technique [103-104]. The advantages of the pulmonary autograft over the homograft include increased cellular viability and therefore possible enhanced

durability; an additional advantage is the growth potential of the autograft in children [103]. However, as this procedure implies a double valve replacement, the operation is technically much more complex and demanding than the homograft aortic valve replacement. Therefore, the Ross procedure is currently considered the valve substitute of choice in children and young adults. In a recent report by Elkins et al. [105] the freedom from autograft reoperation was 90% at 8 years and the freedom from reoperation on the homograft in the pulmonary position was 94%, also at 8 years. There were no other valve related complications such as thrombo-embolism, bleeding or endocarditis.

A point of concern exists with regard to dilatation of the pulmonary autograft when used as a root replacement. This dilatation occurs immediately postoperatively and progresses somewhat further during follow-up [106]. However, when the inclusion technique is used, the dilatation seems much less and growth potential is preserved [103].

Aortic regurgitation

- Repair procedures

Although some attempts were made in the early years of cardiac surgery to repair insufficient aortic valves [107-109], it is only in the eighties that recurrent interest resulted in consistent techniques with regard to specific pathological conditions.

The incidence of rheumatic fever has markedly decreased in Western Europe and Northern America [45], but in some parts of the world, it is still considerable. It is in this patient population that Duran developed his reconstructive techniques for predominantly regurgitant, rheumatic aortic valve disease. He applied these repair techniques in patients undergoing surgery primarily for mitral valve disease, and in whom it was desirable to save the aortic valve, particularly when a mitral valve repair had been possible. In a series of publications [110-114] he described his techniques. In rheumatic aortic valvular disease, regurgitation is mainly caused by decreased cusp mobility (Fig. 3). At the level of the commissure, increased mobility can be obtained by calcium excision and/or commissurotomy. Moderate leaflet edge retraction can be suppressed by free edge unrolling, or shaving whereas severe retraction will need cusp extension with autologous pericardium. Finally, Duran often adds a sinotubular ridge enhancement since this induces an earlier aortic valve closure [115] (Fig. 3).

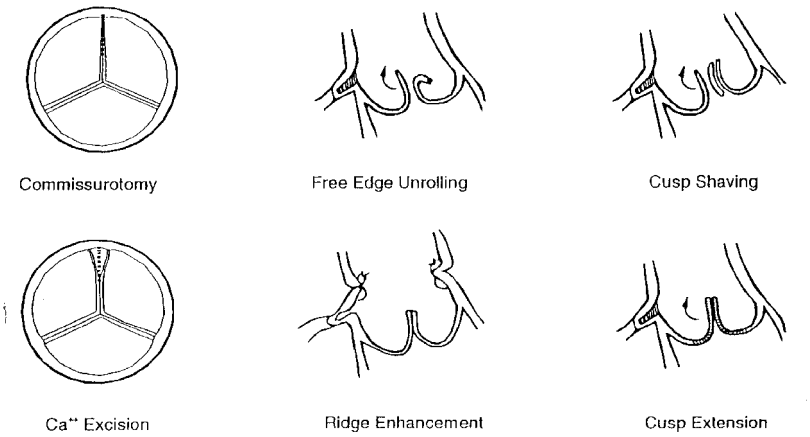

Figure 3: *Diagram of aortic valve lesions and corresponding repair techniques. Aortic regurgitation with decreased cusp mobility. (From: Duran CMG. Aortic valve repair and reconstruction. Oper Techn in Cardiothorac Surg 1996;1:15-29. Reprinted with permission from W.B. Saunders Company and CMG Duran).*

Although early and mid-term follow-up results reported by Duran were encouraging [110-114], and prompted further investigation of the applicability of these techniques, at least by himself, virtually no other authors have reported similar results on this topic which questions the reproducibility of these surgical strategies. In addition, a recent report by Bernal et al., who did a follow-up study of the initial patient population operated by Duran in Spain, showed a disappointingly low freedom from repaired aortic valve structural deterioration of 25.3% at 22 years [116].

For the above mentioned reasons, it is questionable whether there remains any place for aortic valve repair in rheumatic valvular heart disease, except in countries where adequate control of anticoagulation is not feasible.

Other pathological conditions leading to aortic regurgitation, such as cusp prolapse, aortic root and/or sinotubular dilatation regardless of the cause, are more amenable to repair and they constitute the basis of this thesis. Cusp perforation due to endocarditis, reparable with a patch of autologous pericardium, is not further described since this occurs only very seldom.

- Aortic valve replacement

All devices used for aortic valve replacement in aortic stenosis are also applicable in aortic regurgitation. However, results of the Ross procedure for pure aortic regurgitation show an increased rate of recurrent aortic regurgitation during follow-up when compared to aortic stenosis as operative indication [117]. At presence, it is yet unclear whether the Ross procedure should be limited to patients with aortic stenosis.

Combined aortic stenosis and regurgitation

The etiology and morphology in this group is similar to that of aortic stenosis. Accordingly, treatment principles and options follow [118].

Aim of the present thesis

Given the poor results of aortic valve repair in aortic stenosis, and rheumatic aortic regurgitation as discussed above, the present thesis focuses on possible indications for adult aortic valve repair in regurgitation due to other causes. Chapter 2 examines the results of bicuspid aortic valve repair for leaflet prolapse, whereas chapter 3 looks at the results of leaflet prolapse repair in tricuspid aortic valves. Chapter 4 studies the durability of aortic valve preservation in Type A dissection, and chapter 5 reports the initial results of the aortic valve reimplantation technique for the treatment of aortic regurgitation due to dilatation of the aortic root and sino-tubular junction. The present thesis investigates the feasibility and the durability of all these procedures. Essential in these reparative techniques is the presence of (near to) normal valve tissue in order to obtain the best result possible.

All of these techniques avoid the need for permanent anticoagulation. If durability of the techniques could be demonstrated, avoidance of anticoagulation might be an additional benefit, particularly if applied in young patients who still have a long life-expectancy. In order to study the incidence, frequency and severity of very long-term anticoagulation related complications, a follow-up study was undertaken of all patients undergoing a mechanical aortic valve replacement at the St. Antonius Hospital in Nieuwegein, The Netherlands between December 1963 and January 1st 1974, representing the first 10-year experience of mechanical aortic valve replacement at this institution. This study is the subject of chapter 6.

Chapter 7 is a discussion of the obtained results and a correlation with clinical practice. Finally, chapter 8 is a summary of the present thesis.

References

1. Silver MA, Roberts WC. Detailed anatomy of the normally functioning aortic valve in hearts of normal and increased weight. Am J Cardiol 1985;55:454-461.
2. Vollebergh FEMG, Becker AE. Minor congenital variations of cusp size in tricuspid aortic valves: possible link with isolated aortic stenosis. Br Heart J 1977;39:1006-1011.
3. Thubrikar M, Piepgrass WC, Shaner TW, Nolan SP. The design of the normal aortic valve. Am J Physiol 1981;241:H795-801.
4. Kunzelman KS, Grande KJ, David TE, Cochran RP, Verrier ED. Aortic root and valve relationships. Impact on surgical repair. J Thorac Cardiovasc Surg 1994;107:162-170.
5. Mercer JL, Benedicty M, Bahnson HT. The geometry and construction of the aortic leaflet. J Thorac Cardiovasc Surg 1973;65:511-518.
6. Sutton III JP, Ho SY, Anderson RH. The forgotten interleaflet triangles: a review of the surgical anatomy of the aortic valve. Ann Thorac Surg 1995;59:419-427.
7. Anderson RH, Devine WA, Ho SY, Smith A, McKay R. The myth of the aortic annulus: the anatomy of the subaortic outflow tract. Ann Thorac Surg 1991;52:640-646.
8. Zimmerman J. The functional and surgical anatomy of the heart. Ann R Coll Surg Engl 1966; 39:348-366.
9. Reid K. The anatomy of the sinus of Valsalva. Thorax 1970;25:79-85.
10. Robicsek F. Leonardo da Vinci and the sinuses of Valsalva. Ann Thorac Surg 1991;52:328-335.
11. Brewer RJ, Deck JD, Capati B, Nolan SP. The dynamic aortic root. Its role in aortic valve function. J Thorac Cardiovasc Surg 1976;72:413-417.
12. Corrigan DJ. Permanent patency of the mouth of the aorta. Edinburgh Med Surg 1832;37:111.
13. Furukawa K, Ohteki H, Cao ZL, et al. Does dilatation of the sinotubular junction cause aortic regurgitation ? Ann Thorac Surg 1999;68:949-954.
14. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. Am J Cardiol 1970; 26:72-83.
15. Campbell M. Calcific aortic stenosis and congenital bicuspid aortic valves. Br Heart J 1968; 30:606-616.
16. Thubrikar M. Diseases of the aortic valve. In Thubrikar M. 'The aortic valve' CRC press, Boca Raton FL, USA, 1990:157-174.
17. Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. J Am Coll Cardiol 1997;30:1809-1812.
18. Angelini A, Ho SY, Anderson RH, et al. The morphology of the normal aortic valve as compared with the aortic valve having two leaflets. J Thorac Cardiovasc Surg 1989;98:362-367.
19. Deck JD. Orientation of endothelial cells on surfaces of aortic valve leaflets in dogs. Anat Rec 1979;193:518.
20. Deck JD. Endothelial cell orientation on aortic valve leaflets. Cardiovasc Res 1986;20:760-767.
21. Clark RE, Finke EH. Scanning and light microscopy of human aortic leaflets in stressed and relaxed states. J Thorac Cardiovasc Surg 1974;67:792-804.
22. Swanson WM, Clark RE. Dimensions and geometric relationships of the human aortic valve as a function of pressure. Circ Res 1974;35:871-882.
23. Weind KL, Ellis CG, Boughner DR. The aortic valve blood supply. J Heart Valve Dis 2000;9:1-8.
24. Marron K, Yacoub MH, Polak JM, et al. Innervation of human atrioventricular and arterial valves. Circulation 1996;94:368-375.
25. Subramanian R, Olson LJ, Edwards WD. Surgical pathology of pure aortic stenosis: a study of 374 cases. Mayo Clin Proc 1984;59:683-690.

26. Dare AJ, Veinot JP, Edwards WD, Tazelaar HD, Schaff HV. New observations on the etiology of aortic valve disease: a surgical pathologic study of 236 cases from 1990. Hum Pathol 1993;24:1330-1338.
27. Sell S, Scully R. Aging changes in the aortic and mitral valves. Am J Pathol 1965;46:345-365.
28. Fleg JL. Alterations in cardiovascular structure and function with advancing age. Am J Cardiol 1986;57:33C-44C.
29. Kim KM, Valigorsky JM, Mergner WJ, Jones RT, Pendergrass RF, Trump BF. Aging changes in the human aortic valve in relation to dystrophic calcification. Hum Pathol 1976;7:47-60.
30. Schoen FJ. Interventional and surgical cardiovascular pathology: clinical correlations and basic principles. W.B. Saunders Co., Philadelphia, 1989.
31. Thubrikar MJ, Nolan SP, Aouad J, Deck JD. Stress sharing between the sinus and leaflets of canine aortic valve. Ann Thorac Surg 1986;42:434-440.
32. Thubrikar MJ, Aouad J, Nolan SP. Patterns of calcific deposits in operatively excised stenotic or purely regurgitant aortic valves and their relation to mechanical stress. Am J Cardiol 1986;58:304-308.
33. Sahasakul Y, Edwards WD, Naessens JM, Tajik AJ. Age-related changes in aortic and mitral valve thickness: Implications for two-dimensional echocardiography based on an autopsy study of 200 normal human hearts. Am J Cardiol 1988;62:424-430.
34. Christie G, Baratt-Boyes B. Age-dependant changes in the radial stretch of human aortic valve leaflets determined by biaxial testing. Ann Thorac Surg 1995;60(suppl):156-159.
35. Fenoglio JJ, McAllister HA, DeCastro CM, Davia JE, Cheitlin MD. Congenital bicuspid aortic valve after age 20. Am J Cardiol 1977;39:164-169.
36. Hallgrimsson J, Tulinius H. Chronic non-rheumatic aortic valvular disease: a population study based on autopsies. J Chron Dis 1979;32:355-363.
37. Mills P, Leech G, Davies M, Leatham A. The natural history of a non-stenotic bicuspid aortic valve. Br Heart J 1978;40:951-957.
38. Edwards JE. The congenital bicuspid aortic valve. Circulation 1961;23:485-488.
39. Strickberger SA, Schulman SP, Hutchings GM. Association of Paget's disease of bone with calcific aortic valve disease. Am J Med 1987;82:953-956.
40. Maher ER, Young G, Smyth-Walsh B, et al. Aortic and mitral valve calcification in patients with end stage renal diseases. Lancet 1987;II:875-877.
41. Casselman F, Herijgers P, Meyns B, Daenen W. Aortic stenosis in endogenous ochronosis. J Heart Valve Dis 1999;8:445-446.
42. Bonow RO, Carabello B, de Leon AC Jr, et al. ACC/AHA Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology / American Heart Association task force on practice guidelines (Committee on management of patients with valvular heart disease). Circulation 1998;98:1949-1984.
43. Rahimtoola SH. Aortic valve disease. In Alexander RW, Schlant RC and Fuster V, Editors 'Hurst's - The Heart' McGraw-Hill, New York, 1998:1759-1785.
44. Braunwald E. Valvular heart disease. In Braunwald E 'Heart disease: A textbook of cardiovascular medicine' W.B. Saunders Co., Philadelphia, 1997:1007-1076.
45. Olson LJ, Subramanian R, Edwards WD. Surgical pathology of pure aortic insufficiency: a study of 225 cases. Mayo Clin Proc 1984;59:835-841.
46. Schoen FJ, St John Sutton M. Contemporary pathologic considerations in valvular disease. In Virmani R, Atkinson JB and Feuoglio JJ (eds.) 'Cardiovascular pathology' W.B. Saunders Co., Philadelphia, 199: 334.
47. Otto C. Aortic valve insufficiency: changing concepts in diagnosis and management. Cardiologia 1996;41:505-513.
48. Carter JB, Sethi S, Lee GB, Edwards JE. Prolapse of semilunar cusps as causes of aortic insufficiency. Circulation 1971;43:922-932.

49. Schlatmann TJ, Becker AE. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. Am J Cardiol 1977;39:13-20.
50. Dobrin PB. Pathophysiology and pathogenesis of aortic aneurysms. Current concepts. Surg Clin North Am 1989;69:687-703.
51. Heggtveit HA. Syphilitic aortitis: a clinicopathologic autopsy study of 100 cases, 1950 to 1960. Circulation 1964;29:346-355.
52. Honig HS, Weintraub AM, Gomes MN, Hufnagel CA, Roberts WC. Severe aortic regurgitation secondary to idiopathic aortitis. Am J Med 1977;63:623-633.
53. Akikusa B, Kondo Y, Muraki N. Aortic insufficiency caused by Takayasu's arteritis without usual clinical features. Arch Pathol Lab Med 1981;105:650-651.
54. How J, Strachan RW. Aortic regurgitation as a manifestation of giant cell arteritis. Br Heart J 1978;40:1052-1054.
55. Roberts WC, Honig HS. The spectrum of cardiovascular disease in the Marfan syndrome: a clinico-morphologic study of 18 necropsy patients and comparison to 151 previously reported necropsy patients. Am Heart J 1982;104:115-135.
56. Fann JI, Glower DD, Miller DC, et al. Preservation of aortic valve in Type A aortic dissection complicated by aortic regurgitation. J Thorac Cardiovasc Surg 1991;102:62-75.
57. Waller BF, Zoltick JM, Rosen JH, et al. Severe aortic regurgitation from systemic hypertension (without aortic dissection) requiring aortic valve replacement: analysis of four patients. Am J Cardiol 1982;49:473-477.
58. Ferlic RM, Goott B, Edwards JE, Lillehei CW. Aortic valvular insufficiency associated with cystic medial necrosis: surgical and pathologic considerations. Ann Surg 1967;165:1-9.
59. Leier CV, Call TD, Fulkerson PK, Wooley CF. The spectrum of cardiac defects in the Ehlers-Danlos syndrome, types I and III. Ann Intern Med 1980;92:171-178.
60. Stein D, Kloster FE. Valvular heart disease in osteogenesis imperfecta. Am Heart J 1977;94:637-641
61. Perry G, Helmcke F, Nanda N, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9:952-959.
62. Klodas E, Enrique-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. J Am Coll Cardiol 1997;30:746-752.
63. Otto CM, Mickel MC, Kennedy JW, et al. Three-year outcome after balloon aortic valvuloplasty: insights into prognosis of valvular aortic stenosis. Circulation 1994;89:642-650.
64. Moreno PR, Jang IK, Newell JB, et al. The role of percutaneous aortic balloon valvuloplasty in patients with cardiogenic shock and critical aortic stenosis. J Am Coll Cardiol 1994;23:1071-1075.
65. Angel JL, Chapman C, Knuppel RA. Percutaneous balloon aortic valvuloplasty in pregnancy. Obstet Gynecol 1988;72:438-440.
66. Mulder DG, Kattus AA, Longmire WP. The treatment of acquired aortic stenosis by valvuloplasty. J Thorac Cardiovasc Surg 1960;40:731-743.
67. Carpentier A. Cardiac valve surgery: the 'French correction'. J Thorac Cardiovasc Surg 1983; 86:323-337.
68. Shapira N, Lemole GM, Fernandez J, et al. Aortic valve repair for aortic stenosis in adults. Ann Thorac Surg 1990;50:110-120.
69. Weinschelbaum E, Stutzbach P, Oliva M, Zaidman J, Torino A, Gabe E. Manual debridement of the aortic valve in elderly patients with degenerative aortic stenosis. J Thorac Cardiovasc Surg 1999;117:1157-1165.
70. Worley SJ, King M, Edwards WD, Holmes DR. Electrohydraulic shock wave decalcification of stenotic aortic valves: postmortem and intraoperative studies. J Am Coll Cardiol 1988;12:458-462.

71. Freeman WK, Schaff HV, Orszulak TA, Tajik AJ. Ultrasonic aortic valve decalcification: serial Doppler echocardiographic follow-up. J Am Coll Cardiol 1990;16:623-630.
72. McBride LR, Naunheim KS, Fiore AC, et al. Aortic valve decalcification. J Thorac Cardiovasc Surg 1990;100:36-43.
73. Kellner HJ, Pracki P, Hildebrandt A, Binner C, Eisele G, Struck E. Aortic valve debridement by ultrasonic surgical aspirator in degenerative, aortic valve stenosis: follow-up with Doppler echocardiography. Eur J Cardiothorac Surg 1996;10:498-504.
74. Dahm M, Dohmen G, Groh E, et al. Decalcification of the aortic valve does not prevent early recalcification. J Heart Valve Dis 2000;9:21-26.
75. Harken DE, Soroff HS, Taylor WJ, Lefemine AA, Gupta SK, Lunzer S. Partial and complete prostheses in aortic insufficiency. J Thorac Cardiovasc Surg 1960;40:744-762.
76. Lund O, Pilegaard HK, Ilkjaer LB, Nielsen SL, Arildsen H, Albrechtsen OK. Performance of the Starr-Edwards aortic cloth covered valve, track valve, and silastic ball valve. Eur J Cardiothorac Surg 1999;16:403-413.
77. Daenen W, Nevelsteen A, van Cauwelaert P, de Maesschalk E, Willems J, Stalpaert G. Nine years' experience with the Bjork-Shiley prosthetic valve: early and late results of 932 valve replacements. Ann Thorac Surg 1983;35:651-663.
78. Daenen W, Van Kerrebroeck C, Stalpaert G, Mertens B, Lesaffre E. The Bjork-Shiley monostrut valve. Clinical experience in 647 patients. J Thorac Cardovasc Surg 1993;106:918-927.
79. Emery RW, Mettler E, Nicoloff DM. A new cardiac prosthesis: the St Jude Medical cardiac valve. In vivo results. Circulation 1979;30:48-54.
80. Duncan MJ, Cooley DA, Reul GJ, et al. Durability and low thrombogenicity of the St Jude Medical valve at 5-year follow-up. Ann Thorac Surg 1986;42:500-505.
81. Czer LSC, Chaux A, Matloff JM, et al. Ten-year experience with the St Jude Medical valve for primary valve replacement. J Thorac Cardiovasc Surg 1990;100:44-55.
82. Fernandez J, Laub GW, Adkins MS, et al. Early and late-phase events after valve replacement with the St Jude Medical prosthesis in 1200 patients. J Thorac Cardiovasc Surg 1994;107:394-407.
83. de Luca L, Vitale N, Giannolo B, Cafarella G, Piazza L, Cotrufo M. Mid-term follow-up after heart valve replacement with Carbomedics bileaflet prostheses. J Thorac Cardiovasc Surg 1993; 106:1158-1165.
84. Copeland JG. The Carbomedics prosthetic heart valve: a second generation bileaflet prosthesis. Semin Thorac Cardiovasc Surg 1996;8:237-241.
85. Van Nooten G, Caes F, Francois K, Missault L, Van Belleghem Y. Clinical experience with the first 100 ATS heart valve implants. Cardiovasc Surg 1996;4:288-292.
86. Westaby S, Van Nooten G, Sharif H, Pillai R, Caes F. Valve replacement with the ATS open pivot bileaflet prosthesis. Eur J Cardiothorac Surg 1996;10:660-665.
87. Flameng W, Vandeplas A, Narine K, Daenen W, Herijgers P, Herregods M. Postoperative hemodynamic study of two bileaflet heart valves in aortic position. J Heart Valve Dis 1997;6:269-273.
88. Casselman F, Herijgers P, Meyns B, Flameng W, Daenen W. The Bicarbon heart valve prosthesis: short-term results. J Heart Valve Dis 1997;6:410-415.
89. Borman JB, Brands WGB, Camilleri L, et al. Bicarbon valve – European multicenter clinical evaluation. Eur J Cardiothorac Surg 1998;13:685-693.
90. David TE. Aortic valve surgery : where we are and where we shall go. J Heart Valve Dis 1999; 8:495-498.
91. Myken P, Caidahl K, Larsson P, Larsson S, Wallentin I, Berggren H. Mechanical versus biological valve prosthesis: a ten year comparison regarding function and quality of life. Ann Thorac Surg 1995;60(suppl):447-452.

92. Kopf GS, Geha AS, Hellenbrand WE, Kleinman CS. Fate of left-sided cardiac bioprosthesis valves in children. Arch Surg 1986;121:488-490.
93. Pupello DF, Bessone LN, Hiro SP, et al. Bioprosthesis longevity in the elderly: an 18-year longitudinal study. Ann Thorac Surg 1995;60(suppl):270-275.
94. Banbury MK, Cosgrove DM, Lytle BW, Smedira NG, Sabik JF, Saunders CR. Long-term results of the Carpentier-Edwards pericardial aortic valve: a 12-year follow-up. Ann Thorac Surg 1998;66(suppl):73-76.
95. David TE, Puschmann R, Ivanov J, et al. Aortic valve replacement with stentless and stented porcine valves: a case-match study. J Thorac Cardiovasc Surg 1998;116:236-241.
96. Gross C, Simon P, Grabenwoger M, et al. Midterm results after aortic valve replacement with the autologous tissue cardiac valve. Eur J Cardiothorac Surg 1999;16:533-539.
97. O'Brien MF, Stafford EG, Gardner MAH, et al. Allograft aortic valve replacement: long-term follow-up. Ann Thorac Surg 1995;60(suppl):65-70.
98. Yacoub M, Rasmi NRH, Sundt TM, et al. Fourteen-year experience with homovital homografts for aortic valve replacement. J Thorac Cardiovasc Surg 1995;110:186-194.
99. Lund O, Chandrasekaran V, Grocott-Mason R, et al. Primary aortic valve replacement with allografts over twenty-five years: valve-related and procedure-related determinants of outcome. J Thorac Cardiovasc Surg 1999;117:77-91.
100. Dossche KM, Brutel de la Riviere A, Morshuis WJ, Schepens MA, Ernst SM. Aortic root replacement with human tissue valves in aortic valve endocarditits. Eur J Cardiothorac Surg 1997;12:47-55.
101. Ross DN. Replacement of aortic and mitral valves with a pulmonary autograft. Lancet 1967;2:956-958.
102. Chambers JC, Somerville J, Stone S, Ross DN. Pulmonary autograft procedure for aortic valve disease: long-term results of the pioneer series. Circulation 1997;96:2206-2214.
103. Elkins RC, Knott-Craig CJ, Ward KE, McCue C, Lane MM. Pulmonary autograft in children: realized growth potential. Ann Thorac Surg 1994;57:1387-1394.
104. David TE, Omran A, Ivanov J, et al. Dilatation of the pulmonary autograft after the Ross procedure. J Thorac Cardiovasc Surg 2000;119:210-220.
105. Elkins RC, Knott-Craig CJ, Ward KE, Lane MM. The Ross operation in children: 10-year experience. Ann Thorac Surg 1998;65:496-502.
106. Hokken RB, Bogers AJJ, Taams MA, et al. Does the pulmonary autograft in the aortic position in adults increase in diameter? An echocardiographic study. J Thorac Cardiovasc Surg 1997; 113:667-674.
107. Taylor WJ, Thrower WB, Black H, Harken DE. The surgical correction of aortic insufficiency by circumclusion. J Thorac Surg 1958;35:192-205.
108. Cabrol C, Guiraudon G, Bertrand M. Le traitement de l'insuffisance aortique par l'annuloplastie aortique. Arch Mal Cœur 1966;59:1305-1312.
109. Frater RWM. The prolapsing cusp. Experimental and clinical observations. Ann Thorac Surg 1967;3:63-67.
110. Duran CMG, Alonso J, Gaite L, et al. Long-term results of conservative repair of rheumatic aortic valve insufficiency. Eur J Cardiothorac Surg 1988;2:217-223.
111. Duran CG. Reconstructive techniques for rheumatic aortic valve disease. J Card Surg 1988;3:23-28.
112. Duran C, Kumar N, Gometza B, Al Halees Z. Indications and limitations of aortic valve reconstruction. Ann Thorac Surg 1991;52:447-454.
113. Duran CMG. Present status of reconstructive surgery for aortic valve disease. J Card Surg 1993; 8:443-452.
114. Duran CMG. Aortic valve repair and reconstruction. Oper Techn in Cardiothorac Surg 1996;1:15-29.
115. Duran CMG, Balasundaram S, Bianchi S, et al. Hemodynamic effect of supraaortic ridge enhancement on the closure mechanism of the aortic valve and its implication in aortic valve repair. Thorac Cardiovasc Surgeon 1990;38:6-10.

116. Bernal JM, Fernandez-Vals M, Rabasa JM, Gutierrez-Garcia F, Morales C, Revuelta JM. Repair of nonsevere rheumatic aortic valve disease during other valvular procedures: is it safe? J Thorac Cardiovasc Surg 1998;115:1130-1135.
117. Dossche KM, Brutel de la Riviere A, Morshuis WJ, Schepens MA, Ernst SM, van den Brand JJ. Aortic root replacement with the pulmonary autograft: an invariably competent aortic valve ? Ann Thorac Surg 1999;68:1302-1307.
118. Kirklin JW, Baratt-Boyes BG. Aortic valve disease. In Kirklin JW, Baratt-Boyes BG eds. 'Cardiac surgery', Churchill Livingstone Inc., New York, 1993:491-571.

CHAPTER 2

Intermediate-term durability of bicuspid aortic valve repair for prolapsing leaflet

Filip P. Casselman M.D.[1], A. Marc Gillinov M.D.[1], Rami Akhrass M.D.[1], Vigneshwar Kasirajan M.D.[1],Eugene H. Blackstone M.D.[1,2] and Delos M. Cosgrove M.D.[1]

Departments of Thoracic and Cardiovascular Surgery[1] and Biostatistics and Epidemiology[2]
The Cleveland Clinic Foundation, Cleveland, Ohio USA

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Abstract

Objective: To determine the durability of repair of a bicuspid aortic valve with leaflet prolapse, and to identify factors associated with repair failure.
Methods: From November 1988 to January 1997, 94 patients with a bicuspid aortic valve and regurgitation from leaflet prolapse had aortic valve repair. In 66 patients, the repair employed triangular resection of the prolapsing leaflet. The remainder underwent mid-leaflet plication of the prolapsing leaflet. Mean age was 38±10 years and 93% were male. Median follow-up was 5.5 years (range 0.2 to 9 years). Factors associated with aortic valve competence and durability were identified by multivariable logistic and hazard function analyses.
Results: Early valve competence was more difficult to achieve in patients with large, poor functioning ventricles (P=0.02). Aortic valve reoperation was necessary in 12 patients that included three re-repairs and nine aortic valve replacements. Freedom from reoperation was 95%, 87% and 84% at 1, 5 and 7 years, respectively. The instantaneous risk of reoperation was highest immediately after operation, and fell rapidly to approximately 2% per year and less after two years. The only risk factor identified was the presence of residual aortic regurgitation (trace to mild in 35 cases) on immediate intraoperative post-repair transesophageal echocardiography. Late aortic regurgitation did not progress detectably across time ($P=0$.3). There were no deaths, early or late.
Conclusion: Bicuspid aortic valve repair for prolapsing leaflet is a safe procedure with good intermediate-term outcome. However, any residual aortic regurgitation jeopardizes repair durability and initial repair achievement is more difficult in patients with dilated, poor functioning ventricles.

Introduction

Advantages of aortic valve repair over aortic valve replacement include avoidance of anticoagulation and prosthetic valve-related complications. Aortic valve repair may be of particular benefit in young patients, who would be more likely to experience prosthetic valve-related morbidity over a long life-span.

Although early results of aortic valve repair are good [1, 2], intermediate and long-term results of aortic valve repair have not been reported. This study was primarily undertaken to assess the intermediate-term results of aortic valve repair for aortic regurgitation caused by prolapsing bicuspid aortic valve. A secondary goal was to identify factors associated with repair failure.

Materials and methods

Inclusion criteria

Between November 1988 and January 1997, 435 patients underwent an aortic valve reparative procedure at The Cleveland Clinic Foundation. This represents 9.7% of the total aortic valve procedures during the same period. A prolapsing leaflet was present in 136 aortic valves, of which 105 were bicuspid. Ninety-four of these patients were operated upon by the same surgeon (DMC), which constitutes the patient cohort for this report.

Patient characteristics

Mean age was 38±10 (standard deviation, SD) years (range 16 to 67). Ninety-three percent was male. In 74 cases (78.7%), the fused leaflets in the bicuspid valves were the right and left; in 12 patients (12.8%), the fusion was between the right and the non-coronary cusp and in eight patients (8.5%) between the non-coronary and left cusp.

Preoperative New York Heart Association (NYHA) functional class was I in 37 (39.2%) patients, II in 49 (52.1%) patients, III in seven (7.4%) patients and IV in one (1%) patient.

Isolated aortic valve repair was performed in 80 patients. Concomitant procedures included mitral valve repair in eight patients, coronary artery bypass grafting (CABG) in two, and ascending aortic aneurysm repair in four. Two patients had previously undergone coarctation repair, one patient CABG, and one patient congenital aortic balloon valvuloplasty.

Preoperative assessment

All patients had a preoperative Doppler echocardiogram to assess aortic valve pathology, according to previously described criteria [3-5], to determine left ventricular function [6] and left ventricular end-diastolic diameter. Preoperative aortic regurgitation distribution

was 2+ in five patients, 3+ in 28 patients, and 4+ in 61 patients. While 80 patients had no aortic stenosis on the preoperative echocardiography, 12 patients had mild aortic stenosis and two moderate. There were only two patients whose left ventricle was not dilated preoperatively, and the mean left ventricular end-diastolic diameter was 7.0±0.8 cm. Preoperative left ventricular function was normal in 46 patients, mildly impaired in 30, moderately impaired in 13, moderately to severely impaired in three, and severely impaired in two. Coronary catheterization was performed in patients with significant risk factors or who were older than 45 years of age.

Repair technique

Initially, full midline sternotomy was used; however, since January 1996 all isolated valve procedures have been performed via minimally invasive approach (n = 13). After the patient was placed on cardiopulmonary bypass, the aortic valve repair and any concomitant procedure was performed under single aortic cross-clamp. The heart was protected by a variety of techniques throughout the years. The mean aortic cross-clamp and cardio-pulmonary bypass times were 47±17 minutes and 60±28 minutes respectively.

All patients had a commissuroplasty. In addition, further elimination of the prolapsing area was by triangular resection and linear closure in 66 (70%) cases or leaflet plication opposite the raphe in 28 (30%) cases. During the study period, the use of triangular resection decreased in favor of plication (P<0.0001, Table 1). Other interventions on the aortic valve are listed in Table 2. Details of the aortic valve repair are described in earlier publications [7, 8].

Table 1: Decrease in prevalence of triangular resection (vs. plication) in recent experience.

		Triangular Resection	
Year of Operation	**N**	**No.**	**%**
1988	2	2	100
1989	11	11	100
1990	15	15	100
1991	14	11	79
1992	15	13	87
1993	12	5	42
1994	3	2	67
1995	8	4	50
1996	14	3	21
Total	**94**	**66**	**70**

P (logistic trend over time) <0.0001

Assessment of repair and durability

All patients had an immediate intraoperative post-repair transesophageal echocardiogram (TEE) to assess the repair. Residual aortic regurgitation of more than 1+ resulted in a second pump run to improve the repair. The data of the latest available postoperative transthoracic echocardiogram (TTE) were recorded and was available for 86 patients (including nine aortic valve replacements during follow-up). Detailed echocardiographic information was obtained for aortic valve reoperations.

Table 2: Operative techniques for aortic valve repair.

Level of correction		**Technique**	**n**	**% of 94**
Prolapsing area	1	Triangular resection	66	70
	2	Leaflet plication	28	30
Leaflets	1	Closure of incomplete commissure	11	12
	2	Leaflet patching	5	5
	3	Primary closure of a leaflet perforation	4	4
	4	Leaflet debridement	41	44
	5	Leaflet shaving	7	7
Commissure	1	Commissurotomy	1	1
	2	Commissuroplasty	94	100

Postoperative follow-up

Re-exploration for bleeding was necessary in 5 patients. One patient had a perioperative myocardial infarction and one patient required prolonged ventilatory support for respiratory failure. The mean length of postoperative hospital stay was 6.3±1.9 days.

Follow-up was achieved either by outpatient visit or by telephone interview with the patient or referring physician and a questionnaire completed with current status, medication, and information on morbidity and mortality. The data of the most recent echocardiogram were recorded and detailed information obtained for patients who underwent an aortic valve reoperation during follow-up.

Mean duration of follow-up was 5.1±2.4 (SD) years (median 5.5 years - range 0.2 to 9 years) and was complete in all patients. There were no deaths, early or late, nor episodes of thromboembolism or endocarditis. At follow-up, 84 patients were in NYHA functional class I and 10 patients were in class II ($P<0.001$ versus preoperative status).

Reoperations other than aortic valve reoperations were mitral valve repair in one patient, mitral valve replacement in two, and thoracic aneurysm repair in one. One patient underwent an aortic valve replacement after a Ross procedure (patient n° 3 of Table 6).

Data analysis

Durability of repair was assessed primarily by freedom from aortic valve reoperation. Immediate competence of the aortic valve was assessed by intraoperative TEE after initial repair and late aortic valve competence by TTE.

- Overall freedom from aortic valve reoperation

Non-parametric estimates of freedom from reoperation (whether by re-repair or aortic valve replacement) were obtained by the method of Kaplan and Meier [9]. A parametric method was used to resolve the number of hazard phases, identify the shape of the hazard function, and estimate its parameters [10].

- Multivariable analysis of aortic reoperation

Variables: Potential risk factors (variables) were organized for entry into the analysis: demography (age at original aortic repair; sex); aortic valve pathology and function (degree of aortic valve regurgitation; degree of aortic valve stenosis; leaflet fusion); left ventricular function (presence of left ventricular dilatation; degree of left ventricular dysfunction [normal, mild, moderate, moderate-to-severe, and severe]; left ventricular end-diastolic diameter); aortic valve procedure (triangular resection [n=66]; debridement [n=41]; leaflet plication [n=28]; resection of raphe [n=15]; leaflet patching [n=5]; commissurotomy [n=1]; leaflet shaving [n=7]; repair of perforation [n=4]); concomitant operations (coronary artery bypass grafting [n=2]; mitral valve repair [n=8]; repair of ascending aortic aneurysm [n=4]); and echocardiographic assessment (degree of immediate intraoperative post-repair residual aortic regurgitation [none, trace, 1+, 2+, 3+, 4+]).

General conduct of the multivariable analyses: Exploratory analysis included correlation analysis, stratified life table analyses, and decile risk analysis of ordinal and continuous variables to determine possible transformations of scale. A directed technique of stepwise entry of variables into the multivariable risk factor model was then used [11]. The *P* value criterion for retention of variables in the final model was 0.1. Regression coefficients are presented plus or minus one standard error.

Nature and influence of risk factors: Exploration of the influence of risk factors in the parametric multivariable analysis was performed by constructing a nomogram representing the solution of the parametric equation for specific values of each factor.

Immediate assessment of aortic valve competence: Immediate competence of the aortic valve was assessed by TEE in the operating room. When a second pump run was needed to achieve satisfactory repair, the grade of aortic regurgitation prior to the second pump run was used in the analysis. Factors associated with initial grade aortic regurgitation were identified using both multivariable ordinal logistic regression and binary logistic regression analyses on both the presence of trace or more regurgitation and more than mild

regurgitation [12]. The variables were those previously listed except for echocardiographic assessment.

Late aortic valve competence: Factors associated with possible progression of aortic regurgitation were identified by multivariable ordinal logistic regression analysis, incorporating time of late echocardiographic assessment after operation and variables as listed above. When aortic valve reoperation was performed, the grade of regurgitation prior to that reoperation was used in the analysis.

Results

Immediate assessment of the aortic valve

During the same time period, no patient of the same surgeon underwent immediate aortic valve replacement in the same operative session for failure of repair. In eight of the 94 patients a second pump run was required to improve the repair due to residual aortic regurgitation of more than 1+. In one patient, the suture line after triangular resection was partially dehisced; two patients had residual central regurgitation which required adjustment of the commissuroplasty; two patients had their leaflet plication redone; two patients required a more extensive triangular resection due to residual leaflet prolapse, and one patient underwent additional leaflet debridement. One patient had 1+ aortic regurgitation after the first pump run but the jet of regurgitation was considered due to a nodule on one of the aortic valve leaflets and this was debrided on a second pump run.

Table 3: Aortic regurgitation as assessed by intraoperative post-repair TEE.

Grade of regurgitation	After initial repair			Including any secondary repairs		
	n	%	CL	n	%	CL
0	55	59	53 – 64	59	63	57 – 68
Trace	25	27	22 – 32	28	30	25 – 35
1+	6	6	4 – 10	7	7	5 – 11
2+	6	6	4 – 10	0	0	-
3+	2	2	0.7 – 5	0	0	-
4+	0	0	-	0	0	-
Total	94	100		94	100	

Key: CL, 70% confidence limits

Degree of aortic competence, immediately after repair and before any second pump run, are shown in Table 3. One risk factor was identified for immediate intraoperative post-repair aortic regurgitation exceeding 1+ after the first pump run: increasing left ventricular dysfunction (correlated with increasing left ventricular size, r=0.3, *P*=0.02), Table 4. Triangular resection versus plication was not identified as a risk factor. After any secondary repair, the degree of aortic regurgitation was 1+ or less in all patients (Table 3). Five (8%) patients of the 66 who underwent triangular resection versus 3 (11%) of 28 patients who underwent plication, had more than 1+ aortic regurgitation after the first pump run (*P*=0.6). Post-repair, 84 patients had no aortic stenosis and 10 had mild aortic stenosis (*P*=0.1 from preoperative); all of them had aortic stenosis preoperatively.

Table 4: Inadequate aortic valve repair (aortic regurgitation > 1+) after the first pump run (n=8) and its relation to the degree of preoperative left ventricular dysfunction.

Degree of left ventricular dysfunction	**n**	**Aortic regurgitation > 1+**		
		Number of cases	**%**	**CL**
None	46	2	4	1 – 10
Mild	30	1	3	0.4 – 11
Moderate	13	4	31	16 – 49
Severe	5	1	20	39 – 53

P (logistic) 0.02; Key: CL, 70% confidence limits
Note: One patient with normal preoperative left ventricular function had a second pump run although residual aortic regurgitation after the first pump run was 1+ (see text for details).

Durability of repair

A late follow-up TTE prior to any reoperation (mean interval 3.5 ± 2.4 years after surgery) was available in 86 patients. Late aortic regurgitation was not demonstrated to progress with time (*P*=0.3, Table 5). No risk factors for late aortic regurgitation were identified. In particular, triangular resection versus plication as technique to eliminate the prolapsing area did not correlate with late aortic regurgitation (*P*=0.7). Twenty-two (37%) patients of 60 who underwent triangular resection had 2+ or more aortic regurgitation at follow-up versus 10 (38%) of 26 who underwent plication (*P*=0.7).

Table 5: Relationship of late aortic valve regurgitation to interval after repair (n=86; data unavailable in eight patients). In patients who underwent a reoperation, the grade of aortic regurgitation prior to the reoperation was entered in the table.

Interval to echocardiographic follow-up (yrs)	N	Grade aortic regurgitation							
		0 – trace		1+		2+		3+ or 4+	
		N	%	N	%	N	%	N	%
0 - 2	32	16	50	7	22	1	3	8	25
2 - 4	16	5	31	4	25	6	38	1	6
4 - 6	23	7	30	4	17	7	30	5	22
> 6	15	5	33	6	40	3	20	1	7

P (logistic for trend across time) = 0.3; Key: N = number of patients

During follow-up, 12 patients underwent aortic valve reoperation after the initial valve repair and are outlined in Table 6. Seven of the 12 reoperations were due to dehiscence of the suture line at the level of the triangular resection. There were no deaths at reoperation.

Table 6: Aortic valve reoperations after repair of bicuspid aortic valve (n=12).

Pt.	Operation (year)	Technique	Post-repair AR	Pre-reop. AR	Indication	Interval (months) to reop	Reop. Procedure
1	1988	triangular resection	trace	3+	Leaflet suture dehiscence	16	Re-repair
2	1989	triangular resection	none	3+	AS	57	AVR
3	1989	triangular resection	trace	3+	Leaflet suture dehiscence	40	Ross
4	1989	triangular resection	trace	3+	Leaflet suture dehiscence	12	Re-repair
5	1990	triangular resection	none	3+	Dehiscence at commissure	46	AVR
6	1991	triangular resection	trace	3+	Leaflet suture dehiscence	60	Ross
7	1991	triangular resection	none	3+	Leaflet suture dehiscence	6	Re-repair
8	1991	triangular resection	1 +	3+	AS	32	Allograft
9	1991	triangular resection	1 +	3+	Leaflet suture dehiscence	15	Allograft
10	1993	triangular resection	trace	3+	Leaflet suture dehiscence	6	Ross
11	1993	plication	trace	3+	Leaflet suture dehiscence	0. 3	Ross
12	1995	triangular resection	none	3+	Dehiscence at commissure	5	Allograft

Key: AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement;
Pt, patient; Pre-reop., pre-reoperative; Reop., reoperative

After reoperation, the latest echocardiographic findings of aortic regurgitation were available in 77 of the 85 patients who retained their native aortic valve at the time of follow-up (this includes three patients who underwent re-repair during follow-up). The degree of aortic regurgitation was: none in 21 patients, trace in 13, 1+ in 22, 2+ in 16, 3+

in three and 4+ in two. The five patients with severe aortic regurgitation (3+ or 4+) are currently asymptomatic with normal left ventricular function and are being followed closely with regular echocardiogram.

Freedom from aortic valve reoperation was 95%, 87%, and 84% at 1, 5 and 7 years after aortic valve repair, respectively (Fig. 1). The instantaneous risk (hazard function) for reoperation was highest immediately after operation, falling rapidly to approximately 2% per year or less after two years (Fig. 2). Multivariable hazard function analysis revealed the presence of residual aortic regurgitation on immediate intraoperative post-repair TEE as the single risk factor for reoperation (Fig. 3). The methods of repair were not demonstrably associated with reoperation.

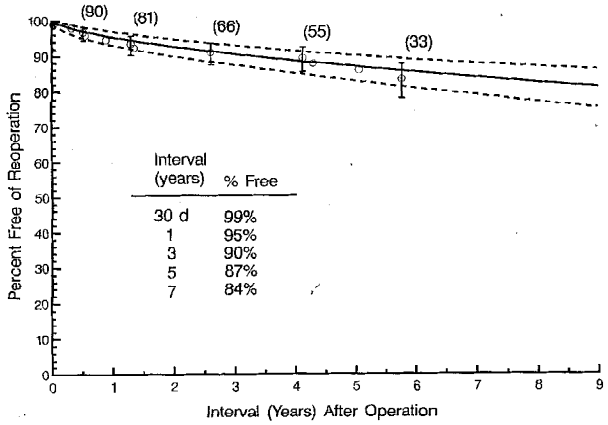

***Figure 1**: Freedom from aortic valve reoperation during follow-up.*

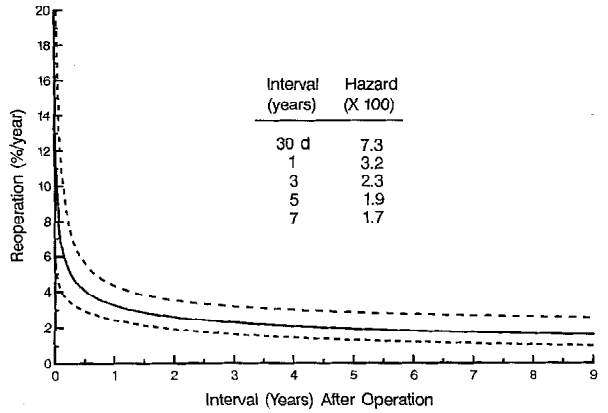

***Figure 2**: Instantaneous risk for aortic valve reoperation during follow-up.*

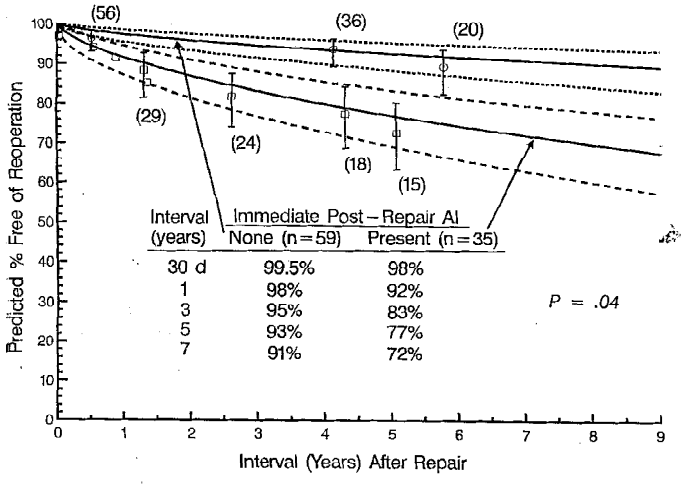

***Figure 3**: Freedom from aortic valve reoperation during follow-up according to the amount of aortic regurgitation on immediate post-repair intraoperative transesophageal echocardiogram..*

Discussion

Isolated aortic regurgitation is uncommon in the bicuspid aortic valve because most cases of aortic regurgitation result from endocarditis [13-15]. Apart from this, bicuspid aortic valve is one of the main causes of isolated aortic regurgitation [4] and, when present, occurs predominantly at a young age [13] which is reflected in our patient population. Up to 64% of patients with bicuspid aortic valves have a normal life-span and never develop clinically significant aortic valve pathology [13-15]. Repair of the insufficient bicuspid aortic valve aims to return patients into the group with a normal life-span and provide a durable repair.

Aortic regurgitation

Guidelines to maximize repair durability are necessary to optimize results of repair of bicuspid prolapsing aortic valve. The result of the repair is assessed in the operating room by TEE which has proved to be reliable [16]. In this series, residual regurgitation greater than 1+ resulted in a second pump run in order to improve the repair. However, analysis indicates that this relatively strict policy should be more strict since patients with *any* residual aortic regurgitation after the repair have an increased risk of late repair failure. In order to reduce the risk of reoperation, the surgeon should aim to eliminate residual aortic regurgitation at operation; however, this is difficult in patients with large, poor functioning ventricles.

The overall 13% prevalence of reoperation at 5 years is higher than reported by Duran et al [17-19]. However, the *maximum* follow-up in his series was only 4 years. Carpentier [20] reported a similar 13% reoperation prevalence but the duration of follow-up is not quoted in his report. Haydar et al [21] reported a reoperation prevalence of 18% after a mean follow-up of 2.6 years in a heterogeneous group of patients. In contrast, we investigated only patients who had a bicuspid valve with leaflet prolapse causing aortic regurgitation. Patients with rheumatic valve disease were excluded.

Haydar et al [21] state that the reoperation prevalence is 11% if immediate failures due to technical errors are excluded. Seven of the 12 reoperations in our series were performed within 16 months of the initial repair. Whether or not these are all attributable to technical failures is doubtful. However, the repair is certainly more stable after the first 18 months. Another consideration was the technique for eliminating the prolapsing area, triangular resection versus central plication. We gradually changed our technique in favour of plication of the central area. The advantage of plication is the preservation of the thicker, central tissue opposite the raphe, which presumably holds the plication suture better. There is also more coapting surface area of the leaflet when no resection is performed. To date, we have not demonstrated that this change has improved results. Longer follow-up and larger numbers should reveal whether plication is more durable than triangular resection.

Another measure of durability is the stability of the repair on follow-up TTE. Carpentier [20] reported that 15% of patients had moderate aortic regurgitation at echocardiographic follow-up, while aortic regurgitation of 2+ or greater was present in 26% of all patients in the present series who still had their native aortic valve. Although all of these patients are asymptomatic, some of them may require late reoperation. Therefore, close echocardiographic follow-up is imperative in these patients.

Aortic stenosis

This study confirms that the repair technique does not create aortic stenosis [1, 2, 7]. However, the technique does not necessarily protect the valve from developing late aortic stenosis. Two patients with mild aortic stenosis required reoperation predominantly for combined aortic stenosis and aortic regurgitation (Table 6). It is therefore essential to keep patients with a history of aortic stenosis in regular echocardiographic follow-up.

Current strategy

All patients with aortic regurgitation from a prolapsing bicuspid aortic valve who require intervention are considered candidates for valve repair. Patients with mild aortic stenosis are also considered candidates for repair; however, the feasibility of repair will have to be evaluated intraoperatively.

Morbidity and mortality is minimal. The native aortic valve is preserved and anticoagulation is unnecessary.

Currently, we accept 1+ residual aortic regurgitation as a satisfactory repair. However, since those patients with any residual aortic regurgitation have an increased risk of reoperation, the benefits and risks of a second pump-run must be carefully and individually considered. Plication is the preferred technique for elimination of the prolapsing area.

Patients should be evaluated by TTE at regular intervals, especially those with residual aortic regurgitation after initial repair.

If aortic valve reoperation becomes necessary, the aortic valve can be replaced using any of the available techniques and the risk of reoperation was very low in this series.

Limitations of the study

This is a single-institution, single-surgeon study. While this achieves homogeneity of repair strategy, it does so at the expense of study size and generalizability. Duration of follow-up is intermediate-term, which limits long-range inferences. Because many of these patients were referred for aortic valve repair, only one post-repair echocardiogram is available on most of the patients. Serial echocardiograms would permit early detection of progressive aortic regurgitation and identify patients who require reoperation at an earlier stage. As a substitute for this, we have used a method of longitudinal analysis for aortic competence assessment that presumes that a group trend, reflecting individual trends, can be detected.

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References

1. Cosgrove D, Rosenkranz E, Hendren W, Barlett J, Stewart W. Valvuloplasty for aortic insufficiency. J Thorac Cardiovasc Surg 1991;102;571-577.
2. Fraser C, Wang N, Mee R, Lytle B, McCarthy P, Sapp S, Rosenkranz E, Cosgrove D. Repair of insufficient bicuspid aortic valves. Ann Thorac Surg 1994;58;386-390.
3. Perry G, Helmcke F, Nanda N, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9;952-959.
4. Otto C. Aortic valve insufficiency: changing concepts in diagnosis and management. Cardiologia 1996;41;505-513.
5. Galan A, Zoghbi WA, Quinones MA. Determination of severity of valvular aortic stenosis by Doppler echocardiography and relation of findings to clinical outcome and agreement with hemodynamic measurements determined at cardiac catheterization. Am J Cardiol 1991;67;1007-1012.
6. Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL, Ribeiro LG, Miller RR. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. Circulation 1981;64;744-753.
7. Fraser C, Cosgrove D. Aortic valve reparative procedures. Advances in Cardiac Surgery 1996;7;65-86.
8. Cosgrove D, Fraser C. Aortic valve repair. Oper Techn in Cardiothorac Surg 1996;1;30-37.
9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53;457-481.
10. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assoc 1986 (September);81;615-624.
11. Baskerville JC, Toogood JH. Guided regression modeling for prediction and exploration of structure with many explanatory variables. Technometrics 1982;24;9-17.
12. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley and Sons, 1989.
13. Fenoglio J, McAllister H, DeCastro C, Davia J, Cheitlin M. Congenital bicuspid aortic valve after age 20. Am J Cardiol 1977;39;164-169.
14. Hallgrimsson J, Tulinius H. Chronic non-rheumatic aortic valvular disease: a population study based on autopsies. J Chron Dis 1979;32;355-363.
15. Mills P, Leech G, Davies M, Leatham A. The natural history of a non-stenotic bicuspid aortic valve. Br Heart J 1978;40;951-957.
16. Moidl R, Moritz A, Simon P, Kupilik N, Wolner E, Mohl W. Echocardiographic results after repair of incompetent bicuspid aortic valves. Ann Thorac Surg 1995;60;669-672.
17. Duran C, Kumar N, Gometza B, Al Halees Z. Indications and limitations of aortic valve reconstruction. Ann Thorac Surg 1991;52;447-454.
18. Duran C. Present status of reconstructive surgery for aortic valve disease. J Card Surg 1993;8;443-452.
19. Duran C. Aortic valve repair and reconstruction. Oper Techn in Cardiothorac Surg 1996;1;15-29.
20. Carpentier A. Cardiac valve surgery: 'The French correction'. J Thorac Cardiovasc Surg 1983; 86;323-337.
21. Haydar H, Ho G, Hovaguimian H, McIrvin D, King D, Starr A. Valve repair for aortic insufficiency: surgical classification and techniques. Eur J Cardiothorac Surg 1997;11;258-265.

CHAPTER 3

Durability of the repair of prolapsing tricuspid aortic valve in adults

Filip P. Casselman, M.D.[1], A. Marc Gillinov, M.D.[1], Eugene H. Blackstone, M.D.[1,2], and Delos M. Cosgrove, M.D.[1]

Departments of Thoracic and Cardiovascular Surgery[1] and Biostatistics and Epidemiology[2]
The Cleveland Clinic Foundation, Cleveland, Ohio USA

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Abstract

Objective: This study was undertaken to evaluate the durability of valve repair in adults with a tricuspid aortic valve and leaflet prolapse.
Methods: Thirty-three patients with a tricuspid aortic valve and regurgitation from leaflet prolapse underwent surgical repair. Mean age was 54±15.9 years. Triangular resection of the prolapsing leaflet and commissuroplasty were performed in 29 patients (88%). Mean follow-up was 4.0±2.4 years.
Results: There were five intraoperative repair failures (15%) requiring immediate aortic valve replacement during the same operative session. Three patients required reoperation during follow-up: one patient for suture dehiscence, one patient for 3+ central aortic regurgitation, and one patient for leaflet tear at a commissure, a rate of 3%/year. Freedom from aortic valve reoperation at one and five years in successfully repaired patients was 96% and 83%, respectively. There were three late deaths: one sudden and two due to a cerebral vascular accident.
Conclusion: Successful repair of tricuspid aortic valves is technically challenging, but has an acceptable midterm outcome when feasible. Regular postoperative assessment of aortic valve function is however recommended because aortic regurgitation develops in a substantial proportion of patients by five years.

Introduction

Literature on aortic valve repair in adults is limited to reports in heterogeneous groups of patients [1-5]. Patient populations include rheumatic disease, congenital valve disease, and bicuspid and tricuspid aortic valve pathology. However, results of aortic valve repair may be influenced by the pathology. We have previously reported our results of *bicuspid* aortic valve repair [6]. This study was undertaken to evaluate the durability of repair of *tricuspid* aortic valves with leaflet prolapse.

Materials and methods

Inclusion criteria

Between November 1988 and January 1, 1997, 33 patients with a tricuspid aortic valve and severe aortic regurgitation due to a prolapsing leaflet were considered candidates for aortic valve repair. Mild aortic stenosis was not an exclusion criterion. Included were five patients who underwent aortic valve repair and in whom it was immediately apparent that the repair was inadequate. Consequently, their valves were replaced. These patients were included in the patient group to portray a realistic picture of the possibility of tricuspid aortic valve repair for leaflet prolapse. This group of 33 patients represents 0.7% of all patients having aortic valve procedures during the time period.

Patient characteristics

Mean age was 54±15.9 years (range 21 to 75). Only two patients were female. The prolapsing leaflet was the right coronary cusp in 27 patients (82%), the non-coronary in two (6%), and the left in three (9%). One patient (3%) had prolapse of both right and left coronary cusps.

Isolated aortic valve repair was performed in 16 patients. Concomitant procedures in the remaining patients included mitral valve repair in seven (21%), coronary artery bypass grafting (CABG) in six (18%), mitral valve repair and CABG in two (6%), mitral valve replacement in one (3%), and ventricular septal defect and patent foramen ovale repair in one (3%). One patient had previously undergone CABG.

Preoperative New York Heart Association (NHYA) functional class was I in 11 patients (33%), II in 15 (45%), III in six (18%), and IV in one (3%).

Postoperatively, patients received antiplatelet or Coumadin therapy, as indicated by the associated procedure or the presence of atrial fibrillation.

Preoperative assessment

All patients had a preoperative Doppler echocardiogram to assess aortic valve pathology and measure left ventricular function and left ventricular dimensions [7-10]. Preoperative aortic regurgitation was 2+ (moderate) in seven patients, 3+ (moderate to severe) in nine patients, and 4+ (severe) in 17. Mild aortic stenosis was present in seven patients and absent in the remainder. There was only one patient without left ventricular enlargement preoperatively, and the mean end-diastolic diameter was 6.9±0.8 cm, ranging from 5.6 to 8.4 cm. The preoperative left ventricular function was normal in 12 patients, mildly impaired in 13, moderately impaired in seven, and severely impaired in one. Preoperative heart catheterization was not routinely performed and was indicated when risk factors for coronary artery disease were present or in patients who were older than 45 years of age.

Repair technique

From 1988 to 1996, the operation was performed via full midline sternotomy; since January 1996, all isolated aortic valve procedures have been performed using minimally invasive techniques (n=6). All procedures were performed under a single period of aortic cross-clamping. The mean aortic cross-clamp and cardiopulmonary bypass times were 54±19.5 and 71±28.3 minutes, respectively.

The valve repair usually required application of several techniques to achieve a competent valve. However, the crucial intervention on the aortic valve was the elimination of the prolapsing area by a triangular resection in 29 cases and leaflet plication in two patients. In addition, all but one patient had a commissuroplasty. Other interventions on the aortic valve included leaflet debridement (n=7), leaflet shaving (n=2), and commissurotomy (n=1). Further details on our technique of aortic valve repair can be found in an earlier publication [11].

Assessment of repair success and durability

All patients had an immediate intraoperative post-repair transesophageal echocardiogram (TEE) to assess success of the repair. Residual aortic regurgitation of more than 1+ (mild) was followed by a second attempt to improve the repair. The ultimate durability of successful repair was assessed by the need for reoperation on the aortic valve. In addition, the latest available transthoracic echocardiogram (TTE) was available in 21 of 24 surviving patients who retained their native aortic valve at the time of follow-up. Detailed echocardiographic information was obtained in patients having aortic valve reoperations.

Postoperative follow-up

Follow-up was achieved either by outpatient visit or by telephone contact with the patient or referring physician, and a questionnaire on current status, medication, morbidity and mortality was completed. Mean follow-up was 4.0±2.4 years and ranged from one to eight years.

Data analysis

Survival and freedom from aortic valve repair failure (including immediate repair failures) were estimated nonparametrically by the Kaplan-Meier estimator and parametrically [12,13].

All parameter estimates (means, proportions, time-related estimates) are accompanied by the standard deviation or asymmetric 68% confidence limits (CL) equivalent to one standard deviation (see appendix 1 for potential risk factors).

Results

Operative morbidity and mortality

There were no hospital deaths (0%, CL 0-6%). Postoperative morbidity included respiratory failure requiring prolonged ventilatory support in one patient, ventricular tachycardia in one patient, and a superficial wound infection in another patient.

Immediate repair success

The grade of aortic regurgitation as assessed by intraoperative post-repair TEE is shown in Table 1. After initial repair, five patients had aortic regurgitation that was 2+ or greater. Each of these patients had a second pump run, resulting in aortic valve replacement in four and successful re-repair in one. Three of the patients that required aortic valve replacement had mild aortic stenosis that was treated by leaflet debridement; in each of these cases, post-repair TEE demonstrated a complex regurgitant jet, and the valve was replaced. One patient with extremely friable leaflet tissue had aortic valve replacement when it became apparent that the leaflet would not hold sutures. Thus, in total, five patients had aortic valve replacement after unsuccessful repair (15%; CL 9-24%, Table 2).

No patient left the operating room with more than 1+ aortic regurgitation. No important aortic stenosis was created by the repair technique; 25 patients had no aortic stenosis postoperatively, and three had mild aortic stenosis as graded by TEE.

Table 1: Aortic regurgitation assessed by intraoperative post-repair TEE**.**

Grade of aortic regurgitation	After 1st aortic valve repair attempt *			At end of operation**		
	N	%	CL	N	%	CL
0	12	36	27-47	12	43	32-54
Trace	11	33	24-44	12	43	32-54
1+	4	12	6-21	4	14	7-24
2+	4	12	6-21	0	--	--
3+	1	3	0.4-10	0	--	--
4+	0	0	--	0	--	--
Total	32	97		28	100	

* Exclusive of 1 patient who underwent aortic valve replacement after attempted repair in a single pump run, ** Exclusive of 5 aortic valve replacements at initial operation, KEY: TEE, transesophageal echocardiography; CL, 70% confidence limits

Table 2: Operative details in the 5 patients who underwent immediate aortic valve replacement.

Pt.	Year of operation	Age	Prolapsing cusp	Aortic root	AS	AR post-repair	Probable cause of failure
1	1988	73	LCC	Normal	None	--	Friable tissue
2	1989	45	RCC	Enlarged	None	2+	Root dilatation
3	1990	62	LCC	Normal	Mild	2+	AS
4	1993	52	RCC	Normal	Mild	2+	AS
5	1995	60	RCC	Normal	Mild	2-3+	AS

Key: AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; LCC, left coronary cusp; RCC, right coronary cusp; Pt, patient

Durability of aortic valve repair

Durability of aortic valve repair was assessed by freedom from reoperation. A total of eight patients required aortic valve replacement. Five of these had aortic valve replacement during the initial operative session when it became evident that the aortic valve repair had failed, as described above. In addition, three patients who had a successful repair required late aortic valve replacement (Table 3). Each of these patients developed aortic regurgitation, which was the primary indication for reoperation.

Table 3: Reoperation after prolapsing trileaflet aortic valve repair.

Pt.	Year of operation	Operative technique	Post-repair AR	Interval (mo.)	Pre-reop AR	Reason	Procedure
1	1989	Triangular resection	None	18	3+	Central AR; no structural abnormalities	AVR, MVR, TVR
2	1990	Plication	Trace	55	3+	Dehiscence of suture	AVR
3	1995	Triangular resection	Trace	11	4+	Tear at commissure	Allograft

Key: AR, aortic regurgitation; AVR, aortic valve replacement; Mo., months; MVR, mitral valve replacement; Pt., patient; Pre-reop, pre-reoperative; TVR, tricuspid valve repair

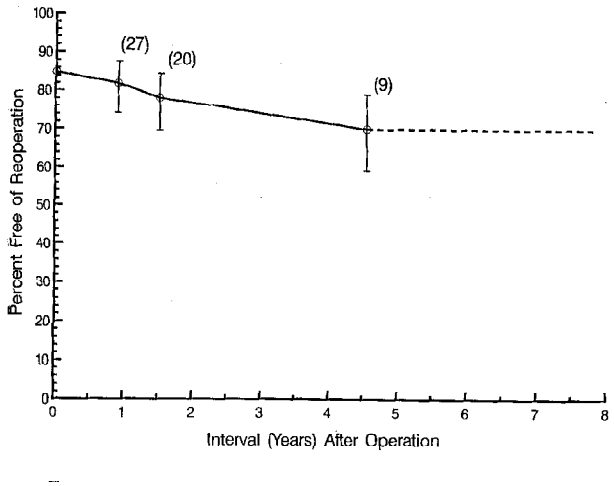

Figure 1*: Freedom from aortic valve repair failure. The five immediate repair failures occurring at the time of repair are represented by the first circle; the other circles are later reoperations. The vertical bars are asymmetric confidence limits equivalent to 1 standard error. The solid line and its confidence limits represent parametric estimates from which the hazard function was determined.*

Freedom from reoperation upon the aortic valve including the five immediate failures was 82% (CL, 74 to 88%) at 1 year, and 70% (CL, 59 to 79%) at 5 years postoperatively (Fig.1). Freedom from reoperation upon the aortic valve in patients with successful repair (n=28) was 96% (CL, 91 to 99%) at 1 year and 83% (CL, 70 to 91%) at 5 years postoperatively. After the early failures, the constant hazard for reoperation was estimated

to be 3.0%/year (CL, 1.7-5.4%/year). The number of events precluded multivariable analysis. Late transthoracic echocardiograms were available in 21 of 24 patients who retained their native aortic valve at the time of follow-up. The average echocardiographic follow-up was 2.6±1.9 years. Aortic regurgitation was 0 to trace in four patients, 1+ in 10, 2+ in three, and 3+ in four.

Late morbidity and mortality

Follow-up morbidity included two transient ischemic attacks (TIA). One occurred 1.5 years postoperatively in a patient who had a 60 to 80% left internal carotid artery stenosis. The second TIA occurred six years postoperatively in a patient who was in atrial fibrillation.

There were three late deaths. One was a sudden death in a 60-year-old man and occurred 1.8 years postoperatively. The patient had undergone coronary artery bypass grafting at the time of the valve repair. The two other deaths occurred in a 73-year-old woman and a 62-year-old man after cerebral vascular accidents. Neither of these patients had a concomitant procedure with the initial aortic valve repair, but both had an immediate aortic valve replacement because of inadequate repair.

The NYHA functional class in the 30 survivors at follow-up was I in 27 patients and II in three patients.

There were no reoperations other than aortic valve reoperation and there were no deaths at reoperation.

Discussion

The etiology of leaflet prolapse in adult patients with tricuspid aortic valve structure is unclear. There is a preponderance of right coronary cusp prolapse, as this was the pathology in 82% of this series. This may be explained in part by the variation in size and dimension of the different aortic valve leaflets [14-16]. The non-coronary cusp tends to be the largest of the three leaflets and the right cusp the smallest. In addition, Kunzelman et al.[16] reported that the right coronary cusp tends to have a shorter height than the left and non-coronary cusp (1.33 cm vs. 1.39 and 1.37 cm, respectively). Kunzelman also found that the length of the free margin of the right cusp is greater than that of the other two cusps (3.3 cm vs. 3.15 and 3.27 cm, respectively). It is conceivable that the reduced height and longer free margin of the right coronary cusp predispose to prolapse. This mechanism, however, is entirely speculative.

Another possible explanation for aortic regurgitation caused by prolapse of the right coronary cusp may be found in the association between ventricular septal defects (VSD) and aortic valve prolapse. It is well known that a VSD can cause aortic valve prolapse and aortic regurgitation; prolapse most commonly involves the right coronary cusp [17,18]. However, such findings are uncommon in adults. In the current series, only 1 patient had a VSD, and this patient did have prolapse of the right coronary cusp. Up to 80% of VSDs

close spontaneously [19]. While it is conceivable that other patients in this series had VSDs that closed spontaneously, this mechanism is also speculative.

The results reported herein support the notion that repair of a tricuspid aortic valve presents a greater challenge than repair of a bicuspid aortic valve. In the current series, five patients had repair failure that was apparent immediately in the operating room; we did not observe such early repair failures in patients with bicuspid aortic valves [6]. There are several reasons that prolapse of a bicuspid aortic valve is easier to correct. The thicker tissue of a bicuspid aortic valve provides a stronger suture line after a triangular resection or plication of a prolapsing leaflet. In contrast, most of the leaflets in patients with tricuspid valves were quite fragile and more difficult to handle surgically. Of more importance, the bicuspid aortic valve with prolapse provides an internal reference point. One of the two leaflets prolapses while the shorter leaflet provides a reference to the surgeon to dictate the dimensions of the triangular resection or plication necessary to result in even coaptation and valve competence. In approaching the tricuspid aortic valve, it is much more difficult to judge the degree of prolapse present and correspondingly more difficult to resect the correct amount of tissue. The commissuroplasty technique provides the surgeon some margin for error by increasing leaflet coaptation.

The presence of mild-to-moderate aortic stenosis complicates repair of the tricuspid aortic valve with regurgitation caused by prolapse. Previous studies demonstrate that mild-to-moderate aortic stenosis does not reduce the ability to repair a bicuspid aortic valve [6]. However, in the current series of patients with tricuspid aortic valves, three of seven patients with mild preoperative aortic stenosis had unsuccessful aortic valve repair, necessitating aortic valve replacement for residual aortic regurgitation. Given these results, repair of the tricuspid aortic valve with leaflet prolapse should be undertaken with caution in patients with any degree of aortic stenosis.

Successful repair of the tricuspid aortic valve with prolapse results in acceptable intermediate-term durability. The 1- and 5-year freedoms from reoperation after successful valve repair in this series were 96% and 83%. This compares favorably to the 95% and 87% 1- and 5-year freedoms from reoperation in patients having repair of bicuspid aortic valves [6]. After repair of bicuspid valves, the risk of reoperation gradually fell over time, from 3.2%/year at 1 year to 2.6%/year at 5 years. The number of reoperations after tricuspid aortic valve repair was too few to detect anything other than a constant risk. At late follow-up in the current series, three patients had 2+ aortic regurgitation and four had 3+ aortic regurgitation. These patients are currently asymptomatic. However, reoperation may become necessary in the future.

Limitations

This report describes an experience with 33 adults undergoing aortic valve repair for aortic regurgitation caused by leaflet prolapse in a tricuspid valve. The numbers of patients and events are too small to perform a multivariable analysis to determine risk factors for repair failure. In addition, systematic serial echocardiographic follow-up was not available. This report contains midterm follow-up. Continued follow-up will be necessary to determine the long-term durability of aortic valve repair in patients with tricuspid valves and leaflet prolapse.

Conclusions

Repair of a tricuspid aortic valve with leaflet prolapse is technically challenging and carries an immediate failure rate higher than that observed in patients with bicuspid aortic valves. In the event of unsuccessful repair (aortic regurgitation that is 2+ or greater), we recommend aortic valve replacement at the same sitting. After successful repair, patients require continued follow-up by echocardiography at regular intervals to assess aortic valve function.

References

1. Carpentier A. Cardiac valve surgery: "The French correction." J Thorac Cardiovasc Surg 1983;86:323-337.
2. Haydar H, Ho G, Hovaguimian H, McIrvin D, King D, Starr A. Valve repair for aortic insufficiency: surgical classification and techniques. Eur J Cardiothorac Surg 1997;11:258-265.
3. Duran C, Kumar N, Gometza B, Al Halees Z. Indications and limitations of aortic valve reconstruction. Ann Thorac Surg 1991;52:447-454.
4. Duran C. Present status of reconstructive surgery for aortic valve disease. J Card Surg 1993;8:443-452.
5. Cosgrove D, Rosenkranz E, Hendren W, Barlett J, Stewart W. Valvuloplasty for aortic insufficiency. J Thorac Cardiovasc Surg 1991;102:571-577.
6. Casselman FP, Gillinov AM, Akhrass R, Kasirajan V, Blackstone EH, Cosgrove DM. Intermediate-term durability of bicuspid aortic valve repair for prolapsing leaflet. Eur J Cardiothorac Surg 1999;15:302-308.
7. Perry G, Helmcke F, Nanda N, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9:952-959.
8. Cohen GI, Duffy CI, Klein AL, Miller DP, Cosgrove DM, Stewart WJ. Color Doppler and two-dimensional echocardiographic determination of the mechanism of aortic regurgitation with surgical correlation. J Am Soc Echocard 1996;9:508-515.
9. Galan A, Zoghbi WA, Quinones MA. Determination of severity of valvular aortic stenosis by Doppler echocardiography and relation of findings to clinical outcome and agreement with hemodynamic measurements determined at cardiac catheterization. Am J Cardiol 1991;67:1007-1012.
10. Quinones MA, Waggoner AD, Reduto LA, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. Circulation 1981;64:744-753.
11. Fraser C, Cosgrove D. Aortic valve reparative procedures. Advances in Cardiac Surgery 1996;7:65-86.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
13. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assoc 1986;81:615-624.
14. Vollebergh FEMG, Becker AE. Minor congenital variations of cusp size in tricuspid aortic valves. Possible link with isolated aortic stenosis. Br Heart J 1977;39:1006-1011.
15. Silver MA, Roberts WC. Detailed anatomy of the normally functioning aortic valve in hearts of normal and increased weight. Am J Cardiol 1985;55:454-461.
16. Kunzelman KS, Grande J, David TE, Cochran RP, Verrier ED. Aortic root and valve relationships. Impact on surgical repair. J Thorac Cardiovasc Surg 1994;107:162-170.
17. Kawashima Y, Danno M, Shimizu Y, et al. Ventricular septal defect associated with aortic insufficiency. Anatomic classification and method of operation. Circulation 1973;47:1057-1064.
18. Tatsuno K, Konno S, Ando M, Sakakibara S. Pathogenetic mechanisms of prolapsing aortic valve and aortic regurgitation associated with ventricular septal defect. Anatomical, graphical, and surgical considerations. Circulation 1973;48:1028-1037.
19. Kirklin JW, Barratt-Boyes BG, eds. Ventricular septal defect. In:.Cardiac Surgery, 2nd ed. New York: Churchill Livingstone;1993:749-825.

Appendix 1. Potential Risk Factors (Variables)

Demography

- Age at original aortic repair
- Sex

Aortic valve pathology and function

- Degree of aortic valve regurgitation
- Degree of aortic valve stenosis
- Leaflet prolapse

Left ventricular function

- Presence of left ventricular dilatation
- Degree of left ventricular dysfunction (normal, mild, moderate, moderate-to-severe, severe)
- Left ventricular end-diastolic diameter

Aortic valve procedure

- Debridement
- Triangular resection
- Commissurotomy
- Leaflet plication
- Leaflet shaving
- Commissuroplasty

Concomitant operations

- CABG
- Mitral valve repair
- Mitral valve repair and CABG
- Mitral valve replacement
- Ventricular septal defect and patent foramen ovale repair

CHAPTER 4

Durability of aortic valve preservation and root reconstruction in acute Type A aortic dissection

Filip P Casselman MD, M Erwin SH Tan MD, Freddy EE Vermeulen MD, Johannes C Kelder° MD, Wim J Morshuis MD PhD, Marc AAM Schepens MD PhD.

From the department of Cardio-Thoracic Surgery and Cardiological Epidemiology°, St. Antonius Ziekenhuis, Nieuwegein, The Netherlands.

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Abstract

Objective: To determine the durability of aortic valve preservation and root reconstruction in Type A aortic dissection with involvement of the aortic root.
Methods: From November 1976 to February 1999, 246 patients underwent surgical treatment for acute Type A aortic dissection at our institution. In 121 patients (49%), all with acute Type A dissection and aortic root involvement, the aortic valve was preserved and one or more of the sinuses of Valsalva were reconstructed. Mean age of this group was 59±11 years and 70 (58%) were male. Thirty patients (25%) were operated in cardiogenic shock. Criteria for aortic root reconstruction were technical feasibility and surgeons preference. Techniques used for reconstruction were valve resuspension in all patients and additional reinforcement of the aortic root with Teflon® felt (n=21), GRF-glue® (n=103) or fibrinous glue (n=5). Mean follow-up was 43.5±46 months.
Results: The operative mortality was 21.5% (n=26). Actuarial survival was 72±4%, 64±5% and 53±6% at 1, 5 and 10 years respectively. Median aortic regurgitation in patients with retained native aortic valve at follow-up was 1 +. All root reoperations included aortic valve replacement (n=12). Freedom from aortic root reoperation was 95±2% at 1 year, 89±4% at 5 years and 69±9% at 10 years. The incidence of aortic root reoperation was 23%, 11% and 40% respectively when Teflon® felt, GRF-glue® or fibrinous glue were used for root reconstruction. Multivariate Cox-proportional hazard analysis revealed the use of fibrinous glue (RR=8.7; p=0.03) as wel as the presence of an aortic valve annulus > 27 mm (RR=4.2; p=0.04) as independent risk factors for aortic root reoperation.
Conclusions: Aortic valve preservation in acute Type A dissection provides relatively durable results. The use of fibrinous glue for root reconstruction seems to compromise the long-term durability of the repair when compared with Teflon® felt and GRF-glue®. A dilated aortic annulus requires a more extensive root procedure.

Introduction

Acute Type A aortic dissection according to the Stanford classification [1] involves, per definition, the ascending aorta. The degree of involvement of the ascending aorta however, may vary from a discrete intramural hematoma to a totally disrupted aortic wall architecture including the aortic root. This usually causes severe aortic regurgitation. While surgical treatment in the former can consist of a short segment replacement of the ascending aorta, surgical options in the latter need to restore a functional aortic root. This can be obtained by the Bentall procedure [2]. Since Type A dissection does not affect the aortic valve annulus neither the valve leaflets, efforts have been made, in individuals without preexisting aortic valve pathology, to reconstruct in some way the sinuses of Valsalva and resuspend the aortic valve commissures [3-6]. This aims to restore the geometry of the aortic root and subsequently aortic valve competence. Reported durability of these different techniques however is not uniformly good [7] and follow-up is mostly short. The present study focuses on the durability of the aortic valve preservation and root reconstructive technique in patients who underwent surgical treatment for an acute Type A aortic dissection with involvement of the aortic root. The second objective of the study was to determine risk factors for aortic root reoperation.

Materials and methods

Inclusion criteria

From November 1976 to February 1999, 246 consecutive patients underwent surgical treatment for acute Type A aortic dissection according to the Stanford classification [1]. The dissection was considered acute if the operation was performed within 14 days after the onset of symptoms. In addition, eligibility for this study required involvement of the aortic root by the dissection with subsequent surgical reconstruction of one or more of the sinuses of Valsalva and preservation of the aortic valve. Patients who received a supracoronary ascending aortic replacement without root reconstruction were excluded from this analysis as well as patients undergoing a David procedure [8]. Following these criteria, 121 patients (49%) were included in the study.

Table 1: Number of patients operated per year throughout the study period (n=121).

Year	76	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
N	1	2	2	2	2	1	3	4	3	11	11	13	10	9	7	14	17	7	2

N: number of patients

Patient characteristics

Mean age was 59±11 years (range 24 to 81) and 58% (n=70) were male. Two patients previously underwent coronary artery bypass grafting (CABG) and another patient previously had a descending thoracic aorta replacement for a ruptured Type B aortic dissection. Marfan's syndrome was present in two patients. The patient distribution per year is mentioned in Table 1. One fourth of the patients (n=30) were operated in cardiogenic shock. Preoperative neurological deficit was diagnosed in 19 patients (Table 2). However, this was transient and fully recovered at the time of surgery in 10 patients. Associated procedures included partial or total arch replacement in 18 patients, CABG in four patients and exploratory laparotomy in another four patients.

Postoperatively patients were anticoagulated with coumadin for three months and were then switched to antiplatelet therapy unless they were in atrial fibrillation.

Table 2: Preoperative neurological deficit (n=19).

Type of deficit	**Total N**	**Transient N**
Paraparesis	2	0
Hemiparesis	11	6
Monoparesis	3	3
Visual disturbance	1	1
Hemiplegia	1	0
Dysphasia	1	0
Total	19	10

N: number of patients

Surgical technique

The technique changed somewhat over the years since a total of 11 surgeons operated on the patients included in this series. Usually the procedure started with a median sternotomy, followed by cannulation through the femoral artery and right atrial appendage. A left ventricular decompression line was inserted through the right superior pulmonary vein. In cases of hemodynamic instability or resuscitation, extracorporeal circulation (ECC) was usually initiated by arterial and venous cannulation in the groin using a long venous cannula, after which median sternotomy was performed.

Once the patient was on ECC, systemic cooling was initiated. In the early experience, the distal ascending aorta was clamped at 25-28°C or earlier if ventricular fibrillation occurred. The proximal aorta was then opened to locate the intimal tear. If the intimal tear extended into the clamped area, the patient was cooled till a nasopharyngeal temperature

of 16°Celsius or, since 1982, until the electro-encephalogram became iso-electric. The proximal reconstruction (see further) was performed during this cooling episode. The arch was then exposed under deep hypothermic circulatory arrest (DHCA) and partially or totally replaced if necessary. If it was unnecessary to replace the arch, an open distal aorto-prosthesis anastomosis was performed and ECC was reinstituted.

If the intimal tear did not extend into the clamped aortic area, the reconstruction of the dissected portion was performed under aortic cross-clamping.

Since 1990 on, antegrade selective cerebral perfusion (ASCP) has progressively been introduced in our institution. The technique has previously been reported [9] and is currently our technique of choice for brain protection. Of the 121 patients involved in this study, a total of 69 had DHCA and 22 patients had ASCP.

Another modification over the years is to avoid aortic cross-clamping. We currently cool the patient down till a nasopharyngeal temperature of 25°C at which the ECC is discontinued. We then install the ASCP and subsequently protect the heart by cold cristalloid antegrade cardioplegia which is administered directly into the coronary ostia. The eventual arch procedure and distal ascending aortic anastomosis are performed under total circulatory arrest. Once this is completed, ASCP is stopped and antegrade perfusion is resumed through a side arm of the prosthesis. The prosthesis is then de-aired and clamped. The proximal ascending aortic procedure is performed during the subsequent rewarming.

All the patients included in this study had a reconstruction of one or more of the sinuses of Valsalva which were affected by the dissection. The decision to perform a root reconstruction rather than a Bentall procedure was taken intra-operatively by the surgeon and dependant upon his preference and estimation of the feasibility. The aortic root was reconstructed with either Teflon® (C.R. Bard, Tempe, AZ, USA) felt (n=21), gelatine-resorcinol-formaldehyde-glue® (GRF-glue®, Fii, Saint-Just-Malmont, France) (n=103), or fibrinous glue (Tissu-col®, Immuno AG, Vienna, Austria) (n=5). The reconstructive material was put between the dissected aortic layers. The total number of applications outranges the total number of patients involved in the study as several patients had a combination of any of the root reconstructive techniques (Table 3). Two patients had a surprising combination of GRF-glue® and fibrinous glue. This was due to unforeseen lack of stock which only became apparent during the operation, when additional glue was required for optimal apposition of the dissected layers.

The aortic valve was resuspended by a commissuroplasty, using pledgetted U-stitches in all patients. The ascending aorta was replaced by a prosthesis starting at the level of the sino-tubular junction, in all but 10 patients who underwent a local repair of the intimal tear. These patients were operated early in the series and we currently do not perform local repair any more.

Mean aortic cross-clamp time, DHCA and ECC were 101±37, 36±18 and 176±61 minutes respectively.

Table 3: Aortic root reconstructive techniques used in the study group (n=121).

Technique used	N
GRF-glue® alone	90
Teflon® felt alone	7
Fibrinous glue alone	1
GRF-glue® + Teflon® felt	11
GRF-glue® + fibrinous glue	1
Teflon® felt + fibrinous glue	2
GRF-glue® + Teflon® felt + fibrinous glue	1
Unknown	8

GRF-glue®: gelatine-resorcinol-formaldehyde-glue® ; N : number of patients

Assessment of repair and durability

The initial repair was assessed intra-operatively, at first by the hemodynamic parameters and from 1988 on also by transoesophageal echocardiography (TEE) whenever available. This was however not always the case in emergency conditions.

The repair durability was primarily assessed by the incidence of aortic valve and root reoperation. All reoperations were analysed and the causes were noted. All other re-operations were also recorded. Causes of death were also analyzed to detect recurrent aortic regurgitation as a possible causative factor.

In addition, the latest available transthoracic echocardiogram (TTE) was used to determine the degree of aortic regurgitation and the presence of aortic root dilatation. TTE was available in 56 of 67 patients who retained their native aortic valve at the time of follow-up. In patients undergoing an aortic valve and root reoperation, the last TTE prior to the reoperation was used.

Table 4: Causes of 30 day mortality (n=26).

Cause of death	N
Stroke	13
Heart failure	5
Hemorrhage	5
Sepsis	2
Unknown	1

N: number of patients

Postoperative follow-up

The 30 day mortality was 21.5% (n=26). Ten of these patients were operated in cardiogenic shock. Causes of death are summarized in Table 4. None of the patients dying of heart failure had recurrent aortic regurgitation. Six of the 13 neurological deaths occurred in patients who had a preoperative persisting central neurological deficit and one in a patient who had preoperatively a transient neurological deficit. Actuarial survival at 30 days was 78±4%.

Postoperative complications were frequent: nine patients required temporary dialysis, 23 patients required prolonged (>5 days) mechanical ventilation and 15 patients experienced a new peri-operative neurological event. In 10 of these, the deficit was central versus peripheral in five.

Follow-up was achieved either by yearly outpatient visit or by phone and letter to the patient and his referring physician. A file on current status, medication, morbidity and mortality was completed per patient. Follow-up was closed June 1st 1999 and was 100% complete. Mean follow-up was 43±46 months with a maximum of 16 years in two patients. There were 20 late deaths. The causes are summarized in Table 5. Four of these deaths occurred after an aortic valve reoperation (see 'Results'). None of the patients died of recurrent aortic regurgitation. Actuarial survival was 72±4%, 64±5% and 53±6% at 1.5 and 10 years postoperatively (Fig. 1).

Table 5: Causes of late death (n=20).

Cause of late death	**N**
Aortic rupture	5
Sepsis	3
Stroke	3
Heart failure	3
Sudden death	2
COPD	1
Malignancy	1
Unknown	2

N: number of patients; COPD: chronic obstructive pulmonary disease

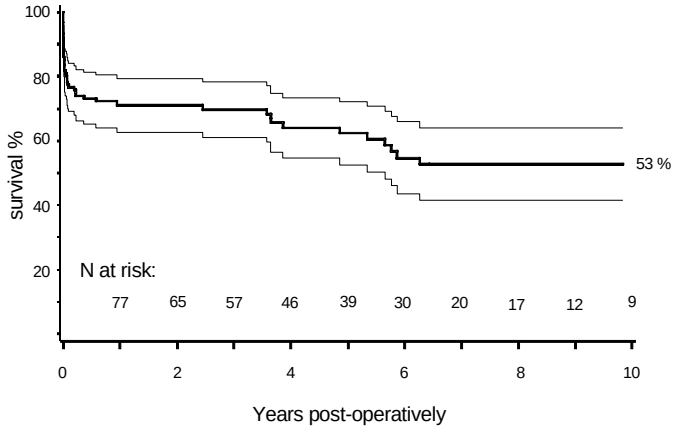

***Figure 1**: Actuarial survival of patients with acute Type A dissection and aortic valve preservation (including 30 day mortality).*

Eight patients with retained native aortic valve experienced a neurological event during late (>30 days) follow-up: six had a transient ischaemic attack (TIA) and two a stroke. One patient had two TIA's; another twice a stroke for a total of 10 postoperative neurological events. With the exclusion of the preoperative and per-operative neurological events, the postoperative freedom from thrombo-embolic event rate was 95% at 1 year and 89% at 10 years (Fig. 2).

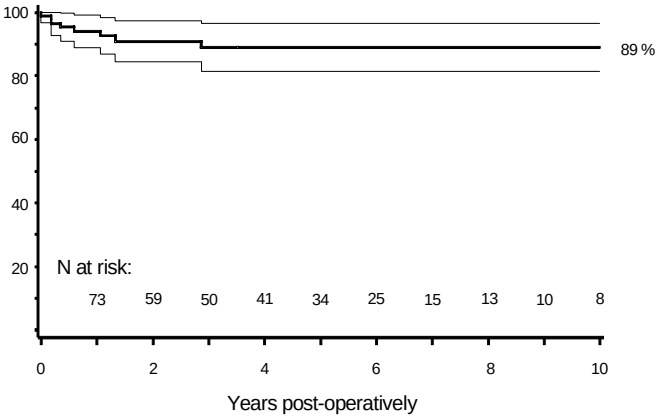

***Figure 2**: Freedom from thrombo-embolic events in patients surviving >30 days (exclusive the preoperative and peri-operative neurological events).*

Statistical analysis

The design of the study was retrospective and analysis was performed with the Statistical Analysis Software (SAS Institute, version 6.12 for Windows, Cary, NC). Data are expressed as the mean ± the standard deviation. Survival and event-free estimates were determined by the method of Kaplan-Meier [10] and are expressed as proportion ± the standard error. Comparison between variables was performed with the chi-square or Fisher exact test when appropriate. A p-value less then 0.05 was considered statistically significant. Cox proportional hazard analysis was used to determine risk factors for aortic valve reoperation. Variables with a p-value < 0.15 on univariate analysis were entered in the multivariate analysis.

Results

Aortic root reoperation

Aortic root reoperation occurred in 12 patients at a mean of 4±2.8 years postoperatively. Details on these patients are summarized in Table 6. Aortic root dilatation with subsequent aortic regurgitation was the major cause of reoperation, occurring in nine patients. All root reoperations included aortic valve replacement. Four patients died at reoperation. Freedom from aortic root reoperation was 95±2%, 89±4% and 69±9% at 1, 5 and 10 years respectively (Fig. 3).

A total of eight patients had an aortic valve annulus > 27 mm measured intraoperatively and four of these patients required a reoperation (Table 6). Reoperation occurred in five of 21 (23%) patients in whom Teflon® was used for reconstruction of the aortic root. With regard to the use of GRF-glue® and fibrinous glue, reoperation occurred in 11 of 103 patients (11%) and 2 of 5 patients (40%) respectively. Multivariate Cox-proportional hazard analysis revealed the use of fibrinous glue (RR=8.7; p=0.03) and the presence of an aortic valve annulus > 27 mm (RR=4.2; p=0.04) as independent risk factors for aortic root reoperation. The use of Teflon® was correlated with an increased risk for reoperation (RR=2.8 on univariate analysis and RR=1.5 on multivariate analysis) but this was not statistically significant (p=0.08 and p=0.5 on uni- and multivariate analysis respectively). Freedom from aortic root reoperation was significantly worse when one or two of the independent risk factors were present as was the case in 11 patients; it was 97% at 1 year, 92% at 5 years and 79% at 7 years if risk factors were absent versus 79% at 1 year, 66% at 5 years and 33% at 7 years when any or both of the risk factors were present (p=0.0001) (Fig. 4). The curve of the patients with risk factors falls to zero since the patient with the longest follow-up in this group was reoperated 7.4 years after the initial operation.

Table 6: Aortic valve/root reoperations during follow-up.

Pt	Operation (year)	Technique	annulus > 27 mm at in. oper	Pre-reop AR	Primary indication for reoperation	Interval to reop (months)	Reoperative procedure	Outcome
1	1985	Teflon	Yes	4 +	Root dilatation	75	Bentall	Alive
2	1988	GRF	No	2 +	False aneurysm; 2 VD	83	Bentall, CABG	Alive
3	1990	GRF	Yes	4 +	Root dilatation	11	Bentall	Reop death
4	1990	Teflon + GRF	No	3 +	Root dilatation	70	Bentall, arch, ET	Alive
5	1990	GRF	Yes	2 +	Root dilatation; 2 VD	66	Bentall, arch, ET, CABG	Alive
6	1991	GRF	No	4 +	Root dilatation	41	AVR, asc, arch, ET	Alive
7	1991	Teflon + GRF + Fibrinous glue	Yes	4 +	Root dilatation; 3 VD	22	Bentall, arch, ET, CABG	Alive
8	1992	Teflon + GRF	No	4 +	Root dilatation; 2 VD	67	Bentall, CABG	Alive
9	1992	GRF	No	3 +	Root dilatation; 2 VD; MR	39	Bentall, arch, ET, CABG, MVR	Alive
10	1992	GRF	No	4 +	Dehiscence at commissure	2	AVR	Reop death
11	1992	Teflon + GRF	No	2 +	Root dilatation	12	AVR, asc	Reop death
12	1997	GRF + Fibrinous glue	No	2 +	Graft infection	7	AVR homograft, omentoplasty	Reop death

AR: aortic regurgitation; arch: aortic arch replacement; asc: ascending aortic replacement; AVR: aortic valve replacement; CABG: coronary artery bypass grafting; ET: elephant trunk; GRF-glue®: gelatine-resorcinol-formaldehyde-glue®; in. oper: initial operation; MR: mitral regurgitation; MVR: mitral valve replacement; Pre-reop: pre-reoperative; Pt: patient; reop: reoperation; VD: vessel disease

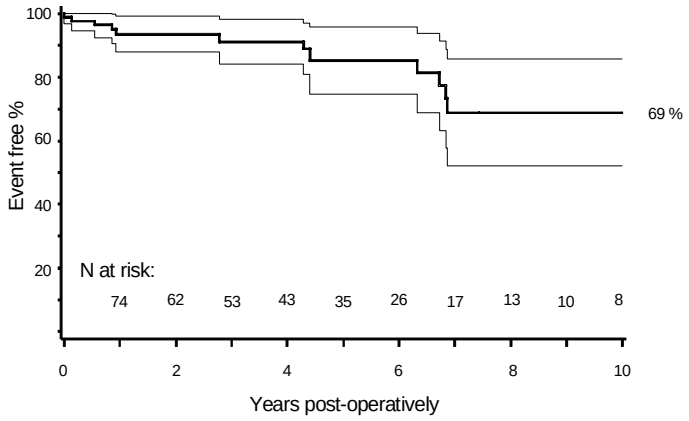

***Figure 3**: Freedom from aortic root reoperation in patients surviving > 30 days.*

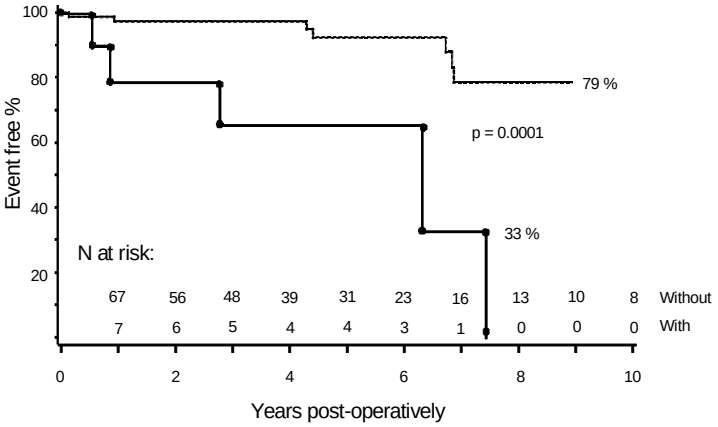

***Figure 4**: Freedom from aortic root reoperation (>30 days) according to the presence of risk factors -.- with risk factors; -- without risk factors.*

Other reoperations

Twelve additional aortic reoperations were performed during follow-up. These included three false aneurysms at the distal prosthesis-aortic arch anastomosis, one more prosthesis infection, two descending aortic aneurysm replacements, two thoracoabdominal aortic aneurysm replacements, three abdominal aortic aneurysm replacements and one iliac artery reconstruction. There were no deaths at these additional reoperations. Freedom from any aortic reoperation was 92±3%, 81±5% and 54±9% at 1, 5 and 10 years postoperatively (Fig. 5).

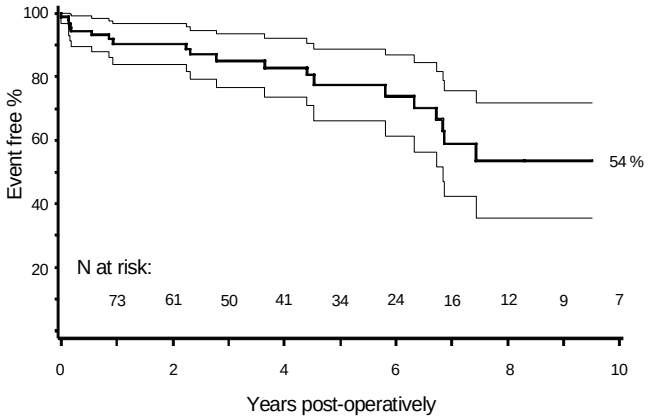

***Figure 5**: Freedom from any aortic reoperation in patients surviving >30 days.*

Assessment of repair durability

As stated earlier, none of the patients who died of heart failure (five operative deaths and three late deaths), had recurrent aortic regurgitation.

At follow-up, 67 patients of 75 survivors had retained their native aortic valve. A TTE was available in 56 of these patients. As indicated in Table 7, the majority of the patients had no or 1+ aortic regurgitation. Median degree of aortic regurgitation was 1+. Twelve patients had 2+ and 2 patients had 3+ aortic regurgitation. They are currently asymptomatic but carefully followed at regular intervals.

Details concerning the aortic root dimensions at the level of the sinuses of Valsalva, measured in the same patient cohort at follow-up, are given in Table 8. Ten patients had an aortic root measuring over 40 mm of whom 2 had a diameter exceeding 50 mm, a limit that is currently considered being an operative indication [8].

Table 7: Results of the follow-up TTE with regard to the presence of aortic regurgitation (n=56 of 67 surviving patients with retained native aortic valve).

Degree of aortic regurgitation	N
0	19
1 +	23
2 +	12
3 +	2

N: number of patients; TTE: transthoracic echocardiogram

Table 8: Follow-up TTE measurements of the aortic root at the level of the Sinuses of Valsalva (n=56 of 67 surviving patients with retained native aortic valve).

Diameter in mm	N
35 or less	37
36 – 40	9
41 - 45	7
46 - 50	1
> 50	2

mm: millimeter; N: number of patients; TTE: transthoracic echocardiogram.

Comment

Operative mortality

Although the outcome of the surgical management of Type A dissection has considerably improved over the years [11-12], operative mortality is still substantial. Reported operative mortality in literature is as low as 6 [5-6] to 8% [13] but is usually between 20 and 30% [3-4, 7, 12, 14-17]. Our operative mortality was 21.5% (n=26) which is comparable with these reports. One of the contributing factors to this high operative mortality is undoubtedly the high proportion of (referred) patients operated in cardiogenic shock (25%). Ten of 30 patients operated in cardiogenic shock died. Major efforts are constantly made to organise prompt referral of patients diagnosed with Type A dissection in order to decrease the incidence of preoperative cardiogenic shock. We hope this will contribute to decrease operative mortality.

Durability of the root repair

Durability was assessed by the incidence of aortic root reoperation and by follow-up TTE. Advantages of preservation of the native aortic valve are avoidance of a valve substitute with its possible adverse effects but also avoidance of a permanent need of anticoagulation in mechanical valve replacement. This need of anticoagulation will impair the spontaneous thrombosis in the false lumen and persistent perfusion of the false lumen will lead to aneurysm formation which has been associated with decreased late survival [11]. The advantages of valve preservation have to be balanced against the risk of reoperation during follow-up. Freedom from aortic valve reoperation at 10 years has been reported to be as high as 95% [17] when valve preservation was performed. However, other reports mention 80% freedom from aortic valve reoperation at 10 years [4, 18]. Freedom from aortic valve/root reoperation at 10 years in the present series was 69%. This is somewhat lower than the previously mentioned reports.

Table 6 indicates that the use of GRF-glue® did not prevent aortic root dilatation in some instances, contrary to a previous report [6]. In addition, follow-up TTE revealed two patients with 3 + aortic regurgitation and 10 patients with an aortic root diameter > 40 mm. It seems undoubtful that some of these patients will need reoperation in the future. Further follow-up of this patient cohort seems therefore mandatory.

Risk factors for root reoperation

Multivariate Cox-proportional hazard analysis revealed the use of fibrinous glue and the presence of an aortic valve annulus > 27 mm as independent risk factors for aortic root reoperation. This negative impact of fibrinous glue is in sharp contrast with the previously reported results with fibrinous glue by Séguin et al. [5]. This paper reports on the use of fibrinous glue in 15 patients with Type A dissection. There was one non-valve-related

operative death and at a mean follow-up of 2.3 years, the mean aortic regurgitation grade was 0.3. No reoperations were reported.

Most authors currently agree that Marfans' disease and annuloaortic ectasia represent a contra-indication to root preservation during surgery for Type A dissection [3-4, 6, 14, 16, 18]. These patients should undergo a Bentall procedure [2] or alternatively the procedure described by David et al. [8]. Four of the reoperations in the current series occurred in patients having an aortic annulus > 27 mm measured peroperatively. All of these initial operations were performed earlier in the series. In retrospect these patients should not have undergone a root reconstructive procedure which would have decreased the reoperation incidence.

Although not statistically significant, the present series demonstrates a trend towards improved durability in patients treated with GRF-glue® versus Teflon®. The reoperation rate in patients treated with GRF-glue® was 11% versus 23% when Teflon® was used. Equally good results with GRF-glue® have been reported by others, either reporting on a single experience with GRF-glue® [3, 6, 14] or in comparison with Teflon® [19]. The use of GRF-glue® for the reapproximation of the dissected aortic layers decreases the incidence of reoperations as wel as the persistence of false lumina thus increasing the event-free survival. However, in the paper by Pessotto et al. [16], the use of GRF-glue® had no impact on the incidence of reoperation which increased with increasing preoperative aortic regurgitation. Another concern with regards to the use of GRF-glue® is the recent paper by Fukunaga et al. [7]. In a series of 148 patients in whom GRF-glue® was used to reinforce the dissected layers, reoperations were necessary in 20 patients. In nine of these patients, complications necessitating reoperation occurred in aortic segments that underwent reconstruction with GRF-glue® at the first intervention. Root redissection was present in seven patients and another patient presented with a rupture near the distal graft-aorta anastomosis. Macroscopically, the areas looked necrotic but histologic examination in two patients revealed media degeneration rather than necrosis. We had no similar experience as reported in this paper. In particular, we haven't seen redissection occurring in areas treated with GRF-glue®. However, this paper raises an important concern which needs further follow-up. In particular, the formaldehyde component, when excessively used, seems to cause tissue necrosis [7].

Limitations of the study

The current series is a retrospective review covering a long time interval. Accordingly, many surgeons have operated on the patients included in this study. Although every surgeon might have his personal approach, the technique used to reconstruct the aortic root was relatively uniform, with the exception of the use of Teflon®, GRF-glue® or fibrinous glue to approximate the dissected layers. Besides, the decision to perform a root reconstruction was taken intra-operatively and entirely dependant on the surgeons preference and estimation of the feasibility. This is of course very subjective and might have contributed

to a selection bias of patients undergoing root reconstruction. In addition, the individual choice of the product used for root reconstruction resulted in different sample sizes and combination of different products. This bias however should have been taken care of by the statistical analysis.

Another limitation of the study is the absence of a grading system reflecting to what extent the aortic root was affected by the dissection. We initially aimed to do so but given the retrospective nature of the study, many operative reports did not mention to what extent the aortic root was affected and we abandoned this idea. We are therefore unable to determine whether reoperations occurred in the more heavily affected aortic root. It is however our current strategy to reconstruct the aortic root only when one sinus is affected completely or two sinuses partially. If the dissection involves more than one sinus of Valsalva, we currently favor the reimplantation technique described by David [8].

Conclusion

Aortic valve preservation and root reconstruction in patients undergoing surgery for acute Type A aortic dissection with involvement of the aortic root, provides relatively durable results. Freedom from aortic root reoperation is 69% at 10 years.

The use of fibrinous glue seems to compromise the durability of the repair and there is a trend towards enhanced durability whenever GRF-glue® is used versus Teflon®.

We believe that an aortic valve reimplantation procedure according to David or a Bentall procedure is more appropriate in patients with an aortic annulus >27 mm.

References

1. Daily PO, Trueblood HW, Stinson EB. Management of acute aortic dissections. Ann Thorac Surg 1970;10:237-247.
2. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. Thorax 1968;23:338-339.
3. Weinschelbaum EE, Schamun C, Caramutti V, Tacchi H, Cors J, Favaloro RG. Surgical treatment of acute Type A dissecting aneurysm, with preservation of the native aortic valve and use of biologic glue. J Thorac Cardiovasc Surg 1992;103:369-374.
4. Mazzucotelli JP, Deleuze PH, Baufreton C, et al. Preservation of the aortic valve in acute aortic dissection : long-term echocardiographic assessment and clinical outcome. Ann Thorac Surg 1993;55:1513-1517.
5. Séguin JR, Picard E, Frapier JM, Chaptal PA. Aortic valve repair with fibrin glue for Type A acute aortic dissection. Ann Thorac Surg 1994;58:304-307.
6. Westaby S, Katsumata T, Freitas E. Aortic valve conservation in acute Type A dissection. Ann Thorac Surg 1997;64:1108-1112.
7. Fukunaga S, Karck M, Harringer W, Cremer J, Rhein C, Haverich A. The use of gelatin-resorcin-formalin glue in acute aortic dissection Type A. Eur J Cardiothor Surg 1999;15:564-570.
8. David TE, Armstrong S, Ivanov J, Webb G. Aortic valve sparing operations: an update. Ann Thorac Surg 1999;67:1840-1842.
9. Dossche KME, Schepens MAAM, Morshuis WJ, Muysoms FE, Langemeijer JJ, Vermeulen FEE. Antegrade selective cerebral perfusion in operations on the proximal thoracic aorta. Ann Thorac Surg 1999;67:1904-1910.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
11. Svensson LG, Crawford ES, Hess KR, Coselli JS, Safi HJ. Dissection of the aorta and dissecting aortic aneurysms: Improving early and long-term surgical results. Circulation 1990;82(suppl IV):24-38.
12. Fann JI, Smith JA, Miller DC, et al. Surgical management of aortic dissection during a 30-year period. Circulation 1995;92(suppl II):113-121.
13. Miller DC. Surgical management of aortic dissections: indications, perioperative management and long-term results. In: Doroghazi RM, Slater EE, eds. Aortic dissection. New York: Mc Graw-Hill, 1983:193-244.
14. Niederhauser U, Kunzli A, Seifert B, et al. Conservative treatment of the aortic root in acute Type A dissection. Eur J Cardiothorac Surg 1999;15:557-563.
15. Pugliese P, Pessotto R, Santini F, Montalbano G, Luciani GB, Mazzucco A. Risk of late reoperations in patients with acute Type A aortic dissection: impact of a more radical surgical approach. Eur J Cardiothorac Surg 1998;13:576-581.
16. Pessotto R, Santini F, Pugliese P, et al. Preservation of the aortic valve in acute Type A dissection complicated by aortic regurgitation. Ann Thorac Surg 1999;67:2010-2013.
17. von Segesser LK, Lorenzetti E, Lachat M, et al. Aortic valve preservation in acute Type A dissection: is it sound ? J Thorac Cardiovasc Surg 1996;111:381-391.
18. Fann JI, Glower DD, Miller DC, et al. Preservation of aortic valve in Type A aortic dissection complicated by aortic regurgitation. J Thorac Cardiovasc Surg 1991;102:62-75.
19. Nguyen B, Muller M, Kipfer B, et al. Different techniques of distal aortic repair in acute Type A dissection: impact on late aortic morphology and reoperation. Eur J Cardiothorac Surg 1999 ;15 :496-501.

CHAPTER 5

Reimplantation of the aortic valve: first experiences in 13 patients

F.P.A. Casselman, I. Deblier, J.M.P.G. Ernst°, J.J.A.M. Defauw, M.A.A.M. Schepens en W.J. Morshuis

From the department of Cardio-Thoracic Surgery and cardiology°,
St. Antonius Ziekenhuis, Nieuwegein, The Netherlands.

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Abstract

Objective: To report our initial experience with the reimplantation technique of the aortic valve.

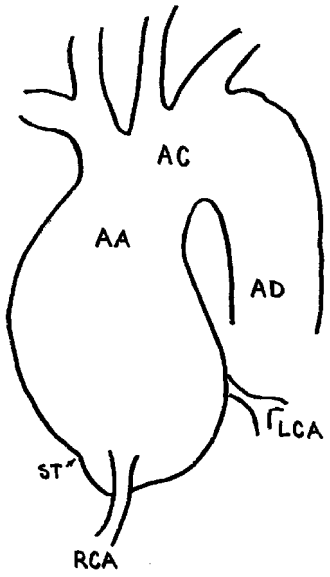
Methods: From January 1st 1998 till January 31st 2000, 13 patients were operated on. Mean age was 52.2±11 years. Median preoperative NYHA functional class was 2 and median preoperative degree of aortic regurgitation was 3. Surgical indications were initially limited to aneurysmal disease of the aortic root (n=6) and ascending aorta (n=4), all complicated by aortic regurgitation. Later on, we also applied the technique in Type A aortic dissection (n=3).

Results: Mean cardiac arrest time and cardiopulmonary bypass time were 184±40 and 254±74 minutes. The primary etiology on histopathological examination was medial necrosis in 5 patients and degenerative disease in the remaining. There was no early neither late mortality and none of the patients was reoperated upon the aortic root. Follow-up was complete at a mean of 12.3±8 months. Median aortic regurgitation at follow-up was 0.5 (p=0.0001 versus preoperative) and median NYHA functional class at follow-up was 1 (p=0.02 versus preoperative).

Conclusions: Our initial experience with the reimplantation technique is promising. The aortic root and ascending aorta are reconstructed and residual aortic regurgitation is minimal. Further experience and follow-up remain necessary to evaluate this technique on the long-term.

Inleiding

De aortawortel bestaat uit de aortaklep met net daarboven de drie sinussen van Valsalva welke apicaal begrensd worden door de sinotubulaire junctie die de overgang vormt naar de eigenlijke (tubulaire) aorta ascendens. De normale aortaklepfunktie is een complexe interactie van deze 3 onderdelen en veronderstelt een appositie van de drie klepblaadjes tijdens diastole zodat er geen lekkage kan optreden van de aorta naar de linker ventrikel. Bij patiënten met een aneurysma van de aortawortel (Fig. 1) ontstaat er vaak een secundaire (centrale) aortaklep lekkage omdat er door het aneurysma een dilatatie optreedt van de sinotubulaire junctie waardoor er tijdens diastole geen goede coaptatie van de klepblaadjes meer kan plaatsvinden. Tot nog toe werden deze patiënten behandeld met een volledige aortawortel vervanging, de zogenaamde 'Bentall' operatie [1]. Deze ingreep omvat een aortaklepvervanging met een conduit bestaande uit een buisprothese waarin de klepprothese (meestal mechanisch) reeds is ingehecht. Dit geheel vervangt aldus de aortaklep, de sinussen van Valsalva, de sinotubulaire junctie en een variabele lengte van de aorta ascendens. De coronair arteriën worden elk afzonderlijk gereimplanteerd in de buisprothese.



***Figuur 1**: Schematische voorstelling van een aneurysmatisch verwijde aortawortel. AA: aorta ascendens; AC : arcus aortae ; AD : aorta descendens ; LCA: linker coronair arterie; RCA: rechter coronair arterie; ST: sino-tubulaire junctie.*

Een lange termijn onderzoek bij patiënten die een Bentall operatie hebben ondergaan leert echter dat er een niet te verwaarlozen incidentie complicaties optreedt waaronder het risico op reoperatie (1.6%/patiënt-jaar), trombo-embolieën (0.4%/patiënt-jaar) en anticoagulantia gerelateerde bloedingsproblemen (1.2%/patiënt-jaar)[2]. Deze laatste twee complicaties zijn inherent aan het levenslang verplicht gebruik van bloedverdunnende medicijnen bij patiënten die een mechanische klepvervanging ondergingen.

Anderzijds is het vaak zo dat bij patiënten met een aneurysma van de aortawortel de eigenlijke aortaklep macroscopisch niet is aangetast en een normale structuur vertoont. Dit betekent dat de aortaklep lekkage bij deze patiënten kan verdwijnen door de dilatatie van de sinotubulaire junctie op te heffen.

Daarom werd door Tirone David een operatietechniek ontwikkeld waarbij de natieve aortaklep gereïmplanteerd wordt in een buisprothese waarmee de sinussen van Valsalva en de proximale aorta ascendens vervangen worden [3-4]. In ons ziekenhuis werd deze techniek in 1998 voor het eerst toegepast. In dit artikel beschrijven wij de opgedane ervaringen.

Patiënten

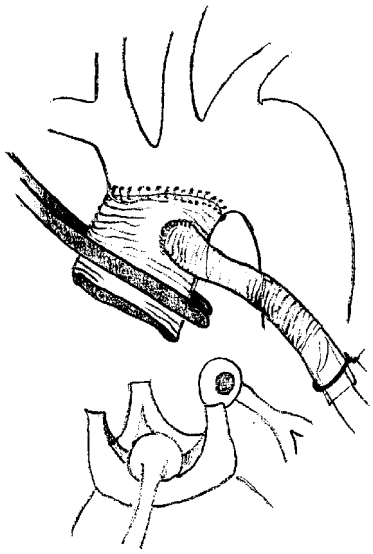
Van 1 januari 1998 tot 31 januari 2000 werden 13 patiënten geopereerd. Dit betrof 9% van alle operaties aan de aortawortel in die periode. Kandidaten voor deze techniek werden geselecteerd op grond van een preoperatief echocardiografisch onderzoek. Hierbij was er een aneurysma van de aortawortel aanwezig en/of een ernstige aortaklep lekkage op basis van een dilatatie van de sinotubulaire junctie bij een morfologisch normale drieslippige aortaklep. Aortaklepstenose of verkalkingen in de aortaklepring waren een exclusie criterium maar een verwijde annulus niet. De definitieve beslissing voor het uitvoeren van de techniek werd peroperatief genomen. De geopereerde patiënten waren 10 mannen en drie vrouwen met een gemiddelde leeftijd van 52.2±11 jaar. De mediane preoperatieve NYHA functionele klasse bedroeg 2 (het betreft hier een schaal van 1 tot 4 waarbij 1 een normale functionele toestand betekent en 4 kortademigheid in rust). Het betrof in alle gevallen een eerste hartoperatie. Initieel werden alleen patiënten met een aneurysma van de aortawortel (n=6) of de aorta ascendens (n=4) geaccepteerd voor deze ingreep. Naderhand werd de techniek ook toegepast bij patiënten met een Type A dissectie (=dissectie waarbij de aorta ascendens is betrokken) waarbij de dissectie doorliep tot in de sinussen van Valsalva met een volledige verstoring van de geometrie van de aortawortel (n=3). Het merendeel van de patiënten had preoperatief een ernstige aortaklep lekkage als gevolg van de pathologie van de aortawortel. De mediane preoperatieve aortaklep lekkage bedroeg 3 (=schaal van 0 tot 4 waarbij graad 4 massale aortaklep lekkage betekent). Behoudens de drie patiënten met een Type A dissectie was de ingreep steeds electief.

De comorbiditeit bestond bij vijf patiënten uit arteriële hypertensie, twee patiënten hadden coronarialijden en een andere patiënt had chronisch obstructief longlijden. Bij zes

patiënten waren reeds familieleden geopereerd aan het hart of de aorta. Geen enkele patiënt had de kenmerken van het syndroom van Marfan.

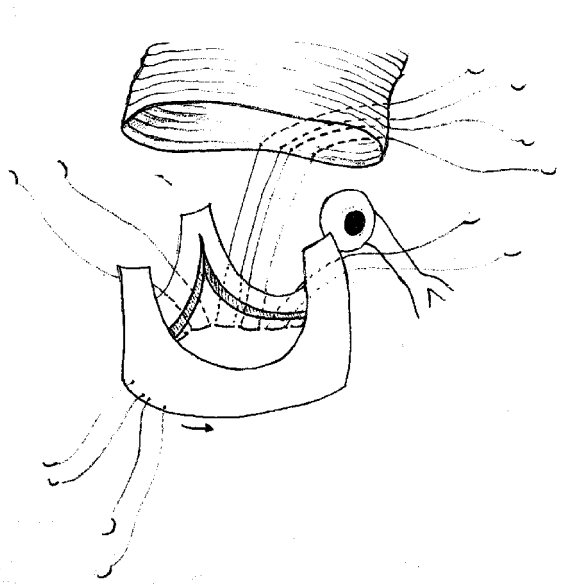
Operatietechniek

De patiënt wordt op de gebruikelijke manier aangesloten aan de hartlong machine. In eerste instantie wordt met behulp van een aparte prothese de distale aorta ascendens, indien nodig, vervangen (Fig. 2).

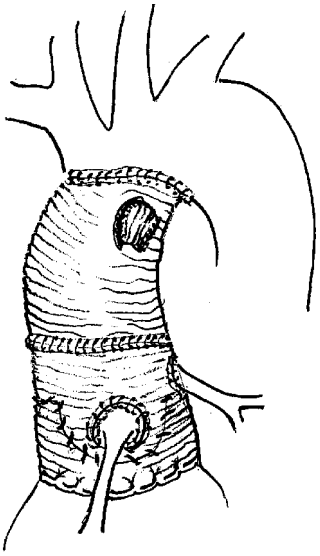


Figuur 2*: De distale anastomose is voltooid; de prothese is afgeklemd en lichaamsperfusie gebeurt via een zijarm op de prothese.*

Nu wordt de aortawand ter hoogte van de drie sinussen van Valsalva uitgesneden en worden de twee coronaire ostia geïsoleerd voor latere reïmplantatie. Vervolgens wordt de proximale hechtlijn gelegd door afzonderlijke draden polypropylene 4/0 als U-hechtingen net onder de aortaklepblaadjes door de aortaklepannulus van binnen naar buiten aan te brengen, waarbij zoveel mogelijk een horizontale lijn wordt aangehouden (Fig. 3). Vervolgens worden deze hechtingen door de prothese gebracht en wordt de prothese ingeknoopt. De maat van de proximale prothese wordt bepaald door de maximale hoogte van de klepblaadjes (KB) en wordt als volgt berekend: KB(in mm) x 2/3 x 2 + 5mm = diameter prothese in mm. De maximale hoogte van de klepblaadjes wordt peroperatief bepaald door directe meting vanaf de annulus tot de vrije rand.



***Figuur 3**: Proximale aortawortel reconstructie : de U-hechtingen worden in een horizontaal vlak door de aortaklepring van binnen naar buiten gebracht en vervolgens door de prothese.*



***Figuur 4**: Eindresultaat nadat de aortaklep in de prothese werd gefixeerd, de coronaire ostia werden gereimplanteerd en de anastomose tussen de 2 prothesen werd voltooid. De zijarm van de prothese werd doorgenomen en overhecht.*

De natieve aortaklep bevindt zich nu centraal in de prothese en wordt hierin gefixeerd: eerst worden de drie commissuren op de juiste hoogte opgehangen; vervolgens wordt een doorlopende hechtlijn gemaakt met polypropylene 5/0 tussen de basis van de oorspronkelijke sinus van Valsalva en de prothese. Daarna worden de coronaire ostia gereimplanteerd met behulp van een polypropylene draad 6/0. Als laatste anastomose worden nu de beide prothesen aan elkaar gehecht (Fig. 4). Het vervolg van de procedure is standaard.

Het resultaat van de plastiek wordt peroperatief beoordeeld door een transoesophagale echocardiografie en postoperatief door een transthoracale echocardiografie. Postoperatief worden de patiënten gedurende drie maanden geanticoaguleerd (gezien de aanwezigheid van kunstmateriaal) of langer indien hiervoor andere indicaties zijn.

Resultaten

Er traden geen technische problemen op welke een verandering of aanpassing van de techniek noodzakelijk maakten. Postoperatieve ondersteuning met inotropica was tijdelijk nodig bij een patiënt. Geassocieerde procedures aan de 'Davidplastiek' waren een totale boog-vervanging bij vier patiënten (waarvan twee met additioneel een elephant trunk procedure en een met additioneel een proximale aorta descendens vervanging); zes patiënten kregen een partiele boog vervanging en twee patiënten ondergingen een myocard revascularisatie. Slechts drie van de 13 patiënten ondergingen geen additionele procedure. De gemiddelde cardiale ischemie tijd en extracorporele circulatie duur bedroegen respectievelijk 184±40 en 254±74 minuten. Bij een patiënt diende een dreigende tamponade ontlast te worden op de eerste postoperatieve dag. Verder waren er geen grote post-operatieve problemen. Er waren geen perioperatieve neurologische afwijkingen. Er was geen operatieve (noch laattijdige) sterfte.

Histologisch onderzoek van de aortawand toonde de aanwezigheid van primaire tunica media degeneratie bij vijf patiënten. De andere patiënten vertoonden degeneratieve veranderingen met uiteraard tekenen van aorta dissectie bij drie patiënten.

Er waren geen reoperaties aan de aortawortel maar een patiënte met een mega-aorta onderging wel een correctie van een thoraco-abdominaal aneurysma, 6 maanden nadat zij een David plastiek, aangevuld met een totale boog vervanging en een elephant trunk, had ondergaan. Een andere patiënt onderging 2,5 maand na de initiële operatie, een subxyphoidale punctie ter ontlasting van een late tamponade. Er waren geen episoden van endocarditis noch traden er trombo-embolische complicaties op.

Na een gemiddelde follow-up tijd van 12.3±8 maanden was de mediane aortaklep lekkage 0.5 ($p=0.0001$ versus preoperatief). De ernst van de preoperatieve aortaklep lekkage hield geen verband met de ernst van de laattijdige graad van lekkage ($p=0.7$). De mediane NYHA functionele klasse bij follow-up was 1 ($p=0.02$ versus preoperatief).

Commentaar

Aortawortel dilatatie is tegenwoordig de meest frequente oorzaak van geïsoleerde aortaklep lekkage. De prevalentie lijkt bovendien ook toe te nemen, waarschijnlijk door een afname van de rheumatische klepaandoeningen [5]. Aortawortel dilatatie kan ontstaan op degeneratieve basis maar kan ook geassocieerd zijn aan het syndroom van Marfan of aan andere aandoeningen die gepaard gaan met een verzwakte aortawand zoals primaire media degeneratie of stoornissen van het bindweefsel zoals het Ehlers-Danlos syndroom [6-8]. Deze diversiteit in etiologie is ten dele ook in onze patiënten populatie aanwezig gezien het histologisch onderzoek degeneratieve veranderingen aantoont bij acht patiënten en een primaire media degeneratie bij vijf patiënten. Patiënten met een andere bindweefsel aandoening werden tot nog toe niet voor deze ingreep in aanmerking genomen.

Daar bij deze aandoeningen de aortaklep annulus alsook de klepblaadjes macroscopisch normaal zijn en er anderzijds nog geen perfecte klepprothese beschikbaar is op de markt, lag het voor pioniers als David voor de hand een operatieve techniek te ontwikkelen waarbij nagenoeg de gehele aortawand ter hoogte van de aortawortel wordt weggenomen en de natieve aortaklep opnieuw wordt opgehangen in een buisprothese [3]. Deze ‘reïmplantatie’ techniek werd voor het eerst gepubliceerd in 1992 maar betrof toen slechts 10 patiënten. Eén van de potentiele nadelen welke toen geopperd werden, was het mogelijk ‘slijtage effekt’ op de klepblaadjes als deze in systole tegen de prothese aan slaan gezien de techniek alle drie sinussen van Valsalva opheft. Of het opheffen van de sinussen van Valsalva op zichzelf een nadelig effect zou uitoefenen op de klepfunctie was evenmin bekend.

Toen ook andere groepen de techniek met mondjesmaat begonnen uit te voeren [9-11] en in 1997 uitstekende middellange resultaten door David gepubliceerd werden [12] besloten ook wij deze techniek te gaan uitvoeren. Aanvankelijk beperkten wij ons tot aneurysmata van de aortawortel en aorta ascendens. Daar deze techniek echter door nagenoeg iedereen die ze toepast ook aangewend wordt ter behandeling van Type A aorta dissecties [3, 9-11] en anderzijds de laattijdige resultaten van aortawortel reconstructie bij Type A dissectie zeker voor verbetering vatbaar zijn [13-14] besloten ook wij deze techniek voor deze indicatie toe te passen, ten minste in die gevallen waar de dissectie doorloopt tot in de sinus(sen) van Valsalva. Hierdoor zal ongetwijfeld het aantal indicaties voor deze techniek toenemen. Bicuspide aortakleppen hebben wij alsnog niet in onze indicatiestelling opgenomen ofschoon dit door anderen wel gebeurt [15].

Onze eerste ervaringen met deze techniek zijn gunstig. Wel is duidelijk dat deze techniek enkel is weggelegd voor chirurgen met ruime ervaring in de aortawortel chirurgie; ook zij ondervinden een zeker leerproces. Dit uit zich ten dele in de relatief lange cardiale ischemie tijd (184±40 minuten) al wordt deze uiteraard ook bepaald door het relatief hoog aantal geassocieerde ingrepen in deze patiëntengroep (slechts drie patiënten hadden geen geassocieerde ingreep en sommigen hadden verscheidene geassocieerde ingrepen). Ondanks de leercurve kenden wij echter geen technische problemen bij het uitvoeren van de techniek, met name traden er geen problemen op van valse aneurysmata op de proximale naad of ontstond er geen myocardischemie door technische problemen met de reïmplantatie van

de coronair arteriën. De twee patiënten die een myocard revascularisatie ondergingen hadden preoperatief aangetoonde letsels.

Morbiditeit was gering en mortaliteit afwezig. Follow-up echocardiografie toont dat de techniek de aortawortel dilatatie corrigeert en de aortaklep lekkage nagenoeg opheft. Het blijft echter belangrijk de patiënten op regelmatige basis te blijven controleren omdat twee gevallen van recidiverende aortaklep lekkage werden gepubliceerd [16-17]. Daar tegenover staan echter de uitstekende middellange termijn resultaten van David waarbij slechts 3% van de patiënten na zes jaar dienden gereopereerd te worden en slechts 2% van de patiënten een aortaklep lekkage heeft van graad 2 of meer [12]. Lange termijn resultaten zijn vooralsnog niet beschikbaar en derhalve kan deze ingreep dan ook nog niet tot de routine cardiochirurgie gerekend worden.

Conclusie

Onze initiële ervaring met de reïmplantatie techniek ter behandeling van patiënten met een aortawortelditatie of een Type A dissectie welke tot in de aortawortel doorloopt, is gunstig verlopen. De korte termijn follow-up toont zeer bevredigende resultaten zowel functioneel als wat de echocardiografische bevindingen betreft. Het blijft echter noodzakelijk deze patiënten echocardiografisch te volgen.

Samenvatting

Doel: Het evalueren van een nieuwe chirurgische techniek voor de behandeling van specifieke aandoeningen van de aortawortel.
Patiënten **:** Van 1 januari 1998 tot 31 januari 2000 werden 13 patiënten geopereerd volgens de aortaklepreimplantatie techniek beschreven door David. De gemiddelde leeftijd was 52.2±11 jaar. De mediane preoperatieve NYHA functionele klasse was 2 en de mediane preoperatieve aortaklep lekkage 3. De indicatie voor operatie was een aneurysma van de aortawortel (n=6) of de aorta ascendens (n=4), meestal met secundair ernstige aortaklep lekkage. In een latere fase van de studieperiode werd de indicatie uitgebreid tot Type A aorta dissecties met uitbreiding tot de aortawortel (n=3).
Resultaten: Er waren geen technische problemen die een verandering of aanpassing van de techniek noodzakelijk maakten. De gemiddelde cardiale ischemie tijd en extracorporele circulatie duur bedroegen respectievelijk 184±40 en 254±74 minuten. Na een gemiddelde follow-up tijd van 12.3±8 maanden was de mediane aortaklep lekkage 0.5 (p=0.0001 versus preoperatief) en de mediane NYHA functionele klasse 1 (p=0.02 versus preoperatief). Histologisch onderzoek van de aortawand toonde de aanwezigheid van primaire media degeneratie bij vijf patiënten. De overige patiënten vertoonden degeneratieve veranderingen

in de aortawand. Geen enkele patiënt overleed en er waren geen reoperaties aan de aortawortel.
Besluit: Op grond van deze eerste ervaringen kan worden gesteld dat de aortaklep re-implantatie techniek volgens David kan worden uitgevoerd met een zeer laag operatief risico en een lage graad van residuele aortaklep lekkage. Na de beginperiode werd de indicatiestelling uitgebreid tot patiënten met een Type A dissectie en ernstige destructie van de aortawortel.

References

1. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. Thorax 1968;23:338-339.
2. Dossche KM, Schepens MAAM, Morshuis WJ, Brutel de la Rivière A, Knaepen PJ, Vermeulen FEE. A 23-year experience with composite valve graft replacement of the aortic root. Ann Thorac Surg 1999;67:1070-1077.
3. David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. J Thorac Cardiovasc Surg 1992;103:617-622.
4. David TE, Feindel CM, Bos J. Repair of the aortic valve in patients with aortic insufficiency and aortic root aneurysm. J Thorac Cardiovasc Surg 1995;109:345-352.
5. Olson LJ, Subramanian R, Edwards WD. Surgical pathology of pure aortic insufficiency: a study of 225 cases. Mayo Clin Proc 1984;59:835-841.
6. Roberts WC, Honig HS. The spectrum of cardiovascular disease in the Marfan syndrome: a clinico-morphologic study of 18 necropsy patients in comparison to 151 previously reported necropsy patients. Am Heart J 1982;104:115-135.
7. Ferlic RM, Goot B, Edwards JE, Lillehei CW. Aortic valvular insufficiency associated with cystic medial necrosis: surgical and pathologic considerations. Ann Surg 1967;165:1-9.
8. Leier CV, Call TD, Fulkerson PK, Wooley CF. The spectrum of cardiac defects in the Ehlers-Danlos syndrome, types I and III. Ann Intern Med 1980;92:171-178.
9. Simon P, Mortiz A, Moidl R, et al. Aortic valve resuspension in ascending aortic aneurysm repair with aortic insufficiency. Ann Thorac Surg 1995;60:176-180.
10. Schafers HJ, Fries R, Langer F, Nikoloudakis N, Graeter T, Grundmann U. Valve-preserving replacement of the ascending aorta: remodeling versus reimplantation. J Thorac Cardiovasc Surg 1998;116:990-996.
11. Harringer W, Pethig K, Hagl C, Wahlers T, Cremer J, Haverich A. Replacement of ascending aorta with aortic valve reimplantation: midterm results. Eur J Cardiothorac Surg 1999;15:803-808.
12. David TE. Aortic root aneurysms: remodeling or composite replacement? Ann Thorac Surg 1997;64:1564-1568.
13. Simon P, Owen AN, Moidl R, et al. Sinus of Valsalva aneurysm: a late complication after repair of ascending aortic dissection. Thorac Cardiovasc Surgeon 1994;42:29-31.
14. Casselman FP, Tan MESH, Vermeulen FEE, Kelder JC, Morshuis WJ, Schepens MAAM. Durability of aortic valve preservation and root reconstruction in acute Type A aortic dissection. Ann Thorac Surg 2000;70:1227-1233.
15. David TE, Armstrong S, Ivanov J, Webb G. Aortic valve sparing operations: an update. Ann Thorac Surg 1999;67:1840-1842.
16. Gallo R, Kumar N, Al Halees Z, Duran C. Early failure of aortic valve conservation in aortic root aneurysm. J Thorac Cardiovasc Surg 1995;109:1011-1012.
17. Kamohara K, Itoh T, Natsuaki M, Norita H, Naito K. Early valve failure after aortic valve-sparing root reconstruction. Ann Thorac Surg 1999;68:257-259.

CHAPTER 6

Repeated anticoagulation events after mechanical aortic valve replacement

Filip P Casselman MD[1,2], Michiel L Bots MD PhD[3], Willem Van Lommel MD[4], Paul J Knaepen MD[1], Ruud Lensen MD PhD[2] and Freddy EE Vermeulen MD[1,2]

Department of Cardio-Thoracic Surgery[1] and 'Stichting Hartenzorg'[2], St. Antonius Ziekenhuis, Nieuwegein, Julius Center for General Practice and Patient Oriented Research, University Medical Center[3], Utrecht; Department of Cardiology[4], Rijnstate Ziekenhuis Arnhem, The Netherlands

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Abstract

Objective: The choice of a valve substitute in young adults requires a decision balancing the risks of long-term anticoagulation versus reoperation(s). This paper analyzes the long-term risk and determinants of anticoagulation related complications after mechanical aortic valve replacement.
Patients and Methods: Between December 1963 and January 1974, 249 patients survived a mechanical aortic valve replacement at our institution. Mean age was 41.8±12.4 years and 81% (n=202) were male. Ball valves were implanted in 24% (n=61) and disc valves in 76% (n=188). Patients were anticoagulated with vitamin K antagonists and antiplatelet drugs. A total of 4855 patient-years was available for analysis. Mean follow-up was 19.5±9.4 years and was 100% complete. Analyses were performed with Kaplan-Meier and multivariable Cox regression methods.
Results: One hundred and two patients had one anticoagulation related event and 58 patients had two events. Six patients had more than five events. Freedom from a first anticoagulation related event was 74.8±2.9%, 55.3±3.5%, 46.8±4.0% at 10, 20 and 30 years. For a second event this was 45.4±5.4%, 29±6.0% and 23.2±7.1%. Multivariate predictors for anticoagulation related complications were ball valve (O.R.=2.9), postoperative endocarditis (O.R.=2.2) and any surgery (O.R.=2.2). The incidence of events was highest the first five years postoperatively.
Conclusions: The risk of adverse events is highest the first five postoperative years. Once an event has occurred, the risk for a second event is increased. The incidence and frequency of events is substantial and should be considered in the choice of a valve substitute.

Introduction

Aortic valve surgery in young adults requires a complex decision. Traditionally, mechanical valves are the preferred device since structural failure occurs relatively seldom. However, mechanical valves require lifelong anticoagulation. Other options include bioprostheses, allografts, autografts or, for a minority, valve repair. None of these strictly requires anticoagulation but long-term follow-up is limited and structural failure with subsequent reoperation occurs more frequently in comparison with mechanical devices [1-4].

Since a considerable proportion of patients in need of an aortic valve replacement still has 25 to 50 years life-expectancy, it is important in the decision-making to consider the lifelong risk of anticoagulation related complications in case of a mechanical valve substitute. Some papers in literature deal with long-term follow-up after mechanical valve replacement [5-8]. However, the follow-up seldomly reaches more than 25 years and is hardly ever complete. Besides, most studies censor the patient at the first event for a given complication, hereby neglecting subsequent events. It is therefore extremely difficult to estimate the real incidence of anticoagulation related complications.
The present study focuses on the very long-term follow-up after mechanical aortic valve replacement with specific emphasis on the occurrence and frequency of anticoagulation related complications and its determinants.

Methods

Patient selection

December 1963 was the start of the aortic valve replacement program at our institution and we considered the first 10 years of this program (December 1963 through January 1st 1974). A total of 312 patients underwent aortic valve replacement during this time frame of whom all hospital survivors were included in the study. Reoperations, urgent or combined procedures were included. Following these criteria, 249 patients were the subject of further analysis in this report.

Demographics

Mean age of these 249 hospital survivors was 41.8±12.4 years (range 14 to 68) and 81% (n=202) were male. Most of the patients had an isolated aortic valve replacement (n=242). The remainder (n=7) had simultaneous coronary artery bypass grafting (CABG). In a minority of patients, the aortic valve replacement was a reoperation after a previous congenital aortic valve commissurotomy (n=13) and in three patients it was a reoperation after a correction of aortic coarctation. The cause of the valve disease in the remaining patients was predominantly rheumatic. Preoperative active endocarditis was present in 28 patients (11%). Isolated aortic stenosis was present in 12.4% (n=31) of patients whereas

isolated aortic regurgitation and mixed disease were present in 42.2% (n=105) and 45.4% (n=113) respectively. The procedure was elective in 94% (n=233) of the patients and urgent in the remainder (n=16). The replaced aortic valve was tricuspid in 202 patients (81%) and bicuspid in 38 patients (15%). It was unknown in nine patients.

Several types of mechanical valves were used during the study period. Types and number of implantations per valve type are given in Table 1. Postoperatively, patients were anticoagulated with vitamin K antagonists in association with an antiplatelet agent (mostly dypiridamole). The level of anticoagulation was followed with the trombotest and the target in those days was between 10 and 6% which corresponds with an INR between 2.8 and 4.2 [9]. Patients were regularly followed by the Dutch thrombosis service, a national organisation with multiple regional offices and especially created to follow anticoagulated patients in order to coordinate an adequate anticoagulation level. This organisation is run by nurses and supervised by doctors who determine the anticoagulant dosis according to predetermined target levels of INR according to the indication for anticoagulation.

Table 1: Types, era of implantation and number of a specific valve implanted (n=312).

Type of mechanical valve	**N**	**Hospital Survivors**
Starr-Edwards 1000 (December 1963 - August 1966)	30	10
Starr-Edwards 1200/1260 (September 1966 - June 1968)	37	23
Starr-Edwards 2300 (July 1968 - October 1969)	20	17
Starr-Edwards 2310/2320 (June 1969 - March 1970)	11	11
Bjork-Shiley A.B. (December 1969 - June 1973)	119	100
Bjork-Shiley A.B.P. (June 1971 – January 1974)	95	88
Total	312	249

N: number of patients;

Follow-up

Follow-up of the patient cohort (which included patients from all over The Netherlands) was initially performed by 6-monthly outpatient visit, alternatively at our institution and by the referring cardiologist. All events were carefully noted. A first follow-up study of the patient cohort was retrospectively conducted in April and May 1975 by the third author. All preoperative, operative, postoperative and follow-up data were collected. The follow-up

was complete and an extensive file with all events on each patient carefully noted, was completed. This study was however never published.

Until about 1980, all surviving patients were annually seen at the cardiology department of our institution. Again, all events were carefully noted. After 1980, the volume of outpatients became considerable and it was decided to restrict the outpatient visits to patients of our geographical area or patients demonstrating any valve related problem e.g. patients having a paravalvular leak, patients having had an aortic valve reoperation, etc. The remaining patients were followed by their referring cardiologist who regularly updated our department, at least in the first years.

A repeat follow-up study of this patient cohort was performed by the first author between May and December 1999. A new individual patient file was created according to the official guidelines [10]. All definitions of events were according to these guidelines with the exception of hemolysis which was defined as any raise in LDH non attributable to other causes. In addition to valve related events, all other events and reoperations were also recorded. Follow-up information was obtained from the clinical charts at our institution as well as from other institutions. In addition, every patients' successive general practitioner (most patients had a fixed doctor for a prolonged time period), cardiologist and eventually neurologist was contacted to obtain information. Also, the neurology departments of all hospitals where patients had been followed, were contacted to detect additional events. All patient files were personally seen by the first author and scrutinized for events. These files included official reporting letters as well as any note on a particular patient. Also, in case of doubt about an exact date of an anticoagulation related event, the Dutch thrombosis service was contacted for surviving patients after 1985 in order to extract these data from their database. This database is virtually complete from the late eighties. In addition, we recorded the anticoagulation treatment for every patient at the time of an event and, if known, the INR.

All surviving patients received and completed a questionnaire regarding their present status and past events. The latter was specifically meant to match the data collected from the patients' file with his own personal history. Also, surviving patients were asked about the frequency of minor bleeding events which were roughly graded as occurring weekly or more frequently, monthly, yearly or only seldomly. In addition, they were asked whether it bothered them to take anticoagulation. If the questionnaire was not adequately completed, patients were contacted by phone in order to have the data as complete as possible.

All files of deceased patients were carefully examined to detect events and causes of death. If the cause of death was unknown, family members were searched and contacted in order to gather additional information.

A total of 4855 patient-years was available for analysis. Mean follow-up was 19.5±9.4 years and was 100% complete. New York Heart Association (NYHA) functional class in 91 surviving patients at follow-up was I in 39% of patients (n=35), II in 46% (n=42) and III in 15% (n=14).

Data analysis

Data are expressed as the mean ± the standard deviation. Survival and event-free estimates were determined by life table analysis [11] and expressed as proportion ± the standard error. Analysis was performed with the SPSS package version 8.0.

Risk factors for outcome were evaluated using Cox proportional hazard models. The first event was used as outcome. Associations are presented as hazard ratio's (i.e. relative risk) with corresponding 95% confidence intervals. First analyses were performed using only the risk factor of interest in the Cox univariate model. Those risk factors whose association showed a statistical significance of less or equal than 0.10 were included into a multivariate Cox regression model. A priori we evaluated the following risk factors of which information was collected at baseline: age, sex, year of operation (before/after 1970), hypertension (systolic pressure ≥160 or diastolic pressure ≥95 or treatment), atrial fibrillation, history of diabetes mellitus, aortic stenosis (peak gradient ≥75), aortic regurgitation (definition AR > grade 1), pre-operative endocarditis, type of valve (Starr Edwards versus Bjork-Shiley), and type of operation (elective/emergency). Postoperative factors that were evaluated were paravalvular leak, postoperative endocarditis, new onset of atrial fibrillation, cardiac events and any surgery (other than aortic valve reoperation). In addition, we evaluated whether baseline characteristics were predictive of a recurrent anticoagulation related complication.

Estimates of the linearized incidence rate with corresponding standard errors were obtained by dividing the number of first events by the corresponding patient-years of follow-up. The standard error was calculated as the square root of the incidence divided by the patient-years of follow-up, assuming a poisson distribution. A two-sided p-value less then 0.05 was considered statistically significant.

Results

Late mortality

Overall actuarial survival among hospital survivors was 80.3±2.6%, 57.4±3.1% and 33.6±4.2% at 10, 20 and 30 years postoperatively (Fig. 1). The linearized incidence rate was 3.2±0.3% per year. Causes of death are shown in Table 2. Multivariate independent risk factors for death were age (hazard ratio per year increase 1.0 [95% CI 1.0 - 1.1], male gender (hazard ratio 1.7 [95% CI 1.1 - 2.7], operation before 1970 (hazard ratio 1.6 [95% CI 1.1 – 2.4], and postoperative endocarditis (hazard ratio 2.2 [95% CI 1.3 - 3.8]. Diabetes and emergency operation were significantly related to mortality in the univariate model but not in the multivariate model.

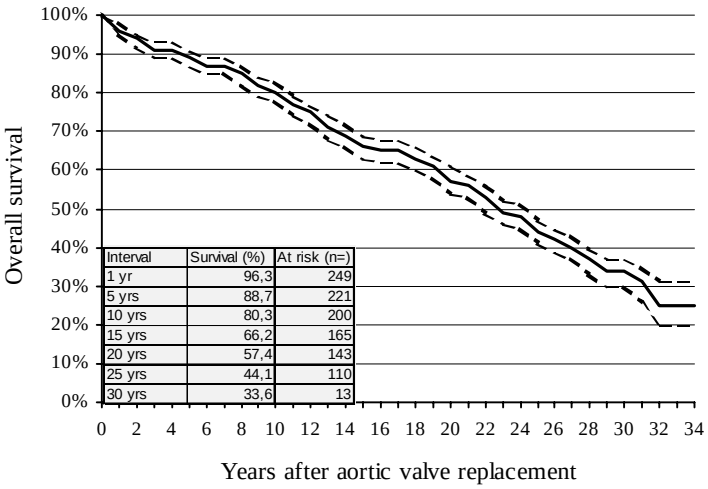


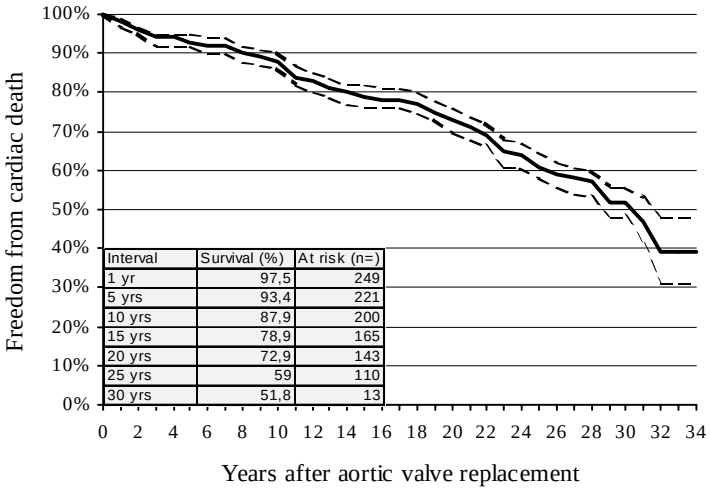
Figure 1*: Overall late survival among hospital survivors (n=249).*

Table 2: Causes of late death (n=158).

Cause of death	**N**	**%**
Cardiac	95	60.1
Malignancy	20	12.6
C.O.P.D.	5	3.2
Trauma	4	2.5
Other	27	17
Unknown	7	4.4
Total	158	100

N: number of patients; C.O.P.D.: chronic obstructive pulmonary disease

Freedom from cardiac death was 87.9±2.6%, 72.9±2.9% and 51.8±4.2%, at 10, 20 and 30 years postoperatively (Fig. 2). The linearized incidence rate was 1.9±0.2% per year. Causes of cardiac death are shown in Table 3. Multivariate independent risk factors for cardiac death were age (hazard ratio per year increase 1.0 [95% CI 1.0 - 1.1], and operation before 1970 (hazard ratio 1.9 [95% CI 1.2 - 3.1]. Male sex, type of valve and postoperative endocarditis were significantly related to cardiac mortality in the univariate model, but not in the multivariate model.



Interval	Survival (%)	At risk (n=)
1 yr	97,5	249
5 yrs	93,4	221
10 yrs	87,9	200
15 yrs	78,9	165
20 yrs	72,9	143
25 yrs	59	110
30 yrs	51,8	13

***Figure 2**: Freedom from cardiac death.*

Freedom from valve related mortality was 92±1.7%, 83.3±2.5% and 75.4±3.7% at 10, 20 and 30 years postoperatively. The linearized incidence rate was 0.9±0.1% per year. Causes of valve related mortality are also shown in Table 3. Multivariate independent risk factors for valve related mortality were age (hazard ratio per year increase 1.0 [95% CI 1.0 - 1.1], and postoperative endocarditis (hazard ratio 2,1 [95% CI 1.1 - 4.2]. Preoperative endocarditis, emergency operation, and aortic stenosis were significantly related to valve related mortality in the univariate model, but not in the multivariate model.

Freedom from anticoagulation related mortality was 97.7±1.3%, 93.2±1.8% and 90.5±3.2% at 10, 20 and 30 years (Fig. 3). The linearized incidence rate was 0.3±0.1% per year. Out of a total of 14 events, 8 were due to bleeding events whereas the remainder were due to thrombo-embolic phenomena (including 4 patients with valve thrombosis – see Table 3). Only age was an independent predictor for anticoagulation related mortality with a hazard ratio per year increase of 1.1 [95% CI 1.0 -1.2]. Diabetes and emergency operation did not reach statistical significance in the multivariate model.

Table 3: Causes of cardiac death (n=95).

Cause		N	%
Heart failure		43	45.3
Myocardial infarction		7	7.4
Arrhythmia		0	0
Valve related:	- sudden death	26	27.4
	- valve thrombosis	4	4.2
	- thrombo-embolic event	2	2.1
	- bleeding event	8	8.4
	- endocarditis	5	5.3
Total		95	100

N : number of patients

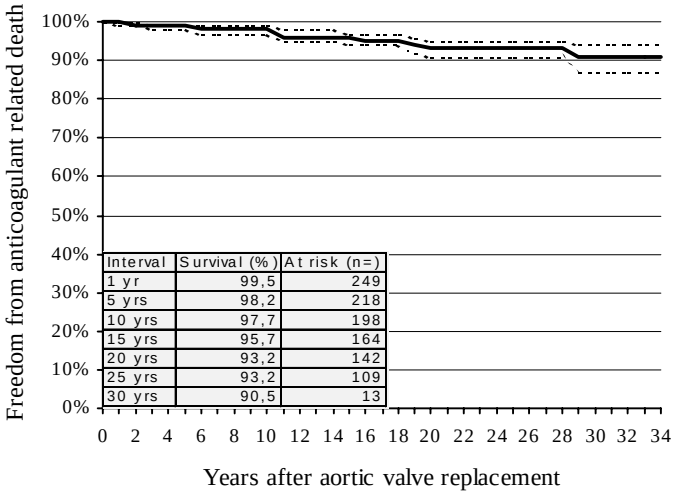
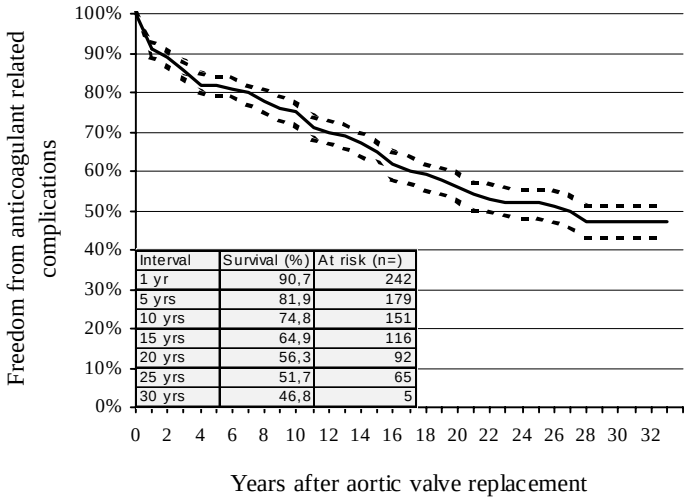


***Figure 3**: Freedom from anticoagulant related death.*

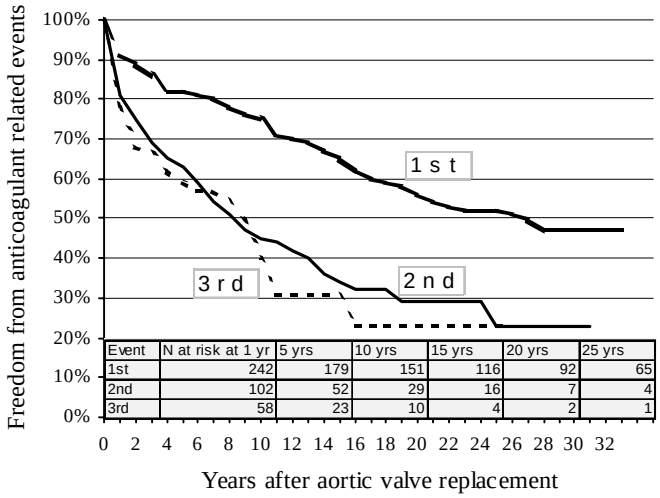
Anticoagulation related complications (any type)

One hundred and two patients experienced an anticoagulation related complication, in the absence of endocarditis, during follow-up. The majority of patients experienced one or two events (n=102 and 58 respectively) but nevertheless, 30 patients experienced three events and 13 patients four events. Six patients had more than five events and one patient even more than 10 events.



Interval	Survival (%)	At risk (n=)
1 yr	90,7	242
5 yrs	81,9	179
10 yrs	74,8	151
15 yrs	64,9	116
20 yrs	56,3	92
25 yrs	51,7	65
30 yrs	46,8	5

Figure 4*: Freedom from a first anticoagulant related complication.*



Event	N at risk at 1 yr	5 yrs	10 yrs	15 yrs	20 yrs	25 yrs
1st	242	179	151	116	92	65
2nd	102	52	29	16	7	4
3rd	58	23	10	4	2	1

Figure 5*: Freedom from a first, second and third anticoagulant related event. Note the increased slope of the multiple-events curves which indicates an increased risk of subsequent events once a first event was encountered.*

Freedom from a first anticoagulation related event was 74.8±2.4%, 56.3±3.5% and 46.8±4.1% at 10, 20 and 30 years postoperatively (Fig. 4). Multivariate predictors for a first anticoagulation related complication were ball valve (hazard ratio 2.9 [95% CI 1.2 - 7.2], postoperative endocarditis (hazard ratio 2.2 [95% CI 1.2 - 4.0], any surgery other than aortic valve reoperation (hazard ratio 2.2 [95% CI 1.3 - 3.7]. Atrial fibrillation and operation before 1970 did not reach statistical significance in the multivariate model. The linearized incidence rate of a first event was 3.0±0.3% per patient-year.

Freedom from a second anticoagulation related event after the first event was 45.4±5.4%, 29±6.0% and 23.2±7.1% at 10, 20 and 30 years postoperatively (Fig. 5). None of the risk factors reached a statistical significant level in association with recurrent events.

The risk of anticoagulation related complications was highest within the first five years after aortic valve replacement, after which the risk decreased (Table 4).

Table 4: Incidence of valve related morbidity during follow-up. Values are 5-years cumulative incidence (with corresponding standard errors) of the event.

Event	Follow-up period (years postoperatively)					
	0 – 4.9	**5 – 9.9**	**10 – 14.9**	**15 – 19.9**	**20 – 24.9**	**25 – 29.9**
ARC	4.5±0.6	1.8±0.5	3.0±0.7	2.9±0.7	1.8±0.7	2.3±1.1
Thromb.	0.3±0.1	0	0.3±0.2	0	0	0
TE	2.7±0.5	1.7±0.4	1.5±0.4	1.7±0.5	1.5±0.6	2.0±1.0
Bleed.	1.3±0.3	0.5±0.2	1.1±0.4	1.9±0.5	0.7±0.4	0.4±0.4
Endoc.	0.5±0.2	0.5±0.2	0.2±0.2	0.4±0.2	0.2±0.2	0.7±0.5
Reop.	1.6±0.4	0.8±0.3	0.8±0.3	0.6±0.3	0.9±0.4	1.5±0.8

ARC: anticoagulation related complication; Thromb.: valve thrombosis; TE: thrombo-embolic event; Bleed.: bleeding event; Endoc.: endocarditis; Reop.: aortic valve reoperation

- Valve thrombosis

Valve thrombosis, in the absence of endocarditis, occurred six times. None of these patients was adequately anticoagulated at the time of the event. In two instances, the patients did not even take vitamin K antagonists which they had stopped spontaneously. The linearized incidence rate of valve thrombosis was 0.1±0.1% per patient-year. Table 4 shows the occurrence of valve thrombosis during follow-up. Freedom from valve thrombosis was 98.7±0.7%, 97.0±1.0% and 97.0± 1.1% at 10, 20 and 30 years postoperatively.

- Thrombo-embolic phenomena

A total of 140 thrombo-embolic (TE) phenomena (excluding valve thrombosis) took place in 77 patients who did not have endocarditis at the time of the event. A second event was experienced by 28 patients, a third event by 17 patients and a fourth event by four patients. Transient ischaemic attack (TIA) occurred in the majority of cases: 82 events in 47 patients.

Stroke occurred 35 times in 28 patients. A minority of the TE events were peripheral emboli (seven events in six patients). Sixteen events were classified as 'other' including nine probable embolic events (according to history) and seven non-specified. Lethal outcome was noted in 2.6% (2 events) of the TE events. The INR at the time of the first event was known in 23 patients (30% of the events). Mean INR at the time of the event was 1.9±1.2 and 85% of these values were below the target baseline of 2.8. Sixty seven% of the values were even below 2.0. Of all 140 TE events, 12.8% of the patients (n=18) were not using anticoagulant drugs at the time of the event.

Freedom from the first TE event was 79.9±2.6%, 68.5±3.3% and 57.3±4.3% at 10, 20 and 30 years postoperatively (Fig. 6). Multivariate independent risk factors for first thrombo-embolic event, excluding valve thrombosis, were age (hazard ratio per year increase 1.0 [95% CI 1.0 - 1.0], operation year before 1970 (hazard ratio of 2.2 [95% CI 1.3 - 3.7]), and not using anticoagulant drugs at the time of the event (hazards ratio 4.1 [95% CI 2.1 - 8.0]. Atrial fibrillation was significantly related to first thrombo-embolic event in the univariate model, but not in the multivariate model.

The linearized incidence rate of a first TE event was 2.0±0.2% per patient-year. Freedom from a second TE event after the first event was 73±5.3%, 63.6±6% and 49.9±7.8% at 5, 10, and 15 years postoperatively (Fig. 7). In the analysis of the determinants of a recurrent TE event, none of the risk factors reached a statistically significant level.

The incidence of TE events was higher within the first 5 postoperative years, after which it remained relatively constant (Table 4).

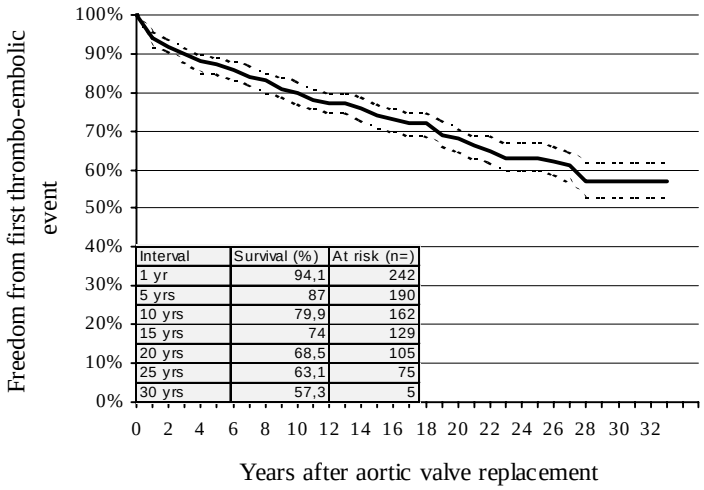
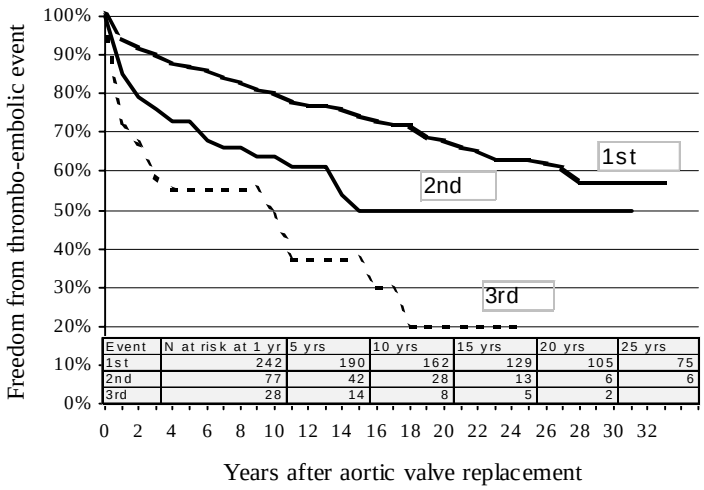


***Figure 6**: Freedom from a first thrombo-embolic (T.E.) event.*



Event	N at risk at 1 yr	5 yrs	10 yrs	15 yrs	20 yrs	25 yrs
1st	242	190	162	129	105	75
2nd	77	42	28	13	6	6
3rd	28	14	8	5	2	

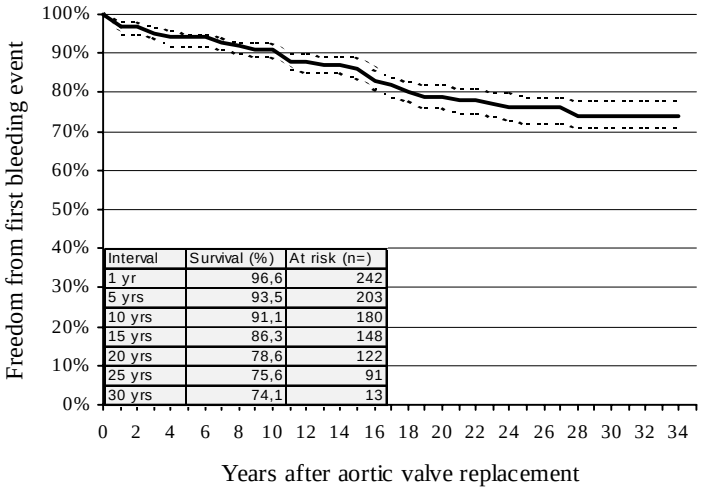
***Figure 7**: Freedom from a first, second and third thrombo-embolic (T.E.) event. Note the increased slope of the multiple-events curves which indicates an increased risk of subsequent events once a first event was encountered.*

- Major bleeding events

A total of 72 major bleeding events, in the absence of endocarditis, occurred. There were 47 first events whereas 15 patients had a second event and 6 a third event. A minority of the events were cerebral bleeding with residual impairment (n=14); lethal outcome was noted in eight patients. The remainder were non-cerebral bleeding events requiring transfusion or surgical evacuation (50 events). All the patients with bleeding events were taking oral anticoagulation at the time of the event. The INR at the time of the first event (n=47) was known in 13 cases. Mean INR was 4.7±1.8 and 69% of these values were above the target maximum INR of 4.2. Freedom from a first bleeding event was 91.1±1.9%, 78.6±2.4% and 74.1±3.4% at 10, 20 and 30 years postoperatively (Fig. 8). Multivariate independent risk factors for a first bleeding event were increasing age (hazard ratio per year increase 1.0 [95% CI 1.0 - 1.1]) and any surgery (hazard ratio 3.8 [95% CI 2.0 - 7.7]). Atrial fibrillation was significantly related to first bleeding event in the univariate model, but not in the multivariate model.

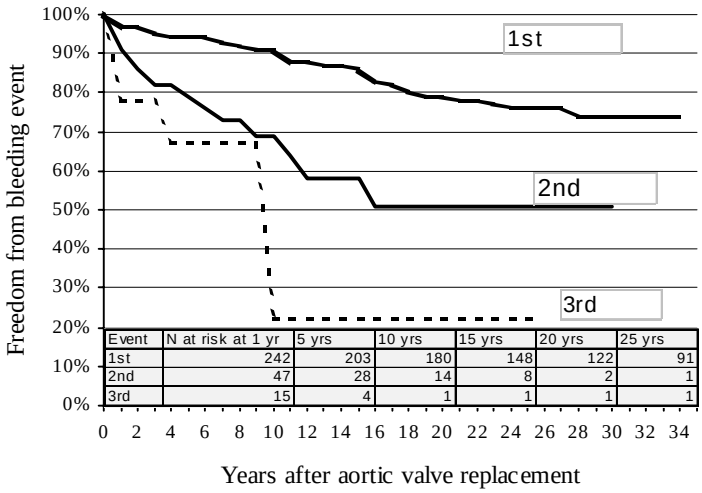
The linearized incidence rate of a first bleeding event was 1.1±0.2% per patient-year. Freedom from a second bleeding event after the first event was 78.7±4.2%, 69±7.6% and 58.3±9.5% at 5, 10, and 15 years postoperatively (Fig. 9). In the analysis of the determinants of a recurrent bleeding event, none of the risk factors reached a statistically significant level.

The incidence of bleeding events was relatively constant over time (Table 4).



Interval	Survival (%)	At risk (n=)
1 yr	96,6	242
5 yrs	93,5	203
10 yrs	91,1	180
15 yrs	86,3	148
20 yrs	78,6	122
25 yrs	75,6	91
30 yrs	74,1	13

***Figure 8**: Freedom from a first bleeding event.*



Event	N at risk at 1 yr	5 yrs	10 yrs	15 yrs	20 yrs	25 yrs
1st	242	203	180	148	122	91
2nd	47	28	14	8	2	1
3rd	15	4	1	1	1	1

***Figure 9**: Freedom from a first, second and third bleeding event. Note the increased slope of the curves with multiple events, indicating an increased risk of subsequent events once a first event was encountered.*

- Minor bleeding events

The frequency of minor bleeding events was estimated by the 91 survivors and graded as very seldom (n=59), yearly (n=17), monthly (n=5) and weekly or more (n=10).

- Attitude towards anticoagulation

Among 91 survivors, 13 patients would prefer not to take anticoagulation whereas 75 patients did not care. The remainder had no opinion.

Other valve related events

- Valve dysfunction

There were no structural valve deteriorations. Leaflet obstruction due to pannus overgrowth necessitating reoperation occurred in two patients.

- Paravalvular leak

Paravalvular leak occurred once in 28 patients, twice in 3 patients and 3 times in 1 patient. The linearized incidence rate was 0.7±0.1% per patient-year. Paravalvular leak was the major cause of aortic valve reoperation (Table 5).

- Hemolysis

Hemolysis occurred frequently with a linearized incidence rate of 4.2±0.4% per patient-year (n=118). The majority of the hemolysis events occurred within the first 5 postoperative years (n=93). However, hemolysis was only once the leading cause of reoperation (Table 5).

- Endocarditis

Postoperative endocarditis occurred in 20 patients. The linearized incidence rate of endocarditis was 0.4±0.1% per patient-year. The incidence of postoperative endocarditis was relatively constant over time (Table 4).

- Aortic valve reoperation

A total of 60 aortic valve reoperations occurred in 46 patients. Twelve patients underwent a third aortic valve operation and 2 patients a fourth. Causes of aortic valve reoperation are listed in Table 5. Paravalvular leak was the leading cause occurring in 60.6% of cases (n=37). Freedom of aortic valve reoperation was 88.7±2.1%, 82.4±2.7% and 67.5±6.2% at 10, 20 and 30 years postoperatively. The linearized incidence rate was 1±0.1% per patient-year. The incidence of aortic valve reoperation was highest within the first 5 postoperative years and beyond 25 years of follow-up (Table 4). None of the patients died at aortic valve reoperation.

Table 5: Causes of aortic valve reoperation (60 events in 46 patients).

Cause	1st reop. (N)	2nd or 3rd reop. (N)
Valvular dysfunction	2	0
Paravalvular leak	29	8
Endocarditis	1	1
Valve thrombosis or recurrent thrombo-emboli	5	1
Hemolysis	1	0
Other	8	4
Total	46	14

N : number of events; reop.: reoperation

Other events

- Other reoperations

A total of 25 cardiac reoperations, other than aortic valve reoperations occurred in 20 patients. They included CABG (n=9), mitral valve operation (n=9), ascending aortic replacement (n=2) and other (n=5). A total of 27 pacemakers were implanted during follow-up.

A total of 199 other, non-cardiac, surgical interventions took place in 100 patients. Freedom from any first surgical intervention (excluding aortic valve reoperation) was 71.2±3.1%, 48.3±3.7% and 28.8±4.5% at 10, 20 and 30 years postoperatively.

- Other cardiac events (exclusive cardiac mortality)

A total of 395 cardiac events in 168 patients were noted during follow-up. They included heart failure (87 events), myocardial infarction (24 events), angina (35 events), supraventricular arrhythmias (93 events), ventricular arrhythmias (41 events), electrical cardioversions (31 events), hypertension treatment (n=43) and other (41 events). Freedom from any first non-operative cardiac event was 56.7±3.3%, 33.1±3.3% and 12.8±4.8% at 10, 20 and 30 years postoperatively.

Comment

Adults requiring an aortic valve replacement at a young age still have a long life expectancy. Traditionally, mechanical valves are the substitute of choice because of excellent performance and rare structural failure, therefore limiting the risk of reoperation [7]. However, mechanical valves require life-long anticoagulation with an inherent complication rate. It is therefore important to balance the life-long risk of anticoagulation

related complications against the risk of (multiple) reoperation(s) when a tissue valve or a valve repair would have been performed.

The present study examined the very long-term incidence of anticoagulation related complications after mechanical aortic valve replacement. We analyzed the first 10 years of our institutional experience which reached a mean follow-up of almost 20 years. Even more important, to accurately investigate the incidence of complications, the follow-up was 100% complete.

Global anticoagulation related complications

In agreement with previous publications, the incidence of anticoagulation related complications was fairly high [8, 12-16]. In the present series, only 46.8% of the patients remained free from a first anticoagulation related event at 30 years postoperatively. However, the linearized incidence rate for a first event in the current series was 3% per patient-year which compares favorably with reported incidence rates of 3-5% for the Starr-Edwards valve [8, 13] and an overall incidence of approximately 3.5% for the Bjork-Shiley standard valve [13].

In addition to a first event, 58 patients (23.3%) had 2 events, 30 patients (12%) a third and 13 patients (5.2%) a fourth event. While this incidence is certainly substantial, the present series demonstrates that only few patients experienced more than 4 events over the entire study period. However, Fig. 5 demonstrates that patients who had a first event are at increased risk for subsequent events.

Although literature usually reports TE phenomena and bleeding complications separately, we also wanted to report the global complication rate since, for a given patient, one wants to inform about the global risk of any anticoagulation related complication. Besides, patients experiencing a TE or bleeding event are by no means separate patient groups but overlap considerably, as previously reported [17].

Interestingly, one of the risk factors for anticoagulation related complications was the occurrence of any surgery other than aortic valve reoperation, during follow-up (O.R.=2.2). Anticoagulation is commonly interrupted and the patient is protected from adverse events with intravenous heparin [15, 18]. The risk of this interruption has been estimated [16] and reported [18] to be low but nevertheless emerges as a risk factor in the present series. It is conceivable that fluctuations in levels of anticoagulation make the patient more prone to complications as both the intensity and consistency of the anticoagulation are important factors in avoiding adverse events [13, 15].

Thromboembolic events

A total of 77 patients (31%) had TE events. Of these, 28 (11.2%) experienced multiple events. Out of a total of 140 TE events, two had lethal outcome and 35 were strokes with residual impairment. This high incidence of 26.4% is undoubtedly related to the fact that 85% of the known INR at the time of the TE event were below the target baseline.

Inadequate or stopped anticoagulation is known to be strongly associated with increased risk of TE events [15-17] as also evidenced by the hazard ratio of 4.1. On the other hand, the current first event linearized incidence rate of 2% per patient-year is very comparable with previously reported rates of 2 – 2.8% per patient-year for the Bjork-Shiley and Starr-Edwards valve [7-8, 19]. Equally, the 10 year freedom from a first TE event is situated around 80% which is however lower than the 86.7% reported by the Mayo Clinic in their long-term follow-up study of Starr-Edwards valves [20].

As for the global anticoagulation related complications, patients who had a first TE event were at increased risk for multiple events (Fig. 7).

Bleeding events

Major bleeding events occurred in 47 patients (72 events). Outcome for bleeding events was generally worse than for TE events (8 lethal events versus 2) as already stated by Cannegieter et al. [21]. Although the INR was known in only a minority of bleeding events, most of these INR's were above the target maximum, in accordance with literature [14-18, 21-22].

The linearized incidence rate of 1.1% for first bleeding event in this series is better than in the previously mentioned studies [7-8, 13] where rates of 1.2 to 2.2% per patient-year were found. An exceptionally high incidence rate of 5% per patient-year was found in the study by Borkon et al. without obvious reason [19]. In the conference discussion of that paper it was suggested that the favourable incidence of anticoagulation related complications in the Netherlands was probably thanks to the nationally organized thrombosis service. However, equally good or even better results have also been reported without the aid of such an organisation [20].

As for the global anticoagulation related complications and the thromboembolic events, patients with a first event were at increased risk for subsequent events (Fig. 9).

Practical inferences

One hundred and two patients (41% of all study patients) had 37 major TE events (out of 140 events), six valve thromboses and 72 major bleeding events. This means that of a total of 218 anticoagulation related events, with the exception of minor bleeding events, 115 or 53% were major events. In addition 6.4% of all events were lethal. This high proportion has occurred despite the fact that the target INR of 2.8 to 4.2 was not much different from the current recommendations: according to literature, the overall target INR should be between 2.5 and 4.0 [21-24]. It is therefore clear that, although INR levels were regularly followed by a specialized organization who closely followed the official guidelines for anticoagulation, the incidence of anticoagulation related events on the very long-term is still considerable and above all in this series not substantially worse than other published series. It was the purpose of this study to determine this long-term incidence which in itself should be born in mind whenever a doctor is advising a young adult who needs aortic valve

surgery. The counterpart of the balance will be determined by the risk of (multiple) reoperation(s) for failing bioprostheses or valve repair.

Age per year was in the current series a risk factor for both TE events and bleeding events. This is still controversial in literature as it confirms the findings by Cannegieter et al. [19] but contradicts the findings of several other studies [5, 13-14, 17, 25-26]. The fact that younger age could be less prone to complications than older age may be an argument in favor of mechanical aortic valve replacement.

Of all other identified risk factors, only the type of valve and careful consistent anticoagulation regimen are correctable factors. As the incidence of anticoagulation related complications was highest during the first 5 years, but remained present throughout the study period, careful monitoring seems the most important determinant of outcome.

Limitations of the study

The present series is a retrospective analysis over a long time period. This inevitably raises the concern of the completeness of our data collection despite major efforts to reduce this error to a minimum. While it is unlikely that we missed major events, the registration of minor events (especially minor bleeding events) was more difficult. The reported risk may thus be underestimated and the proportion of major events consequently overestimated.

A limitation is the lack of registration of preoperative neurological events. Some reports indicate history of neurological events as a risk factor for future events [15, 21], but the original 1975-follow-up of the patient cohort did not register this information and we were therefore unable to evaluate this variable. However, the demographics of the patient population suggest that probably only very few patients might have had a preoperative neurological event: mean age was 41.8 years, only 13 patients (5.2%) had an aortic valve reoperation and only seven patients (2.8%) had simultaneous CABG (indicative of systemic atherosclerosis). It is therefore unlikely that the lack of this information affected our risk estimates.

Another remark concerns the valves implanted in the series. Ball valves were implanted in 24% of hospital survivors and tilting disc valves in the remainder. While these valves are known to have an increased risk of anticoagulation related complications as compared to the more recently available bileaflet mechanical valves [7-8, 13, 15-16, 18, 21-22, 27], ball valves and tilting disc valves are currently still being implanted. Moreover, some recent reports suggest a lower target INR in current bileaflet valves with consequently lower bleeding complications without increasing TE events [28-29]. It is undoubtful but yet unproven that the very long-term incidence of anticoagulation related complications with the currently available bileaflet prostheses will be less than the currently reported incidence. With this in mind, we feel that the present series should serve as a reference for future very long-term follow-up studies.

Conclusion

At 30 years follow-up, 46.8% of the patients remained free of any anticoagulation related complication and about one fourth of the patients (23.3%) experienced multiple events. This incidence of adverse events should be considered whenever aortic valve surgery is considered for a particular patient.

References

1. Banbury MK, Cosgrove DM, Lytle BW, Smedira NG, Sabik JF, Saunders CR. Long-term results of the Carpentier-Edwards pericardial aortic valve: a 12-year follow-up. Ann Thorac Surg 1998;66(suppl):73-76.
2. Lund O, Chandrasekaran V, Grocott-Mason R, et al. Primary aortic valve replacement with allografts over twenty-five years: valve-related and procedure-related determinants of outcome. J Thorac Cardiovasc Surg 1999;117:77-91.
3. Chambers JC, Somerville J, Stone S, Ross DN. Pulmonary autograft procedure for aortic valve disease: long-term results of the pioneer series. Circulation 1997;96:2206-2214.
4. Casselman FP, Gillinov AM, Akhrass R, Kasirajan V, Blackstone EH, Cosgrove DM. Intermediate-term durability of bicuspid aortic valve repair for prolapsing leaflet. Eur J Cardiothorac Surg 1999; 15:302-308.
5. Baudet EM, Puel V, McBride JT, et al. Long-term results of valve replacement with the St Jude Medical prosthesis. J Thorac Cardiovasc Surg 1995;109:858-870.
6. Debetaz LF, Ruchat P, Hurni M, et al. St Jude Medical valve prosthesis: an analysis of long-term outcome and prognostic factors. J Thorac Cardiovasc Surg 1997;113:134-148.
7. Grunkemeier GL, Starr A, Rahimtoola SH. Prosthetic heart valve performance: Long-term follow-up. Current problems in Cardiology 1992;17:329-406.
8. Lund O, Pilegaard HK, Ilkjaer LB, Nielsen SL, Arildsen H, Albrechtsen OK. Performance of the Starr-Edwards aortic cloth covered valve, track valve, and silastic ball valve. Eur J Cardiothorac Surg 1999; 16:403-413.
9. van den Besselaar AM, Broekmans AW, Loeliger EA. INR: een internationaal geaccepteerde maatstaf voor de controle van orale antistollingsbehandeling. Ned Tijdschr Geneesk 1986;130:1975-1976.
10. Edmunds LH, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Eur J Cardiothorac Surg 1996;10:812-816.
11. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.
12. Best JF, Hassanein KM, Pugh DM, Dunn M. Starr-Edwards aortic prosthesis: A 20-year retrospective study. Am Heart J 1986;111:136-142.
13. Edmunds LH. Thrombotic and bleeding complications of prosthetic heart valves. Ann Thorac Surg 1987;44:430-445.
14. Petty GW, Lennihan L, Mohr JP, et al. Complications of long-term anticoagulation. Ann Neurol 1988; 23:570-574.
15. Isreal DH, Sharma SK, Fuster V. Antithrombotic therapy in prosthetic heart valve replacement. Am Heart J 1994;127:400-411.
16. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635-641.
17. Gitter MJ, Jaeger TM, Petterson TM, Gersh BJ, Silverstein MD. Bleeding and thromboembolism during anticoagulant therapy: A population-based study in Rochester, Minnesota. Mayo Clin Proc 1995; 70:725-733.
18. Carrel TP, Klingenmann W, Mohacsi PJ, Berdat P, Althaus U. Perioperative bleeding and thromboembolic risk during non-cardiac surgery in patients with mechanical prosthetic heart valves: an institutional review. J Heart Valve Dis 1999;8:392-398.
19. Borkon AM, Soule L, Baughman KL, et al. Ten-year analysis of the Bjork-Shiley standard aortic valve. Ann Thorac Surg 1987;43:39-51.

20. Orszulak TA, Schaff HV, Puga FJ, et al. Event status of the Starr-Edwards aortic valve to 20 years: a benchmark for comparison. Ann Thorac Surg 1997;63:620-626.
21. Cannegieter SC, Rosendaal FR, Wintzen AR, Van der Meer FJM, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995;333:11-17.
22. Cannegieter SC, Torn M, Rosendaal FR. Oral anticoagulant treatment in patients with mechanical heart valves: how to reduce the risk of thromboembolic and bleeding complications. J Int Med 1999; 245:369-374.
23. Liem TK, Silver D. Coumadin: principles of use. Sem Vasc Surg 1996;9:354-361.
24. Stein PD, Alpert JS, Copeland J, et al. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1995;108:371S-379S.
25. Masters RG, Semelhago LC, Pipe AL, Keon WJ. Are older patients with mechanical heart valves at increased risk ? Ann Thorac Surg 1999;68:2169-2172.
26. Gurwitz JH, Goldberg RJ, Holden A, Knapic N, Ansell J. Age-related risks of long-term oral anticoagulant therapy. Arch Intern Med 1988;148:1733-1736.
27. Butchart EG, Bodnar E. Thrombosis, embolism and bleeding. ICR Publishers, London, 1992, 123-244.
28. Horstkotte D, Schulte H, Bircks W, Strauer BE. Unexpected findings concerning thromboembolic complications and anticoagulation after complete 10 year follow-up of patients with St Jude Medical prosthesis. J Heart Valve Dis 1993;2:291-301.
29. Horstkotte D, Schulte HD, Bircks W, Strauer BE. Lower intensity anticoagulation therapy results in lower complication rates with the St Jude Medical prosthesis. J Thorac Cardiovasc Surg 1994;107:1136-1145.

CHAPTER 7

General discussion

Introduction

The aim of the present thesis was to define the feasibility and durability of aortic valve reconstructive surgery in adults. As in mitral valve repair, reconstructive surgery of the valve is highly dependent on the anatomy of the valve as well as the anatomy and interaction of the structures influencing valve competence. The normal aortic valve consists of three valvular cusps attached in a semilunar fashion along the annulus fibrosus. Congenital variations that may result in a failing aortic valve in adulthood have a different number of cusps : one cusp in the unicuspid aortic valve (this is rare), two cusps in the bicuspid aortic valve (this is by far the most common congenital variation), and four cusps in the quadricuspid aortic valve (this is also rare) [1]. The aortic valve cusps (irrespective of their number), the aortic valve annulus, the sinuses of Valsalva and the sinotubular junction constitute the aortic root and their interaction determines proper aortic valve functioning [2].

In adults, there are essentially two pathological conditions of the aortic valve : aortic stenosis and aortic regurgitation [3]. These two conditions may also co-exist which is then called ‘mixed’ aortic valve disease. Aortic stenosis in adults is situated at the level of the aortic valve cusps and is due to an insufficient opening of the these cusps. Mixed aortic valve disease is due to insufficient opening and closing of the aortic valve, resulting in aortic stenosis and aortic regurgitation. Both pathological conditions are generally managed by aortic valve replacement when intervention is indicated. Indeed, attempts of valve repair for aortic stenosis have been associated with high failure rates [4-6] and are largely abandoned.

In contrast to aortic stenosis, aortic regurgitation in adults may be caused at different levels of the aortic root. At the level of the aortic valve leaflets, aortic regurgitation may be caused by leaflet retraction due to rheumatic aortic valve disease, by leaflet prolapse or by leaflet perforation. Aortic regurgitation may also be due to dilatation of the sinotubular junction in the presence of normal aortic valve leaflets [7]. This dilatation can occur in aneurysms of the sinuses of Valsalva and/or ascending aorta. In addition, destruction of the aortic root in acute Type A aortic dissection will lead to dilatation of the sinotubular junction and commissural prolapse with subsequent aortic regurgitation. Aortic valve repair for rheumatic aortic regurgitation has been reported previously [8-10]. The short-term results were satisfactory but long-term results have shown a disappointing failure rate [11]. It seems therefore unreasonable to advocate valve repair for rheumatic aortic regurgitation, except in countries where budgets for expensive valve substitutes are limited, or where adequate control of oral anticoagulation is difficult.

Aortic valve repair for leaflet perforation, usually due to endocarditis, is a feasible option. Patch closure of the perforation restores aortic valve competence [12]. In order to be successful, the defect has to be fairly small and may not interrupt the continuity of the leaflet circumference. This is relatively rare and was therefore not further described in this thesis.

The present thesis considers the remaining indications for conservative aortic valve surgery: aortic regurgitation due to leaflet prolapse (chapters 2 and 3), and aortic regurgitation resulting from a distorsion and/or dilatation of the sinotubular junction (chapters 4 and 5).

In order to validate aortic valve repair in these conditions, one has to balance the results of aortic valve repair against the possible disadvantages of valve replacement.

For bioprosthetic aortic valve replacement, this includes the risk of structural deterioration with subsequent need of reoperation. This is a complex issue since reoperation of an aortic valve bioprosthesis can be indicated for intrinsic structural failure (which in turn can depend on possible comorbidity, e.g. dialysis), for structural failure due to endocarditis (and the risk of endocarditis may be different for different types of valve substitutes), associated replacement of an aortic valve bioprosthesis during surgery for primarily other indications like mitral valve pathology, or coronary artery disease, …. The complexity of this issue precluded further analysis of this topic in the current thesis.

For mechanical aortic valve replacement, the main disadvantage is the lifelong necessity and risk of oral anticoagulation. Since many studies censor the patients at the first anticoagulation related event, it is hardly possible to estimate the real incidence of anticoagulation related events since the same patient may experience multiple events. Therefore, a long-term follow-up study after mechanical aortic valve replacement was performed to estimate the incidence, frequency and severity of anticoagulation related events.

This thesis therefore focuses on the following questions : what are possible indications for repairing the regurgitant aortic valve; are these operations technically feasible and what is their durability; and finally, what is the long-term incidence, frequency and severity of anticoagulation related events after mechanical aortic valve replacement?

Aortic regurgitation due to cusp prolapse (chapters 2 and 3)

Aortic regurgitation may result from leaflet prolapse which prohibits correct apposition of the valve leaflets in diastole [12]. Leaflet prolapse may occur in the bicuspid and tricuspid aortic valve as is described in Chapters 2 and 3. Efforts to eliminate aortic regurgitation should aim at restoring normal leaflet configuration. This is accomplished by a triangular resection of the prolapsing area, or its plication. Both of these techniques can be used in either the bicuspid or the tricuspid aortic valve. To date, no differences in outcome (durability) between the two techniques have been documented. However, a plication is easier to accomplish since it eliminates the difficult decision of the correct amount of tissue that should be resected. Moreover, the plication of tissue provides a stronger basis to hold the suture and preserves more coaptation area (chapter 2).

As pointed out in Chapter 3, the technique of repair is more difficult in tricuspid aortic valves compared to bicuspid aortic valves. This is undoubtedly due to an easier reference in bicuspid aortic valves where the two leaflets are exactly opposed to each other. Besides,

valve tissue in bicuspid aortic valves is usually thicker than in tricuspid aortic valves. This explains the considerable immediate repair failure (15%) in the tricuspid group (chapter 3).

One could argue about a repair attempted in a bicuspid aortic valve, since this is a congenitally abnormal valve. However, it is known that about 64% of patients with a bicuspid aortic valve will never develop functional aortic valve pathology [13]. It is therefore an attractive idea to try to 'relocate' a patient with a regurgitant bicuspid aortic valve into the group of patients whose bicuspid valve will perform satisfactorily throughout the rest of their life.

Another remark concerns the evidence of aortic wall abnormalities in patients with a bicuspid aortic valve [14]. Repairing the aortic valve in these patients leaves the aortic tissue intact and subsequent aortic dilatation may cause central aortic regurgitation [7, 15]. This is certainly an important issue. Echocardiographic studies in our patient group could not demonstrate such an aortic dilatation but our mean follow-up was only 5 years. It is thus important to follow these patients at regular intervals. This is true for all patients with a known bicuspid aortic valve since they are at increased risk for aortic dissection when compared with normal subjects [16-19].

The freedom from aortic valve reoperation was 84% at 7 years in the bicuspid aortic valve group and 83% at 5 years in the successfully repaired tricuspid aortic valve group. These results indicate a rather high failure rate. However, these patients do not need anticoagulation which is of particular importance in patients with an active life-style or women of child-bearing age. The use of anticoagulation has a significant incidence of adverse events (see chapter 6), and is known to cause congenital abnormalities in pregnant women [20]. Moreover, subcutaneous heparin in pregnant women does not prevent thromboembolic phenomena [21]. For these reasons, patients might want to take the risk of reoperation which in the presented series had no mortality. In addition, it seems reasonable to assume that the risk of reoperation after valve repair will probably prove to be lower than after aortic valve replacement.

In conclusion, aortic valve repair for prolapsing leaflet seems a very reasonable treatment option, particularly in patients who want to avoid anticoagulation.

Aortic regurgitation due to distorsion or dilatation of the sinotubular junction (chapters 4 and 5)

Even though the aortic valve may be structurally entirely normal, aortic regurgitation can result from distorsion or dilatation of the sinotubular junction [7]. This causes failure of cusp coaptation during diastole with subsequent, usually central, regurgitation. Conditions possibly associated with distorsion or dilatation of the sinotubular junction are Type A aortic dissection (chapter 4), aneurysms of the aortic root and ascending aortic aneurysm. The latter two conditions may exist separately, or co-exist (chapter 5). Restoring the aortic root geometry and sinotubular junction will restore aortic valve competence.

Valve preservation in acute Type A aortic dissection

Chapter 4 studies the outcome of aortic valve preservation in the surgical treatment of Type A aortic dissection with involvement of the aortic root. At a mean follow-up of 44 months, 12.6% of the hospital survivors had an aortic valve/root reoperation, all with aortic valve replacement. Interestingly, only one reoperation was due to an intrinsic abnormality of the aortic valve, a dehiscence of the commissuroplasty (see Table 6). All other reoperations were due to other causes: graft infection (n=1), false aneurysm (n=1) and aortic root dilatation (n=9). In retrospect, with the exception of the patient with graft infection and the failed commissuroplasty, it should have been possible to save the aortic valve at reoperation. A false aneurysm should not imply an aortic valve replacement, and all patients with aortic root dilatation could have benefited from the valve sparing operation described in chapter 5. Besides, as stated in the conclusions of chapter 4, given the relatively high incidence of native aortic root dilatation at follow-up, we currently favour this 'David' procedure (see chapter 5) in Type A dissection with involvement of more than one sinus of Valsalva.

A possible contributing factor for aortic regurgitation associated with aortic root dilatation is prosthetic dilatation. All prostheses were anastomosed to the native aorta at the level of the sinotubular junction and prosthetic dilatation may therefore cause aortic regurgitation. Prosthetic dilatation has been described, both in the abdominal and thoracic aorta, and is more pronounced in knitted than woven prostheses [22-23]. Knitted prostheses were used in the majority of the patients. Our follow-up echocardiograms did not sufficiently register aortic measurements at the level of the ascending aorta. Hence, it is impossible to estimate the impact of prosthetic dilatation on the occurrence of late aortic regurgitation. However, the majority of the patients were reoperated for aortic root dilatation which, in this particular study, was due to native aortic tissue dilatation. Despite the lack of evidence for prosthetic dilatation as a cause of subsequent aortic regurgitation in the present study, it might be wise to reinforce the prosthesis at the level of the sinotubular junction with an external wrap of Teflon® felt or pericardium. Whenever prosthetic dilatation occurs, dilatation of the sinotubular junction could be prevented in this way.

Aortic valve reimplantation technique ('David procedure')

Chapter 5 describes the initial experience with the David procedure. This technique completely replaces the aortic root with the exception of the aortic valve which is reimplanted in a tubular Dacron prosthesis [24-27]. Our initial experience is encouraging: aortic regurgitation is eliminated, and the functional capacity of the patients is substantially improved.

Although the results reported by David and our initial experience are encouraging, some concern exists about this 'new' aortic root. Indeed, this reconstruction abolishes the sinuses of Valsalva which are known to share diastolic stress with the aortic valve leaflets, thereby

probably playing a role in leaflet longevity [28]. If the sinuses are absent, all diastolic stress will now be exerted on the valve leaflets. It is specifically for this reason that another technique was developed by Yacoub (historically, this technique was actually developed first but promoted less and hence is less known by the cardiac surgical community) [29-30]. This technique replaces the diseased sinuses by three separate, tongue-shaped extensions of the Dacron tube. Comparison of both techniques by echocardiographic studies demonstrated some sinus of Valsalva-like function in Yacoub's technique and also near-normal opening and closing characteristics of the aortic valve [31]. This was not the case with David's technique which, in addition, showed systolic contact between the aortic valve cusps and the Dacron tube. This may cause leaflet abrasion and therefore compromise leaflet longevity.

Recent additional evidence of the importance of the sinuses of Valsalva has been provided by Grande-Allen et al. [32]. This group studied the impact of three valve-sparing techniques on leaflet stress: David's technique, Yacoub's technique and a recent modification of David's technique creating a pseudo-sinus [33]. All three techniques significantly altered leaflet stress patterns but the pseudosinus model showed the smallest increase in stress and leaflet coaptation was closest to normal.

Since long-term follow-up with any of these techniques is limited, further observation of the patients seems mandatory to detect clinical consequences of theoretical observations.

In conclusion, the results of aortic valve preservation for acute Type A dissection can still improve as about 12% of hospital survivors are reoperated within four years. The main reason for reoperation was native aortic root dilatation. This problem may be solved by applying any aortic valve sparing technique at the time of the initial operation. Long-term follow-up with these techniques is however still lacking.

Long-term anticoagulation

All aortic valve reconstructive, or leaflet reimplantation techniques avoid the necessity of oral anticoagulation. The durability of these techniques is however still inferior to mechanical valve prostheses. In all of the above procedures, the incidence of reoperation is higher than that after mechanical aortic valve replacement [34]. On the other hand, when choosing for a mechanical valve substitute, one needs to consider the risks associated with oral anticoagulation. Chapter 6 demonstrates that this risk is substantial at a mean follow-up of 20 years (up to 33 years), at least with the studied types of valve prostheses in this particular Dutch patient population. Almost half of the patients experienced at least one event, 23% had multiple events, and about half of all events were major with a variable degree of permanent residual deficit. This high incidence of events occurred despite the existence of the 'Dutch Trombosedienst', a national organisation especially created to follow and manage anticoagulated patients according to preset standards. It is conceivable that, due the lack of such an organisation, the incidence of anticoagulation related events

in other countries is even higher. This incidence can probably be somewhat reduced by rigorous anticoagulation management since most of the patients with known INR at the time of the event were not appropriately anticoagulated. It is however impossible to prevent any patient from withdrawing, or inadequately taking anticoagulant drugs, and anticoagulation will therefore always keep its related complications.

One may argue that the prostheses studied are older types. This is correct but some are still in use. Also, long-term follow-up studies of this kind obligatorily have to deal with older prostheses. Some reports suggest lower anticoagulation levels with the modern bileaflet prostheses without increasing adverse events [35-36]. Hopefully, the long-term incidence of adverse events with these newer types of prostheses will prove to be lower than the unacceptable high rate in the present study.

Conclusion

Whenever a patient needs aortic valve surgery, one should consider valve repair. The current indications for aortic valve repair in modern western society are localized leaflet perforation, cusp prolapse and regurgitation secondary to sinotubular distorsion or dilatation. The preoperative echocardiogram is able to provide sufficient information to estimate the technical possibilities for valve repair. The surgeon and the patient will have to balance the risk of repair failure against the risk of adverse events associated with valve replacement. The present thesis demonstrates that conservative aortic valve surgery is feasible with reasonable mid-term outcome. Chapters 2, 3 and 4 have a 5-year freedom from reoperation of 87%, 84% and 89% respectively. Experience with aortic valve sparing operations in the present thesis was still limited but a 5-year freedom from reoperation of 97 and 89% has been documented [27, 30]. All other surgical options include valve replacement, either with mechanical devices, bioprostheses, autografts or allografts. As discussed in chapters 1 and 6, all of these also have disadvantages. In particular, mechanical aortic valve replacement with its need for life-long oral anticoagulation is associated with a substantial risk of adverse events over a long time period: almost half of the patients had adverse events; 23% had multiple adverse events and half of the events resulted in permanent deficit.

It is time to further improve repair techniques and to develop more durable prostheses avoiding oral anticoagulation!

References

1. Thubrikar M. 'The aortic valve' CRC press, Boca Raton FL, USA, 1990.
2. Brewer RJ, Deck JD, Capati B, Nolan SP. The dynamic aortic root. Its role in aortic valve function. J Thorac Cardiovasc Surg 1976;72:413-417.
3. Bonow RO, Carabello B, de Leon AC Jr, et al. ACC/AHA Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology / American Heart Association task force on practice guidelines (Committee on management of patients with valvular heart disease). Circulation 1998;98:1949-1984.
4. Shapira N, Lemole GM, Fernandez J, et al. Aortic valve repair for aortic stenosis in adults. Ann Thorac Surg 1990;50:110-120.
5. Weinschelbaum E, Stutzbach P, Oliva M, Zaidman J, Torino A, Gabe E. Manual debridement of the aortic valve in elderly patients with degenerative aortic stenosis. J Thorac Cardiovasc Surg 1999;117:1157-1165.
6. McBride LR, Naunheim KS, Fiore AC, et al. Aortic valve decalcification. J Thorac Cardiovasc Surg 1990;100:36-43.
7. Furukawa K, Ohteki H, Cao ZL, et al. Does dilatation of the sinotubular junction cause aortic regurgitation? Ann Thorac Surg 1999;68:949-954.
8. Duran CG. Reconstructive techniques for rheumatic aortic valve disease. J Card Surg 1988;3:23-28.
9. Duran C, Kumar N, Gometza B, Al Halees Z. Indications and limitations of aortic valve reconstruction. Ann Thorac Surg 1991;52:447-454.
10. Duran CMG. Present status of reconstructive surgery for aortic valve disease. J Card Surg 1993; 8:443-452.
11. Bernal JM, Fernandez-Vals M, Rabasa JM, Gutierrez-Garcia F, Morales C, Revuelta JM. Repair of nonsevere rheumatic aortic valve disease during other valvular procedures: is it safe? J Thorac Cardiovasc Surg 1998;115:1130-1135.
12. Duran CMG. Aortic valve repair and reconstruction. Oper Techn in Cardiothorac Surg 1996;1:15-29.
13. Mills P, Leech G, Davies M, Leatham A. The natural history of a non-stenotic bicuspid aortic valve. Br Heart J 1978;40:951-957.
14. de Sa M, Moshkovitz Y, Butany J, David T. Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease : clinical relevance to the Ross procedure. J Thorac Cardiovasc Surg 1999;118:588-596.
15. Hahn RT, Roman MJ, Mogtader MJ, Devereux RB. Association of aortic dilatation with regurgitant, stenotic and functionally normal bicuspid aortic valves. J Am Coll Cardiol 1992;19:283-288.
16. Gore I. Dissecting aneurysms of the aorta in persons under forty years of age. Arch Pathol 1953; 55:1-13.
17. Edwards WD, Leaf DS, Edwards JE. Dissecting aortic aneurysm associated with congenital bicuspid aortic valve. Circulation 1978;57:1022-1025.
18. Larson EW, Edwards WD. Risk factors for aortic dissection: A necropsy study of 161 cases. Am J Cardiol 1984;53:849-855.
19. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. J Am Coll Cardiol 1991;17:712-716.
20. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 1980;68:122-140.
21. Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. J Am Coll Cardiol 1996;27:1698-1703.

22. Alimi Y, Juhan C, Morati N, Girard N, Cohen S. Dilatation of woven and knitted aortic prosthetic grafts: a CT-scan evaluation. Ann Vasc Surg 1994;8:238-242.
23. Mattens E, Engels P, Hamerlijnck R, et al. Gelseal® versus Gelweave® dacron prosthetic grafts in the descending thoracic aorta: a two-year computed tomography scan follow-up study. Cardiovasc Surg 1999;7:432-435.
24. David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. J Thorac Cardiovasc Surg 1992;103:617-622.
25. David TE, Feindel CM, Bos J. Repair of the aortic valve in patients with aortic insufficiency and aortic root aneurysm. J Thorac Cardiovasc Surg 1995;109:345-352.
26. David TE. Aortic root aneurysms: remodeling or composite replacement? Ann Thorac Surg 1997; 64:1564-1568.
27. David TE, Armstrong S, Ivanov J, Webb G. Aortic valve sparing operations: an update. Ann Thorac Surg 1999;67:1840-1842.
28. Thubrikar MJ, Nolan SP, Aouad J, Deck JD. Stress sharing between the sinus and leaflets of canine aortic valve. Ann Thorac Surg 1986;42:434-440.
29. Sarsam MA, Yacoub M. Remodeling of the aortic valve anulus. J Thorac Cardiovasc Surg 1993; 105:435-438.
30. Yacoub MH, Gehle P, Chandrasekaran V, Birks EJ, Child A, Radley-Smith R. Late results of a valve preserving operation in patients with aneurysms of the ascending aorta and root. J Thorac Cardiovasc Surg 1998;115:1080-1090.
31. Leyh RG, Schmidtke C, Sievers HH, Yacoub MH. Opening and closing characteristics of the aortic valve after different types of valve-preserving surgery. Circulation 1999;100:2153-2160.
32. Grande-Allen KJ, Cochran RP, Reinhall PG, Kunzelman KS. Re-creation of sinuses is important for sparing the aortic valve: a finite element study. J Thorac Cardiovasc Surg 2000;119:753-763.
33. Cochran RP, Kunzelman KS, Eddy AC, Hofer BO, Verrier ED. Modified conduit preparation creates a pseudosinus in an aortic valve-sparing procedure for aneurysm of the ascending aorta. J Thorac Cardiovasc Surg 1995;109:1049-1058.
34. Agathos EA, Starr A. Aortic valve replacement. Current Problems in Surgery 1993;30:603-710.
35. Horstkotte D, Schulte H, Bircks W, Strauer BE. Unexpected findings concerning thromboembolic complications and anticoagulation after complete 10 year follow-up of patients with St Jude Medical prosthesis. J Heart Valve Dis 1993;2:291-301.
36. Horstkotte D, Schulte HD, Bircks W, Strauer BE. Lower intensity anticoagulation therapy results in lower complication rates with the St Jude Medical prosthesis. J Thorac Cardiovasc Surg 1994; 107:1136-1145.

CHAPTER 8

Summary

Summary

Chapter 1 reviews the current knowledge of the aortic valve. The normal anatomy and possible variations are described. The different pathological conditions are explained as wel as their natural history and the indications for intervention. The various surgical options with regard to the pathological condition are described. In particular, the results of aortic valve repair, when available, are presented. All other types of aortic valve substitutes are also described and their main advantages and disadvantages are mentioned. Finally, the aim of the present thesis is defined.

Chapter 2 studies the durability of bicuspid aortic valve repair for prolapsing leaflet. Ninety-four patients were operated over an 8-year period with a mean follow-up of 5 years. Successful repair was more difficult to achieve in dilated ventricles. A total of 12 patients underwent reoperation. In three of them, the aortic valve was re-repairable. The risk of reoperation was highest the first postoperative year and then relatively constant at 2% per year. The overall freedom from aortic valve reoperation was 84% at 7 years. The repair was less durable in patients with residual aortic regurgitation after the initial procedure.

Chapter 3 examines the results of valve repair in tricuspid aortic valves with leaflet prolapse. The repair was attempted in 33 patients but failed immediately in five. During a mean follow-up of 4 years, three more patients required aortic valve replacement. The freedom from aortic valve reoperation after successful initial repair was 83% at 5 years. The size of the patient group and the number of events were too small to detect risk factors for repair failure.

Chapter 4 is an analysis of the results of aortic valve preservation during surgical intervention for acute Type A aortic dissection with involvement of the aortic root. From 1976 to 1999, 121 patients were operated with various techniques for aortic root reconstruction and followed for a mean of almost 4 years. Ten percent of the patient population underwent aortic valve replacement during follow-up but only one was due to intrinsic aortic valve pathology. Nine reoperations were due to aortic root dilatation. The use of fibrinous glue for aortic root reconstruction and the presence of an aortic valve annulus > 27mm were associated with a statistically significant higher incidence of aortic root reoperation. There was a trend towards better durability using GRF-glue® over Teflon® felt for aortic root reconstruction.

Chapter 5 describes the initial St. Antonius Hospital experience with the aortic valve reimplantation technique as published by David. The technique replaces the aortic root with the exception of the aortic valve. Indications include aneurismal disease of the aortic root or ascending aorta but also aortic wall destruction due to aortic dissection, all complicated by (severe) aortic regurgitation. The experience with the first 13 patients was positive. The preoperative aortic regurgitation is corrected and the patients are functionally

markedly better postoperatively. Further follow-up of this patient group remains necessary to evaluate the long-term outcome of this technique.

All the above techniques avoid oral anticoagulation which is one advantage of reparative aortic valve surgery. The very long-term incidence of anticoagulation related complications after mechanical aortic valve replacement is not well known but is an important consideration, especially if a young adult, who still has a considerable life-expectancy, needs aortic valve surgery. *Chapter 6* therefore analyses the incidence of anticoagulation related complications in patients who underwent a mechanical aortic valve replacement between 1963 and 1974. Follow-up was complete at a mean of almost 20 years and revealed that about half of the patients experienced one anticoagulation related event and 23% more than one event. The incidence of events was highest the first 5 postoperative years and the risk for a second event was higher than the risk for a first event. The freedom from a first anticoagulation related event was 46.8 % at 30 years. About half of the events resulted in a variable degree of permanent deficit.

Chapter 7 is a comprehensive discussion in which the results of the presented studies are correlated with clinical practice.

CHAPTER 9

Samenvatting

Samenvatting

Hoofdstuk 1 geeft een overzicht over de huidige kennis van de aortaklep en de aortaklep chirurgie. De anatomie, met inbegrip van de anatomische varianten, wordt besproken. De verschillende aandoeningen van de aortaklep worden uiteengezet evenals hun beloop en de indicaties voor interventie. De verschillende chirurgische mogelijkheden worden elk met hun voor- en nadelen besproken. De opzet van dit proefschrift besluit dit hoofdstuk.

Hoofdstuk 2 bestudeert de resultaten van klepreconstructie bij een prolaberende tweeslippige aortaklep. Gedurende een periode van acht jaar werden 94 patiënten geopereerd en gemiddeld vijf jaar gevolgd. De reconstructie was moeilijker te verwezenlijken bij patiënten met een gedilateerde linker ventrikel. Gedurende de follow-up dienden 12 patiënten gereopereerd te worden aan de aortaklep maar deze kon bij drie van hen opnieuw gereconstrueerd worden. Het risico op een reoperatie bleek het hoogst het eerste jaar na de ingreep en bleef nadien vrij constant op 2% per jaar. Na zeven jaar was 84% van de patiënten vrij van reoperatie. Een mislukking van de reconstructie was frequenter bij patiënten die na de initiële reconstructie nog resterende aortaklep insufficiëntie hadden.

Hoofdstuk 3 analyseert de resultaten van aortaklepreconstructie bij een prolaberende drieslippige aortaklep. De techniek werd toegepast bij 33 patiënten maar mislukte onmiddellijk bij vijf. Gedurende een gemiddelde follow-up van 4 jaar ondergingen nog drie patiënten een aortaklep vervanging. Na 5 jaar was 83% van de patiënten met een geslaagde initiële reconstructie, vrij van reoperatie. Het aantal patiënten was onvoldoende om eventuele risicofactoren voor reoperatie te kunnen opsporen.

Hoofdstuk 4 is een analyse van de resultaten van de aortaklepsparende chirurgische behandeling van acute Type A aorta dissecties met aortawortel destructie. Van 1976 tot 1999 werden 121 patiënten geopereerd. De aortawortel werd op verschillende manieren gereconstrueerd. De gemiddelde follow-up bedroeg nagenoeg 4 jaar. Tien procent van de patiëntenpopulatie onderging een aortaklepvervanging maar dit was slechts bij een patiënt ten gevolge van intrinsieke aortaklep pathologie. Negen patiënten werden gereopereerd voor aortawortel dilatatie. Het gebruik van fibrine lijm voor de aortawortel reconstructie en de aanwezigheid van een aortaklep annulus > 27 mm was een significante risico factor voor reoperatie. Daarnaast was er een positieve invloed van GRF-lijm® ten opzichte van Teflon® vilt voor de aortawortel reconstructie doch dit was statistisch niet significant.

Hoofdstuk 5 beschrijft de eerste ervaringen in het St. Antoniusziekenhuis met de aortaklep reïmplantatie techniek, beschreven door David. Deze techniek vervangt de aortawortel, met uitzondering van de aortaklep, en is voornamelijk geïndiceerd bij een aneurysma van de aortawortel en eventueel de aorta ascendens. De techniek kan echter ook aangewend worden bij patiënten met een Type A aorta dissectie die doorloopt tot in de aortawortel.

De eerste ervaringen waren positief. De aortaklep insufficiëntie wordt nagenoeg volledig opgeheven en de patiënten zijn functioneel sterk verbeterd. Verder vervolgen van deze patiënten blijft geïndiceerd gezien de duurzaamheid van deze techniek nog niet bewezen werd.

Alle hoger beschreven technieken vermijden het gebruik van orale anticoagulantia. Dit zou een belangrijk voordeel kunnen betekenen, bijvoorbeeld indien een jonge patiënt aortaklepchirurgie dient te ondergaan. Daar de precieze incidentie van anticoagulantia gerelateerde complicaties op zeer lange termijn niet goed bekend is, analyseert *hoofdstuk 6* deze problematiek bij patiënten die tussen 1963 en 1974 een mechanische aortaklep-vervanging ondergingen. De follow-up was volledig en bedroeg gemiddeld nagenoeg 20 jaar. Gedurende die studieperiode had nagenoeg de helft van de patiënten één anti-coagulantia gerelateerd event en 23% meer dan één. De incidentie van deze complicatie was het hoogste gedurende de eerste vijf jaar postoperatief en het risico voor een tweede event was hoger dan dat voor een eerste event. Na 30 jaar had 46.8% van de patiënten nog geen anticoagulantia gerelateerde complicatie doorgemaakt. Ongeveer de helft van de events werden als ‘majeur’ bestempeld daar ze resulteerden in een permanent deficit.

Hoofdstuk 7 is een algemene discussie waarin de resultaten van de hoofdstukken 2 tot en met 6 bezien worden in het licht van de klinische praktijk.

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My dearest Rebecca, every time I come home during the weekend, I feel home. Your happiness and that of the children make me realize each time that there is more in life than Lima-LAD. At the same time, it injects me with new energy for the coming week. I am glad however that our weekend-marriage is almost over. And I am sure that you and the children are too.

Curriculum Vitae

Filip P. A. Casselman was born on July 31st, 1966 in Bruges, Belgium. His Latin-Greek secondary school certificate was obtained at the Abdijschool van Zevenkerken in 1984. The first three years of his medical studies were followed at the 'Facultés Notre Dame de la Paix' in Namur, Belgium. He continued at the Katholieke Universiteit Leuven where he obtained his medical degree, magna cum laude, in 1991.

His training in general surgery was done from 1991 to 1997 at the Katholieke Universiteit Leuven, Belgium and affiliated hospitals (Imelda Ziekenhuis, Bonheiden and St. Trudo Ziekenhuis, St. Truiden). He has been registered as a general surgeon in Belgium since August 1997. In 1997, he was the recipient of the Young Surgeons award of the Royal Belgian Society of Surgery.

The last two years of his general surgery training were entirely devoted to cardiac surgery and were done in the department of Cardiac Surgery of the University Hospital Gasthuisberg, Katholieke Universiteit Leuven (Prof. Dr. W. Daenen, head, Prof. Dr. W. Flameng and Prof. Dr. P. Sergeant).

He continued his training in cardiac surgery in the department of Thoracic and Cardiovascular Surgery (head: D.M. Cosgrove M.D.) of The Cleveland Clinic Foundation, Cleveland, Ohio, USA (July 1997 – October 1998). Topics of interest included valve reconstructive surgery, redo surgery, minimally invasive surgery, ventricular assist devices and transplant surgery. He was the 1998 recipient of the 'Rene Favarolo International Fellow in Cardiac Surgery' award.

Since November 1998 he works as a fellow in the department of Cardio-Thoracic Surgery of the St. Antonius Hospital in Nieuwegein, The Netherlands (head of the training program: H.A. Van Swieten M.D., Ph.D.). Special topics of interest include off-pump coronary artery bypass grafting, valve surgery, aortic surgery and arrhythmia surgery.

In January 2001, he will start working in the department of Cardiovascular and Thoracic Surgery of the Onze-Lieve-Vrouw Clinic, Aalst, Belgium (head: H. Vanermen M.D.).

Publications

Original articles
(only publications in journals listed in the Index Medicus)

1. Aneurysm of the left pulmonary artery:surgical allograft repair. *F. Casselman*, H. Deferm, P. Peeters, H. Vanermen. Ann Thorac Surg 1995;60:1423-1425.
2. Balloon-expandable Endobypass (B.E.E.B.) for Femoral-Popliteal Atherosclerotic Occlusive disease. H. Spoelstra, *F. Casselman* and O. Lesceu. Cardiovascular Surgery 1996; Sept. ESCVS Abstracts p.89.
3. Balloon expandable endobypass (B.E.E.B.) for femoral-popliteal atherosclerotic occlusive disease. A preliminary evaluation of 55 patients. H. Spoelstra, *F. Casselman*, O. Lesceu. J Vasc Surg 1996;24:647-654.
4. Traumatic rupture of the thoracic aorta:the diagnostic challenge. *F. Casselman*, K. Depuydt, H. Deferm, P. Peeters. Acta chir belg 1996;96:291-294.
5. Femoropopliteal endobypass:a feasibility study in 41 patients. *F. Casselman*, F. Van Elst, H. Spoelstra. Acta chir belg 1997;97:23-26.
6. An unusual cause of thoracic outlet syndrome. *F. Casselman*, K. Vanslembroek, L. Verougstraete. J Trauma 1997;43:142-143.
7. The Bicarbon heart valve prosthesis. Short term results. *F. Casselman*, P. Herijgers, B. Meyns, W. Flameng, W. Daenen. J Heart Valve Dis 1997;6:410-415.
8. Pulmonary artery aneurysm: is surgery always indicated? *F. Casselman*, B. Meyns, P. Herijgers, L. Verougstraete, F. Van Elst and W. Daenen. Acta Cardiol 1997;52:431-436.
9. Hemopump support for recovery of the failing heart:can we predict the outcome? B. Meyns, P. Sergeant, *F. Casselman*, P. Herijgers, W. Daenen, W. Flameng. Artificial Organs 1998;22:159 (abstract).
10. Twelve-year experience with Carpentier-Edwards Perimount pericardial valve in the mitral position: a multicenter study. M. Marchand, M. Aupart, R. Norton, I.R.A. Goldsmith, C. Pelletier, M. Pellerin, T. Dubiel, W. Daenen, *F. Casselman*, M. Holden,T.E. David, E.A. Ryba. J Heart Valve Dis 1998;7:292-298.
11. Fetal cardiac tamponade due to an intrapericardial teratoma. T. Tollens, *F. Casselman*, H. Devliegher, M. Gewillig, K. Vandenberghe, T. Lerut, W. Daenen. Ann Thorac Surg 1998;66:559-560.
12. Ascending aortic dissection after previous cardiac surgery: differences in presentation and management. A. Marc Gilinov, Bruce W. Lytle, Richard Kaplon, *Filip P. Casselman*, Eugene H. Blackstone and Delos M. Cosgrove. J Thorac Cardiovasc Surg 1999;117:252-260.
13. Injury to a patent left internal thoracic artery graft at coronary reoperation. Gillinov AM, *Casselman FP*, Lytle BW, Blackstone EH, Parsons EM, Loop FD and Cosgrove DM. Ann Thorac Surg 1999;67:382-386.
14. Intermediate-term durability of bicuspid aortic valve repair for prolapsing leaflet. *Casselman FP*, Gillinov AM, Akhrass R, Kasirajan V, Blackstone EH, Cosgrove DM. Eur J Cardiothor Surg 1999;15:302-308.
15. Aortic valve replacement after substernal colon interposition. Gillinov AM, *Casselman FP*, Cosgrove DM. Ann Thorac Surg 1999;67:838-839.
16. Risk factors for intracranial hemorrhage in adults on extracorporeal membrane oxygenation. V Kasirajan, NG Smedira, JF McCarthy, *F Casselman*, N Boparai, PM McCarthy. Eur J Cardiothor Surg 1999;15:508-514.

17. Use of the anterior mitral leaflet to reinforce the posterior mitral annulus after debridement of calcium. *Casselman FP*, Gillinov AM, McDonald ML and Cosgrove DM. Ann Thorac Surg 1999;68:261-262.
18. Aortic stenosis in endogenous ochronosis. *F. Casselman*, P. Herijgers, B. Meyns, W. Daenen. J Heart Valve Dis 1999;8:445-446.
19. Primary synovial sarcoma of the left heart. *FP Casselman*, AM Gillinov, V Kasirajan, NB Ratliff, DM Cosgrove. Ann Thorac Surg 1999;68:2329-2331.
20. An unusual cause of right-leg ischemia. Michael G. Licina, *Filip Casselman*, Charles Hearn and Bruce Lytle. J Cardiothorac Vasc Anesth 2000;14:95-96.
21. Reimplantation of the aortic valve: first experiences in 13 patients. *Original title:* Reimplantatie van de aortaklep: eerste ervaringen bij 13 patiënten. *FPA Casselman*, I Deblier, JMPG Ernst, JJAM Defauw, MAAM Schepens en WJ Morshuis. Ned Tijdschr Geneesk 2000;144:1402-146.
22. Mechanical support with microaxial blood pumps for postcardiotomy left ventricular failure: can we predict outcome? Bart Meyns, Paul Sergeant, Patrick Wouters, *Filip Casselman*, Paul Herijgers, Willem Daenen, Kris Bogaerts and Willem Flameng. J Thorac Cardiovasc Surg 2000;Vol 120:393-400.
23. Durability of aortic valve preservation and root reconstruction in acute Type A aortic dissection. *FP Casselman*, MESH Tan, FEE Vermeulen, JC Kelder, WJ Morshuis and MAAM Schepens. Ann Thorac Surg2000;70:1227-1233.
24. Wedge carinal resection for closure of the main bronchus after pneumonectomy. H Fahimi, *F Casselman*, M Mariani,W van Boven and H van Swieten. Ann Thorac Surg (in press).
25. Current management of postoperative chylothorax. H Fahimi, *F Casselman*, M Mariani, W van Boven, P Knaepen and H van Swieten. Ann Thorac Surg (in press).
26. Durability of the repair of prolapsing trileaflet aortic valves in adults. *F.P. Casselman*, A.M. Gillinov, E.H. Blackstone, and D.M. Cosgrove. J Thorac Cardiovasc Surg (accepted for publication).
27. Repeated anticoagulation events after mechanical aortic valve replacement. *FP Casselman*, ML Bots, W Van Lommel, PJ Knaepen, R Lensen and FEE Vermeulen. Ann Thorac Surg (accepted for publication).

Bookchapters

1. Minimally invasive heart valve surgery:operative technique and results. Gillinov AM, *Casselman FP*, Cosgrove DM.
   In: Yim, Hazelrigg S, Izzat, Landreneau R, Mack M, Naunheim K, eds. Minimal Access Cardiothoracic Surgery. W.B. Saunders Co 1999; chapter 71:1452-1456.