Aortic Valve Replacement in Young Adults

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Aan mijn ouders

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Chapter 1

General Introduction

General Introduction

Worldwide the incidence and burden of heart valve disease is increasing due to aging of the world population and the problem of rheumatic cardiac disease in developing countries and in parts of the population in the developed world.[1] Between 2007 and 2050 the world population will increase from 6.5 to 9.1 billion inhabitants.[1] Furthermore, the annual number of patients requiring heart valve replacement is estimated to triple from approximately 290,000 in 2003, to over 850,000 by 2050.[2]

In the Netherlands cardiovascular disease is the leading cause of death. According to the annual report of the Dutch Heart Association, 308.828 patients required admission due to cardiovascular disease in the Netherlands in 2004 of which 7286 patients were admitted due to rheumatic heart disease or valve disease (2.4%). Subsequently, 1449 patients died of heart valve disease (3.2%).[3] Furthermore, approximately 3000 patients require valve replacement due to aortic valve disease per year in the Netherlands.[4]

Specific Valve Lesions

Functionally, aortic valve disease can be subdivided in aortic stenosis, aortic valve regurgitation and the combination of these two.

Aortic valve stenosis

Aortic valve stenosis in adults is most commonly caused by calcification of a normal trileaflet valve or a bicuspid valve (congenital abnormality).[5] Calcific disease develops at the base of the cusps progressing to the leaflets, causing a reduction in leaflet motion and effective valve area without commissural fusion. Although less common in the developed countries, aortic valve stenosis can also be caused by rheumatic fever. This is characterized by diffuse fibrosis in the leaflets of a tricuspid valve with fusion of one or two of the commisures.[6] Calcification may be present.

Aortic stenosis can be graded as follows: Mild (aortic valve area more than 1.5 cm^2, mean aortic gradient less than 25 mm Hg, or jet velocity less than 3.0 m per second), moderate (area 1.0 to 1.5 cm^2, mean gradient 25 to 40 mm Hg, or jet velocity 3.0 to 4.0 m per second) or severe (area less than 1.0 cm^2, mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m per second).[5]

Natural history

Aortic stenosis in adults can be asymptomatic for long periods of time, although this period can vary widely among individuals.[7] Eventually, symptoms of angina

pectoris, heart failure, and syncope will develop and when symptoms are present, the average survival is 2 to 3 years with an increased risk of sudden death.[5] Thus, the development of symptoms marks a critical point in the natural history of aortic stenosis. Aortic stenosis progresses more rapidly in patients in whom it is caused by the degenerative calcific process than in patients in whom stenosis is caused by rheumatic fever or has a congenital origin. However, the rate of progression of aortic stenosis and development of symptoms varies widely per patient. For this reason regular clinical follow-up is advised for all patients with asymptomatic mild or moderate aortic stenosis.[5]

Treatment options

There is no medical treatment to delay the progression of aortic stenosis. Underlying conditions such as systemic hypertension should be medically treated in asymptomatic patients, and antibiotic prophylaxis is indicated in patients with aortic stenosis for prevention of infective endocarditis and in patients with aortic stenosis caused by rheumatic fever for preventing recurrent episodes. For patients with aortic stenosis who have developed symptoms there is yet no proper medical treatment and surgery is indicated as early as possible.[5, 7]

According to the ACC/AHA guidelines for the management of patients with valvular heart disease,[5] aortic valve replacement is indicated for symptomatic patients with severe aortic stenosis (Class I, level of evidence B) and for patients with severe aortic stenosis undergoing coronary artery bypass graft surgery (CABG; Class I, level of evidence C). It is also indicated for patients with severe aortic stenosis undergoing surgery on the aorta or other heart valves (Class I, level of evidence C) and is recommended for patients with severe aortic stenosis and left ventricular systolic dysfunction (ejection fraction less than 0.50; Class I, level of evidence C). Furthermore, aortic valve replacement is reasonable for patients with moderate aortic stenosis undergoing CABG or surgery on the aorta or other heart valves (Class IIa, level of evidence B). If the patient is asymptomatic with severe aortic stenosis and has a high likelihood of progression, an abnormal response to exercise or the patient has mild aortic stenosis with signs of rapid progression and requires CABG; aortic valve replacement may be considered (Class IIB, level of evidence C).

Finally, aortic valve replacement may be considered for asymptomatic patients with extremely severe aortic stenosis when the patient's expected operative mortality is 1.0% or less.

Aortic valve regurgitation

Aortic valve regurgitation may have several causes.[5,7] These causes comprise congenital abnormalities, rheumatic disease, infective endocarditis, and systemic hypertension, dissection of the ascending aorta, myxomatous degeneration or perforation of the valve cusps after balloonvalvulotomy or surgical commisurotomy.

Natural history

Aortic valve regurgitation may develop acutely or gradually as a chronic condition. Some of the above mentioned conditions, in particular infective endocarditis, dissection of the ascending aorta or unsuccessful balloonvalvulotomy or surgical commisurotomy for congenital aortic stenosis can cause acute aortic regurgitation. Acute severe aortic regurgitation can result in a sudden increase of left ventricular filling pressures and reduction in cardiac output causing cardiogenic shock or pulmonary oedema with poor prognosis.[7]

However, the majority of above mentioned conditions cause slowly progressive chronic aortic regurgitation.[5] Patients with chronic aortic valve regurgitation remain asymptomatic for a long time throughout a compensated phase, which is characterized by recruitment of preload reserve and compensatory ventricular hypertrophy allowing the left ventricle to maintain a normal ejection fraction despite an increased afterload. Severe aortic regurgitation develops when the compensatory phase can not be maintained and the preload reserve may be exhausted resulting in a further increase in afterload with a reduction in ejection fraction causing left ventricular systolic dysfunction. Dyspnoea, angina and heart failure may be present at that time.[5]

The natural history of aortic regurgitation depends primarily on its severity.[8] After onset of symptoms in acute severe aortic regurgitation, 1-year survival is only 10-30%.[6] Mild or moderate chronic aortic regurgitation may hardly affect daily activity or reduce life expectancy. The progression rate to the development of symptoms with or without left ventricular dysfunction is 4.3% per year according to the ACC/AHA guidelines.[5]

Treatment options

Medical treatment consists of vasodilating agents to improve forward stroke volume and reduce regurgitant volume. Medical treatment is indicated in patients with severe aortic regurgitation who have symptoms or left ventricular dysfunction when surgery is not an option due to additional cardiac or non-cardiac factors.[5] Furthermore, in patients with severe heart failure and severe left ventricular dysfunction awaiting aortic valve replacement, vasodilators can be used to optimize

haemodynamic performance of these patients.[7] Asymptomatic patients in the compensated phase with normal left ventricular function may also benefit from vasodilators. Vasodilator therapy is not recommended for asymptomatic patients with mild or moderate aortic regurgitation and a normal left ventricular function in absence of systemic hypertension because of the excellent outcome of these patients without medical treatment.[5]

The majority of patients with severe aortic regurgitation require aortic valve surgery, mostly replacement.[5, 7] Aortic valve replacement is indicated especially in symptomatic patients with severe aortic regurgitation regardless of left ventricular systolic function (Class I, level of evidence B), in asymptomatic patients with chronic severe aortic regurgitation and left ventricular systolic dysfunction (ejection fraction 0.50 or less) at rest (Class I, level of evidence B), or in patients with chronic severe aortic regurgitation while undergoing CABG or surgery on the aorta or other heart valves (Class I, level of evidence C).

Aortic valve replacement is reasonable for asymptomatic patients with severe aortic regurgitation with normal left ventricular systolic function (ejection fraction greater than 0.50) but with severe left ventricular dilatation (Class IIa, level of evidence B). Finally, aortic valve replacement may be considered in patients with moderate aortic regurgitation while undergoing CABG or surgery on the ascending aorta (Class IIb, level of evidence C) or in asymptomatic patients with severe aortic regurgitation with normal left ventricular systolic function at rest (ejection fraction greater than 0.50), with left ventricular dilatation, when there is evidence of progressive left ventricular dilatation, declining exercise tolerance, or abnormal haemodynamic responses to exercise (Class IIb, level of evidence C) .

Combined aortic valve stenosis and aortic valve regurgitation

In patients with combined aortic stenosis and aortic regurgitation and in some patients with aortic valve regurgitation with aortic stenosis, the predominant lesion causes the symptoms and form the basis of management.[5, 7] In combined aortic valve disease, 1 lesion usually predominates over the other. Unlike the management of a severe single valve lesion, firm guidelines for mixed aortic valve disease are difficult to establish. The most obvious approach is to surgically correct disease that produces more than mild symptoms. In an aortic stenosis-dominant aortic valve disease operation is required in the presence of even mild symptoms. In regurgitant dominant lesions, surgery can be delayed until symptoms develop or asymptomatic left ventricular dysfunction becomes evident.[5]

Valve Substitute Options

Although aortic valve repair may be an option in severe heart valve disease,[9] a large number of valves are not suitable for repair and therefore require replacement. Aortic valve replacement has significantly improved the life expectancy of patients with severe aortic valve disease receiving optimum medical therapy if possible. Nowadays, different aortic valve substitutes are available with each specific advantages and disadvantages.

A recent development concerns the percutaneous and transapical valve replacement techniques using biological valve substitutes. However at present, these techniques are only applied in the elderly.

Biological prostheses

Biological prostheses (or xenografts or heterografts) are the most commonly used prostheses for aortic valve replacement in current practice.[5] Figure 1 displays examples of biological prostheses. They can be divided in stented and stentless biological prostheses. Stented biological prostheses are made of animal tissue, for example porcine valve tissue or bovine pericardial tissue. Main advantages are the low thrombogenicity, no requirement of anticoagulation treatment, relatively standard implantation technique with a standard reoperation risk and are readily availability. Important disadvantages of these valves are their limited durability and its deteriorating haemodynamic performance.

Stentless biological prostheses are a newer generation biological prostheses. They are composed of bovine pericardium or porcine aortic valves with a smaller amount of cloth for stabilization, sewing or tissue ingrowth and are supposed to have a better haemodynamic performance compared to the stented biological prostheses. However, long-term results on durability are not yet available. Advantages of a stentless biological valve are the lower degree of stenosis because of absence of the stent and lower transvalvular gradients that presumably should improve long-term survival and these valve substitutes are readily available. Disadvantages are the incomplete long-term results and complexity of implantation compared with stented biological prostheses.

The ACC/AHA guidelines recommend that the biological prostheses preferably should be implanted in patients older than 65 years. The rate of structural failure of biological prostheses is age-dependent, higher in younger patients. In patients younger than 40 years almost half of these valve substitutes degenerates within 10 years.[5] For patients older than 65 years this failure rate is less than 10% at 15 years

after operation and furthermore a survival benefit is shown for patients receiving a bioprosthesis. Furthermore, there is an increased risk of bleeding in this group. Patients younger than 65 years and requiring aortic valve replacement who do not wish to use anticoagulation treatment are also eligible for aortic valve replacement with a biological prosthesis.[5]

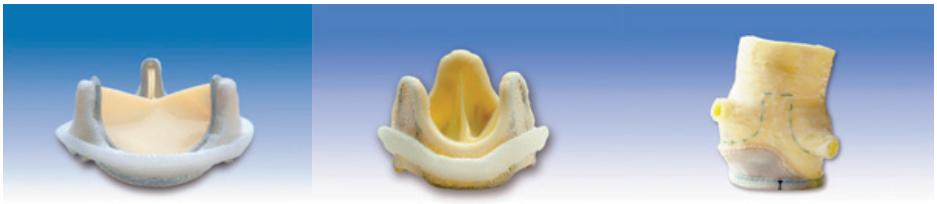

Figure 1. a. pericardial bovine biological prosthesis, b. stented porcine biological prosthesis, c. stentless porcine biological prosthesis

Mechanical prostheses

Mechanical valves were for the first time used as valve substitutes in the 1960's by Harken.[10] Since then, they have become widely used valve substitutes in aortic valve replacement. Most currently used mechanical valve prostheses are bileaflet valves. See figure 2 for examples. Unileaflet and ball valves are less commonly used because their design is being regarded as not optimal, because of the greater extension of the valve construction above the annulus, the increased embolization risk, and they are associated with greater noise compared to bileaflet valves.[11] The main advantage of mechanical valves is their life-long durability and these valve prosthesis are readily and easy to implant.[12] Main disadvantage of mechanical prostheses is the high thrombogenicity requiring life-long anticoagulation. This results in increased risk of bleeding and risk of thrombo-embolism despite anticoagulation therapy. Furthermore, for women who are in the childbearing age the mechanical prosthesis has several potential disadvantages, including not only an increased maternal mortality risk during pregnancy (1-4%) mainly due to valve thrombosis, but also an increased risk of embryopathy due to side effects of oral anticoagulant drugs.[13] When anticoagulation treatment is necessary during pregnancy, the ACC/AHA guidelines[5] give no specific recommendations although frequent monitoring of women during pregnancy is indicated. Warfarin crosses the placenta and is contraindicated because it is associated with an increase in spontaneous abortions, stillbirths and prematurity.[5] Furthermore, it is associated with embryopathy during the first trimester and central

nervous system abnormalities after exposure during any trimester. Unfractionated heparin does not pass the placenta and is not teratogenic but the risks of maternal valve thrombo-embolic complications and maternal death are highly increased during the first trimester. Low-weighted-molecular-heparin seems to have a low risk of bleeding complications, does not pass the placental barrier and is relatively safe for the foetus, however evidence for this meeting the treatment goals is not adequately available. [5]

Figure 2. a. Starr-Edwards ball- in-cage prosthesis, b. Medtronic Hall unileaflet valve, **c. St. Jude** Medical® bileaflet mechanical valve

Allografts

Since the introduction into clinical practice in 1962, allografts (or homografts) have become established in clinical practice. Although by far not as common as mechanical prostheses and biological prostheses, allografts are used in approximately 4% of valve replacements.

The allograft was firstly implanted in the aortic valve position by Donald Ross in 1962.[14] Over time the surgical implantation technique used changed from the subcoronary technique to the root replacement technique. The use of the root replacement technique seemed to be associated with less structural or technical failure compared with the subcoronary implantation technique.[15] Allografts can be implanted in two ways: as a subcoronary implant or as a complete aortic root, both technically more demanding compared with implantation of stented valve prostheses. When using the subcoronary technique, only the allograft cusps and hinge points of the aortic segment were implanted in the immediately adjacent aortic wall, leaving the coronary arteries untouched. The root replacement technique requires reimplantation of the coronary arteries but leaves the geometry of the aortic valve and root unchanged. Especially in patients with endocarditis, the root replacement technique offers the advantage of allowing excision of all infected tissue with

subsequent replacement by the allograft. The advantages of allografts are superior haemodynamics and the low thrombogenicity making anticoagulation treatment unnecessary. Disadvantages are its limited availability, the surgical expertise that is required for insertion and the limited durability. Due to the non-viable character of the allograft, these valve substitutes are subject to calcification, inevitably resulting in reoperation later in life.[15, 16] An age-dependent mode of structural failure compared to stented biological prosthesis is observed.[16, 17]

Figure 3: Cryopreserved aortic allograft with aortic arch

Autografts

The autograft procedure was introduced by Donald Ross in 1967.[18] Ross initially used the scalloped subcoronary implantation technique to insert the pulmonary valve into the left ventricular outflow tract with encouraging results.[19] It became a worldwide-accepted procedure for aortic valve replacement despite the need for specific surgical expertise to perform this double valve operation on both the aortic and pulmonary valve. Although initially the Ross operation was employed using the subcoronary implantation technique, over the years most centers shifted towards the root replacement technique, nowadays the most commonly used implantation technique. The root replacement technique appeared to be easier to apply and was associated with a decreased incidence of early and late failure compared to the other techniques.[20, 21] However, there are centers that successfully and exclusively employ the subcoronary implantation technique.[22] Potential advantages are the use of the patient's own living valve with favourable haemodynamic characteristics, low risk of endocarditis risk, low rate of thrombo-embolic events and avoidance of anticoagulant treatment. The alleged claim of growth potential of the autograft valve in children became a matter of discussion as dilatation may play a role in diameter increase as well. [23, 24] The autograft is the only living valve substitute providing long-term viability of most or all components of the valve.[18, 25] However, the autograft procedure is a technically demanding operation that requires replacement of both

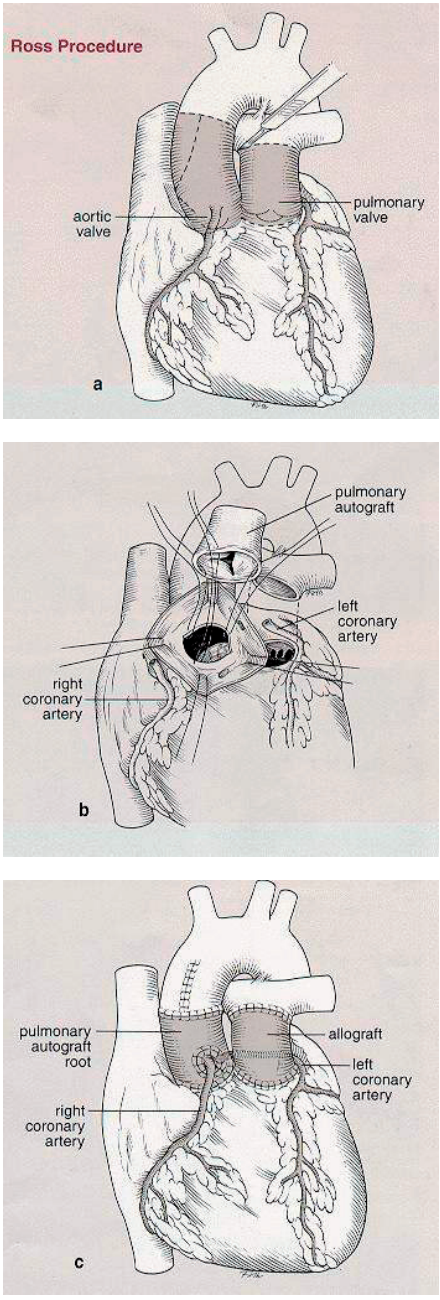

Figure 4: Schematic overview of the pulmonary autograft procedure (Ross operation)

the aortic and the pulmonary valve. Also, both the autograft in aortic position and the valve substitute in the right ventricular outflow tract may develop structural failure over time. Therefore, the durability of the autograft procedure depends on the lifetime of both valve substitutes.

Young adult patients who require aortic valve replacement

Since the first heart valve replacement in 1960, prognosis of patients with aortic valve disease has improved dramatically.[10] However, in particular young adult patients, who have to undergo aortic valve replacement, have an impaired survival compared to the age-matched general population. Nevertheless, young adult patients still have a relatively long life ahead, and complications associated with the different prosthetic valve substitutes need careful consideration.

The ideal valve substitute does not exist. This ideal valve substitute would be easy to implant, would have a life-long durability, would have low thrombogenicity, no need to use medication, be resistant to endocarditis with few or no complications on the early and long-term.[11]

Concerning the available valve substitutes, over the past decades multiple studies have reported on the outcome of aortic valve replacement with the different prosthesis types.[11,26,27]

Mechanical prostheses are a good option in young adult patients since they are durable and designed to outlive the patient. However, due to their thrombogenicity they require lifelong anticoagulation that carries an increased risk of bleeding. Especially for young adult patients who live an active lifestyle and young women who want to become pregnant, the use of anticoagulation may result in an unfavorable outcome.

Biological valve substitutes like the porcine and bovine biological prostheses do not require anticoagulation. On the downside, all biological prostheses have a limited durability, and in young adult patients this implies that a considerable proportion of patients will need a reoperation during the remainder of life. This has led to a recommendation that a biological prosthesis should be used for older patients (> 65 years).[5] Some centers have started to use stentless biological prostheses in adult patients younger than 65 years in the past decade, anticipating that the durability of these valve substitutes may have improved compared to older biological valve substitutes, and that their haemodynamic profile is superior to that of stented biological prostheses, both important potential advantages in particular for young adult patients who lead an active life.[5]

Allografts can offer young adult patients to live an active life without the limitations of anticoagulation necessary after aortic valve replacement with a mechanical prosthesis. Furthermore, their haemodynamic profile is compared with mechanical prostheses and biological prostheses. Besides the absence of anticoagulation use, allografts are a good valve substitute in active endocarditis to reconstruct of the anatomy of the aortic valve and adjacent structures, to have a low risk of both prosthetic valve endocarditis and of thrombo-embolic events.[28]

Autografts are the only living valve substitute available and have a proper haemodynamic adaptation, no anticoagulation treatment is necessary, patients can live an active lifestyle and patient survival could to be superior compared with survival of patients with other valve substitutes.[19, 29] These characteristics may be especially important for young adult patients.

Prognosis after aortic valve replacement depends on multiple factors that are associated with the patient and the type of prosthesis used. Given the number and complexity of these factors that affect outcome after aortic valve replacement, balanced and objective selection of the preferred valve substitute for the individual patient remains difficult. In particular in young adult patients, who have a relatively long life expectancy, optimal valve selection is important to ascertain a minimal burden of prosthetic valve disease. The 2006 AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease[5] do not provide specific instructions for valve selection in young adult patients, just general guidelines:

"Although the Ross operation, homograft, heterograft, and valve repair each offer an attractive alternative to a mechanical valve for those with relative contraindication to Warfarin therapy for anticoagulation (e.g., athletes or women desiring pregnancy), in the absence of long-term results, it is not believed that the indications for surgery with the Ross operation, heterograft, or homograft differ from those for mechanical valve replacement at this time".

This statement shows that the choice of an aortic valve prosthesis is a complex one that needs to be tailored to the individual patient. With the current knowledge on outcome of patients after aortic valve replacement with different types of prosthesis, no specific recommendations can be given. This is especially true for the subset of young adult patients, in whom only a limited amount of evidence on outcome is yet available.

Aim of the thesis

The focus of this thesis is on prognosis of young adult patients after aortic valve replacement with the different available valve substitutes. By studying different cohorts of young adult patients who underwent aortic valve replacement with different valve substitutes, it is attempted to gain further insight into the factors that determine outcome and provide more specific and evidence-based guidelines for prosthetic valve selection.

To achieve this, the following research questions were proposed:

1. What are the most important factors predicting outcome after aortic valve replacement in young adult patients who underwent aortic valve replacement?
2. What are the results with allograft aortic valve and root replacement?
3. Are there specific young adult patient populations potentially benefiting from the autograft or the allograft as a valve substitute?
4. Is the autograft still the favorable option in young adult patients?
5. What determines outcome of reoperative root replacement in patients who underwent previous aortic root surgery?

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Chapter 2

Outcome After Aortic Valve Replacement In Young Adults: Is Patient Profile More Important Than Prosthesis Type?

Presented at the Third Biennial Meeting of the Society for Heart Valve Disease in Vancouver, Canada, June 17-20, 2005

Outcome After Aortic Valve Replacement In Young Adults: Is Patient Profile More Important Than Prosthesis Type? Klieverik LMA, Noorlander M, Takkenberg JJM, Kappetein AP, Bekkers JA, van Herwerden LA, Bogers AJJC. J Heart Valve Dis. 2006 Jul;15(4):479-87.

Short abstract

The optimal prosthesis choice in young adults requiring aortic valve replacement (AVR) remains controversial. We studied whether implanted prosthesis type is an important determinant of outcome after AVR in 414 young adults (age 16-55) who underwent 438 AVRs between 1991 and 2001, using 204 mechanical prostheses, 3 bioprostheses, 150 allografts and 81 autografts. We evaluated peri-operative characteristics, early and late mortality, occurrence of valve-related events and predictors of adverse outcome and prosthesis selection. Prosthesis type was not a predictor of late mortality. Important predictors of increased late mortality were prior aortic valve surgery, impaired left ventricular function, concomitant mitral valve surgery and older patient age.
In conclusion, survival after AVR in young adults in this series is mainly determined by patient factors and not by prosthesis type.

Abstract

Background and aim of the study

The optimal prosthesis choice in young adults requiring aortic valve replacement (AVR) remains controversial. We studied whether implanted prosthesis type is an important determinant of outcome after AVR in young adults.

Methods

Between 1991 and 2001 414 young adults (age 16-55) underwent 438 consecutive AVRs using 204 mechanical prostheses (MP), 3 bioprostheses (BP), 150 allografts (AL) and 81 autografts (AU). We evaluated peri-operative characteristics, early and late mortality, occurrence of valve-related events and predictors of adverse outcome and prosthesis selection.

Results

Mean age was 41±11 years; for MP 45, for BP 50, for AL 39, for AU 31 years. MP selection was associated with: older age, impaired left ventricular function (LVF) and concomitant mitral valve surgery (concMVS); AL selection: ascending aortic aneurysm, active endocarditis; Marfan's disease; AU selection: younger age, prior balloonvalvuloplasty and isolated valve disease.

Hospital mortality was 2.3% (N=10). During follow-up (97% complete) 30 patients died. Ten-year survival was better for AU (96%±2%) compared to MP (84%±4%) and AL (92%±2%). Prosthesis type was not predictive of late mortality. Predictors of increased late mortality were prior aortic valve surgery, impaired LVF, concMVS and older patient age.

Ten-year freedom from bleeding and thrombo-embolism was 89%±3% for MP versus 94%±3% for AL and 99%±1% for AU (p=0.054). Ten-year freedom from reoperation was 95%±2% for MP versus 79%±5% for AL and 87%±5% for AU (p=0.003).

Conclusions

Survival after AVR in young adults in Rotterdam is mainly determined by patient factors and not by prosthesis type. A randomized controlled trial is necessary whether valve prosthesis type indeed plays a crucial role in improving survival in young adult patients.

Introduction

For patients who require aortic valve replacement, the two valve substitutes available are mechanical prosthesis and tissue valves (bioprosthesis, allograft and autograft). All valve types have their specific advantages and disadvantages. Mechanical prostheses are designed to last a lifetime but require lifelong anticoagulation therapy due to their increased thrombogenicity. Even though anticoagulation therapy is relatively safe, it does increase the risk of bleeding complications. Tissue valves require no anticoagulation therapy and their hemodynamic performance is more favorable. However tissue valves have a limited durability and therefore the patient may require a reoperation later in life.

Over the past decades multiple studies have reported on the outcome of aortic valve replacement with the different prosthesis types.[1,2,3] This has led to a recommendation that a bioprosthesis should be used for older patients (> 65 years).[2] Yet the optimal prosthesis choice for young adults remains controversial. Although mechanical prostheses provide a durable solution in these patients who have a relatively long life ahead of them, tissue valves do not require anticoagulation and their superior haemodynamic performance may result in a better patient survival.[4,5,6] We studied outcome of patients aged 16 to 55 years who underwent aortic valve replacement at our institution between 1991 and 2001 to assess whether implanted prosthesis type is an important predictor of outcome after aortic valve replacement in young adult patients or whether outcome is related to patient factors.

Material and Methods

Patients

Between 1991 and 2001 414 consecutive patients aged 16 to 55 years underwent aortic valve replacement at Erasmus University Medical Center in Rotterdam, The Netherlands. These patients underwent a total of 438 aortic valve replacements: 204 mechanical prostheses (MP) were implanted, consisting of 199 St. Jude prostheses, 4 ATS prostheses and one Björk Shiley prosthesis. Three stented bioprostheses (BP), all Carpentier-Edwards Perimount prostheses, were implanted, 150 allografts (AL) and 81 autografts (AU). Because of the limited number of bioprostheses implanted, they were excluded from further analyses. All operations were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection and in some cases circulatory arrest was needed.

For patients who received a mechanical prosthesis information on patient characteristics, perioperative details and follow-up was reported according the guidelines for reporting morbidity and mortality after cardiac valvular operations[7] and was collected retrospectively from hospital records, correspondence with treating physicians and through the civil registry. For patients who received allografts and autografts this information was obtained from our ongoing prospective cohort study.[8,9] All information was entered into a relational database (Microsoft Access W2000) and cross-checked for completeness and correctness.

Mortality and Follow Up

Early mortality and morbidity were registered and the causes of death were documented. Hospital mortality was defined as death of the patient within any time interval after operation if the patient was not discharged from the hospital. Thirty-day mortality was defined as mortality within 30 days after surgery regardless of the patient's geographical location.[7]

Statistical analysis

The collected information was analyzed using SPSS 12.1 for Windows (SPSS, Chicago, Ill). Continuous variables are displayed as mean ± 1 SD, discrete variables as proportions, unless stated otherwise. Means were compared using the independent sample T-test or ANOVA. Proportions were compared using the chi-square test. Using univariate logistic regression predictors of prosthesis selection were determined. Potential risk factors for increased early mortality were determined using univariate logistic regression analysis. The Kaplan-Meier method was used to analyze freedom from valve related events, reoperation and late mortality. Univariate and multivariate Cox proportional hazard regression analysis was done to determine predictors of late death (death > 30 days postoperative), reoperation and valve-related events.

Results

Patient characteristics are listed in Table 1 and perioperative details in Table 2. Seventy-one percent of the patients were male; this did not differ between the valve types. Aortic stenosis was more common in the mechanical and autograft recipients, while aortic regurgitation was most common in the allograft recipients.

Two hundred and four mechanical prosthesis were implanted. Factors that were associated with mechanical prosthesis implantation were older patient age (1.1; 95% CI 1.07-1.12; $p<0.001$), impaired left ventricular function (1.5; 95% CI 1.2-1.9; $p=0.002$) and need for concomitant mitral valve surgery (3.4; 95% CI 1.7-6.8; $p=0.001$).

Table 1. Preoperative patient characteristics

	All (n=438)	Mechanical (n=204)	Allograft (n=150)	Autograft (n=81)	Biological (n=3)
Males (%)	71% (n=313)	73% (n=149)	73% (n=110)	63% (n=51)	100% (n=3)
Age (years, mean, range)	41 (16-55)	45 (18-55)	39 (16-54)	31 (16-52)	50 (43-54)
Creatinin (µmol/l, mean, range)	92 (27-1152)	93 (27-1152)	99 (39-900)	73 (38-121)	87 (66-110)
Sinus rhythm	93%	90% (n=184)	94% (n=141)	99% (n=80)	100% (n=3)
NYHA class					
I-II	62% (n=270)	58% (n=118)	59% (n=88)	78% (n=63)	33% (n=1)
III-IV	37% (n=164)	42% (n=86)	38% (n=58)	22% (n=18)	67% (n=2)
V	1% (n=4)	-	3% (n=4)	-	-
Normal LVF[$]	69%	63% (n=129)	75% (n=112)	72% (n=59)	100% (n=3)
Diagnosis[1]					
AR†	45% (n=199)	41% (n=83)	58% (n=87)	36% (n=29)	-
AS†	28% (n=121)	32% (n=65)	19% (n=28)	32% (n=26)	67% (n=2)
AS+AR	27% (n=117)	27% (n=55)	23% (n=35)	32% (n=26)	33% (n=1)
Etiology					
Congenital*	38% (n=170)	34% (n=69)	35% (n=53)	56% (n=45)	100% (n=3)
Prosthesis/valve repair	19% (n=82)	21% (n=42)	16% (n=24)	20% (n=16)	-
Degenerative	12% (n=52)	18% (n=37)	8% (n=12)	4% (n=3)	-
Endocarditis	10% (n=42)	5% (n=11)	18% (n=27)	5% (n=4)	-
Aneurysm/dissection	9% (n=37)	7% (n=14)	15% (n=22)	1% (n=1)	-
Rheumatic	10% (n=44)	12% (n=24)	7% (n=10)	12% (n=10)	-
Other	3% (n=11)	3% (n=7)	1% (n=2)	2% (n=2)	-
Previous valve surgery	25% (n=110)	26% (n=53)	21% (n=32)	31% (n=25)	-
Emergent procedure	6% (n=28)	5% (n=10)	12% (n=18)	-	-
Preoperative ventilatory support	2% (n=9)	1% (n=2)	5% (n=7)	-	-

[1]One patient had a Bjork-Shiley type mechanical valve and underwent prophylactic replacement
*P<0.01 autograft vs mechanical prosthesis and allografts
† P<0.001 allograft vs mechanical prosthesis and autografts
$ P<0.02 mechanical prosthesis vs allografts and autografts

A total of 150 allografts were implanted. Factors that were associated with allograft implantation were NYHA class > III (2.4; 95% CI 1.2-4.6; p=0.009), the presence of an aneurysm of the ascending aorta (2.4; 95% CI 1.4-4.2; p=0.002), active endocarditis (6.7; 2.9-15.3; p<0.001) and Marfan's disease (n=19) (5.8; 95% CI 2.1-16.5; p=0.001).

The 81 patients who received an autograft were younger compared to the other valve types (1.1; 95% CI 1.09-1.15; p<0.001), had more often prior balloon valvuloplasty (10.8; 95% CI 3.6-32.0; p<0.0001) and had more often isolated aortic valve disease (7.9; 95% CI 1.9-33.0; p=0.005).

Table 2. Peri-operative details

	All (n=438)	Mechanical (n=204)	Allograft (n=150)	Autograft (n=81)	Biological (n=3)
Cross-clamp time (min)	123 (23-650)	106 (38-650)	132 (23-326)	149 (90-238)	115 (84-155)
CPB time (min)	179 (64-1125*)	158 (64-1125)	190 (95-485)	214 (114-685)	159 (113-244)
Circulatory arrest (min)	35 (1-269*)	42 (1-269)	33 (5-99)	22 (5-64)	-
Concomitant procedures#					
Other valve surgery[1]	13%	21%	9%	<1%	-
CABG	12%	17%	9%	4%	66%
CABG +other valve surgery	<1%	1%	-	-	-
Other[2]	20%	14%	32%	9%	-
Complications					
Bleeding/Tamponade	17%	16%	16%	21%	-
Sternal wound infection	<1%	<1%	-	<1%	-
Pacemaker	1%	1%	<1%	-	-
CVA/TIA	2%	1%	5%	-	-
Early mortality	10 (2.3%)	4 (2.0%)	4 (2.7%)	2 (2.4%)	0 (0%)

* The CPB time of 1125 min concerned one extreme case. This patient had a familiar connective tissue disorder with difficulty performing the anastomoses in the fragile tissue. The circulatory arrest was intermittently applied.

Not exclusive categories

[1] Other valve surgery includes mitral valve surgery, tricuspid valve surgery and pulmonary valve surgery

[2] Other concomitant procedures includes closure of an atrial/ventricular septum defect, surgery on ascending and/or aortic arch and enucleation of a subvalvular membrane

Hospital morbidity and mortality

Rethoracotomy was necessary in 76 patients (17%). Main causes were bleeding (n=51, 67%) and tamponade (n=22, 29%). The number of rethoracotomies for bleeding or tamponade decreased significantly in more recent years (p=0.02). One patient required a rethoracotomy due to a rhythm disorder and one due to pericarditis constrictiva. Two patients had a deep sternal wound infection requiring reintervention (<1%). Eight patients had a stroke postoperatively (2%).

Ten patients died in hospital (overall hospital mortality 2.3%); 4 mechanical prosthesis patients, 4 allograft patients and 2 autograft patients. Details on the hospital deaths are shown in Table 3.

No significant difference in hospital mortality was observed between the different valve types. Of these deaths, 4 were patients who underwent elective surgery. For these elective patients causes of death were as follows: One elective patient underwent a triple valve operation with implantation of an allograft and died of right and left ventricular failure 4 days after operation. The second patient had Turner syndrome, received a mechanical prosthesis and died of a myocardial infarction 6 days after

Table 3. Hospital deaths (n=10). Number of patients (n=415)

Sex	Age	Type operation	Valve type in situ preoperative	Indication for surgery	Valve type in situ postoperative	Cause of death	Time after operation (days)
F	24	Elective	Native valve	Aortic stenosis	Autograft	Heart failure	13
F	40	Urgent	Native valve	Aortic stenosis	Autograft	Heart failure	0
F	42	Emergency	Homograft	Abscess/remains endocarditis	St Jude 21 mm	CVA	27
F	48	Elective	Native valve	Bicuspid valve, aortic stenosis	St Jude 21 mm	Myocardial Infarction	6
F	50	Elective	Native valve	Rheumatic aortic regurgitation and stenosis	Homograft 21 mm	Tamponade	11
F	53	Elective	St Jude	Aortic regurgitation	Homograft 22 mm	Heart failure	4
M	46	Emergency	Native valve	Active endocarditis	Homograft 21 mm	Intracranial hemorrhage	8
M	47	Emergency	Native valve	Bicuspid valve, aortic stenosis	St Jude 29 mm	Heart failure	15
M	51	Urgent	Native valve	Active endocarditis	Homograft 23 mm	Heart failure	0
M	54	Emergency	Native valve	Aneurysm ascending aorta, aortic regurgitation	Björk Shiley 25 mm	Myocardial Infarction	0

operation. The third elective patient received an allograft and died suddenly 11 days postoperatively. Finally, one elective patient also with Turner syndrome and extreme left ventricular hypertrophy, received an autograft, required 13 days after the in initial operation a reoperation due to bleeding of lesions in the ascending aorta and died during reoperation of severely depressed left ventricular function.

Univariate logistic regression analysis identified female gender, prior combined aortic and mitral valve surgery, active endocarditis, impaired renal function, an abnormal cardiac rhythm pre-operative, NYHA class IV and urgent surgery as potential risk factors for hospital mortality.

Survival

Mean follow-up for the entire study population was 6.8 years (SD 3.3 years; range 0-12.9 years). Total follow-up comprised 2977 patient years. For mechanical prosthesis allografts and autografts mean follow-up duration was 6.2 yrs (SD 3.2; range 0-12.8 yrs, 1268 patient years), 7.2 yrs (SD 3.6; range 0-12.9 yrs, 1086 patient

years) and 7.7 yrs (SD 2.6; range 0-12.9 yrs, 622 patient years), respectively and was significantly different between the three groups (p=0.001).

The end point of the study follow-up was set on 1 January 2004. Follow-up was 97% complete to this date. Thirty patients died during follow-up: 20 mechanical prosthesis patients, 9 allograft patients and 1 autograft patient. Causes of death during follow-up are described below by valve type.

Three patients who received a mechanical prosthesis died after a massive brain hemorrhage, 2 patients died after a stroke, 6 patients died suddenly, 1 patient died due to arrhythmia, 1 died after a myocardial infarction, 1 due to progressive heart failure, 2 because of renal failure, 2 died of cancer and 2 patients died of unknown causes.

Three allograft patients died because of aortic valve endocarditis, 2 patients died suddenly, 2 patients died due to heart failure, 1 patient died after a reoperation due to an aneurysm of the ascending aorta and 1 patient died after a myocardial infarction. The autograft patient died of a myocardial infarction 2 months after reoperation for structural valve deterioration and implantation of a mechanical prosthesis.

Overall ten-year survival was 89.5% ± 1.8%. Ten-year survival was 84.2%±3.8% for the mechanical prosthesis group compared to 91.8%±2.3% for the allograft group and 96.2%±2.1% for the autograft group (Log-rank test p=0.08; Figure 1).

Table 4 shows the results of the univariate and the multivariate Cox regression analysis to identify factors that may affect late mortality. In the univariate model mechanical prosthesis (p=0.03) and autograft (p=0.05) were significant potential predictors of late mortality, yet failed to show a significant effect on late mortality in the multivariate model.

Valve related events

Table 5 displays the occurrence of valve related events by valve types. Twelve patients had a thromboembolic event (0.40%/ patient year, none lethal), of whom six had a mechanical valve. Thirteen patients had a major bleeding during follow-up and one patient had two bleeding episodes (0.47%/ patient year, 6 lethal). Two patients with mechanical prosthesis had valve thrombosis (0.16%/ patient year; none lethal) of which one had two incidents of valve thrombosis.

Prosthetic valve endocarditis occurred in 13 patients (0.44%/patient year). Of these patients 7 were treated with antibiotics, 5 required an aortic valve replacement and one patient with an allograft had a valve-sparing operation with removal

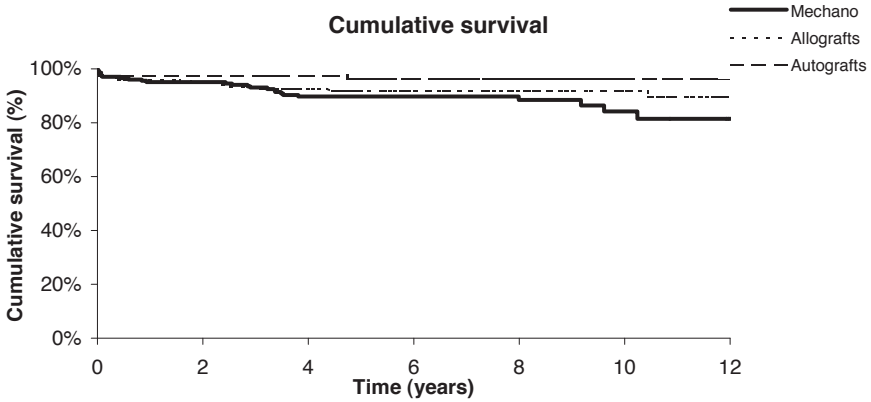

Figure 1. Cumulative survival after aortic valve replacement by implanted valve type

of vegetations off the cusps. There were 3 deaths resulting from prosthetic valve endocarditis. These patients died before surgical treatment could take place. Paravalvular leakage occurred in 7 patients, all requiring reoperation (0.24%/patient year) and structural failure happened to 33 patients (1.1%/patient year).

Table 4. Risk factors for late mortality

Risk factors	Univariate analysis model	Multivariate analysis model
	HR 95% C.I. P-value	HR 95% C.I. P-value
Pre-operative impaired renal function#	1.003 (1.002-1.005) <0.001	1.004 (1.002-1.006) <0.001
Pre-operative left ventricular function	5.6 (2.6-12.2) <0.001	5.1 (2.2-11.6) <0.001
Concomitant mitral valve surgery	3.6 (1.6-8.1) 0.002	3.0 (1.3-7.1) 0.01
Prior aortic valve surgery	3.0 (1.4-6.1) 0.003	3.7 (1.7-7.7) 0.001
Age*	1.04 (1.004-1.09) 0.03	1.02 (0.98-1.1) 0.41
Prosthesis type		
- Mechanical prosthesis	8.8 (1.2-65.4) 0.03	0.9 (0.03-1.9) 0.85
- Allograft	4.8 (0.6-38.0) 0.14	0.2 (0.4-2.1) 0.18
- Autograft (reference group)	1.0	1.0

HR = hazard ratio, with 95% confidence intervals

#Renal function was analyzed as a continuous variable. The HR represents the increase in risk per additional grade of creatinin

*Age was analyzed as a continuous variable. The HR represents the increase in risk per additional year of age.

Table 5. Late valve-related events

Type valve-related event	Number valve-related events N= 80	Occurrence rate (% per patient year)	Reoperation N=44	Valve related deaths N=8
SVD				
Mech	-	-	-	-
Allo	22	2.0	21	0
Auto	9	1.4	9	0
NSVD				
Mech	4	0.32	4	0
Allo	3	0.28	3	0
Auto	-	-	-	-
Endocarditis				
Mech	6	0.47	4	0
Allo	6	0.55	1	3
Auto	1	0.16	-	0
TE				
Mech	6	0.47	-	2
Allo	4	0.37	-	0
Auto	2	0.32	-	0
Bleeding				
Mech	11	0.87	-	3
Allo	3	0.28	-	0
Auto	-	-	-	-
Valve thrombosis				
Mech	3	0.24	2	0
Allo	-	-	-	-
Auto	-	-	-	-

SVD= structural valve deterioration, NSVD= non-structural valve deterioration, TE= Thrombo-embolic event.
Mech = mechanical prosthesis, allo = allograft, auto = autograft

Overall ten-year freedom from thromboembolic events (TE), valve thrombosis and bleeding was 92.7% ± 1.7%. For mechanical prosthesis ten years freedom from TE and bleeding was 89.1% ± 3.3% and worse compared to allografts or autografts 93.5% ± 2.6% and 98.7% ± 1.3% respectively (Log Rank test p=0.054).
Overall 10-year freedom from endocarditis was 96.8% ± 1.0%. For patients with a mechanical prosthesis the ten-year freedom from endocarditis was 97.4%±1.2, for the allograft patients 96.5%±1.5% and for the autograft patients 96.7%±2.4% (Log Rank test p=0.73).

Reoperation

A total of 42 patients underwent 44 aortic valve reoperations, see table 5. Of these 25 had an allograft, 10 a mechanical valve patients and 9 an autograft. Two patients underwent a re-reoperation within 30 days of the reoperation. In one patient this

was due to prosthetic valve endocarditis and in the second patient due to patient-prosthesis mismatch.

Freedom from reoperation at 10 years was for the entire study population 87.4%±2.1%.

Freedom from reoperation for the mechanical prosthesis, allograft and autograft at 10 years was 94.8%±1.9%, 78.8% ±4.5% and 87.0%± 4.5% respectively. See also Figure 2. Patients receiving a mechanical prosthesis had a significantly better freedom from reoperation compared to allograft patients (p=0.003). No significant difference was found between mechanical prosthesis patients and the autograft patients (p=0.11), or between the allograft and autograft patients (p=0.21).

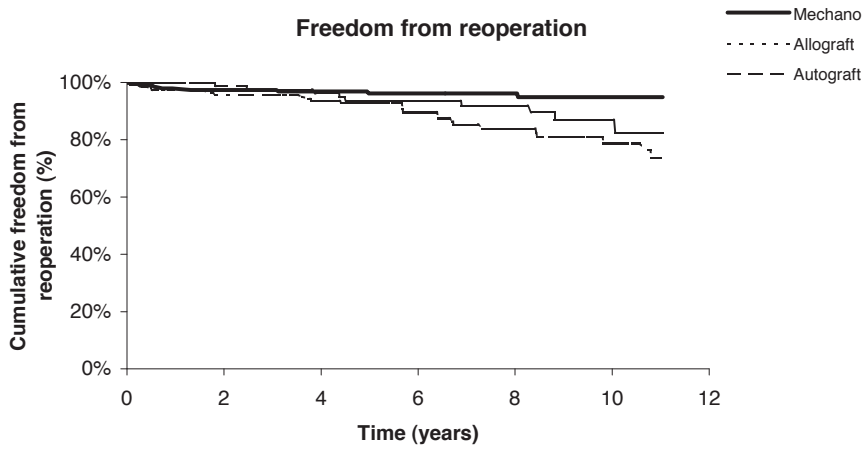

Figure 2. Estimated freedom from reoperation by implanted valve type

Comments

Prosthetic valve selection

When choosing a prosthetic aortic valve type for young adult patients who have a relatively long life expectancy, the increased hazard of thrombo-embolism and bleeding associated with the use of mechanical valves is weighed against the increased hazard of structural failure when using tissue valves. For women who are pregnant the mechanical prosthesis has several disadvantages, including not only an increased mortality risk during pregnancy (1-4%), mainly due to valve thrombosis but also an increased risk of embryopathy with oral anticoagulants.[10] In addition, hemodynamic profile, availability, and resistance to endocarditis of the prosthetic valve type may play an important role, next to patient preference. The AHA/ACC guidelines for the management of patients with valvular heart disease

only provide major criteria for valve selection in patients who require aortic valve replacement.[11] Valve selection particularly in young adult patients is left more or less completely at the discretion of the treating physician. It is obvious from our study that the patient profile is an important predictor of valve selection. Patients who receive a mechanical valve are older, more often have an impaired left ventricular function and more frequently need concomitant mitral valve surgery compared to allograft and autograft recipients. Patients, who receive allograft valve replacement more often present acutely, have a worse preoperative NYHA class, aortic root pathology, active endocarditis or Marfan's disease. Finally, patients who undergo autograft aortic valve replacement are usually younger, present with isolated aortic valve disease, and are more frequently previously treated by balloon valvuloplasty implying that congenital heart disease is involved.

Whether prosthetic valve selection also affects patient survival is still unclear. Several authors hypothesize that the use of stentless biological prostheses may be associated with better patient survival through faster regression of left ventricular hypertrophy and superior hemodynamics.[12,13] The present study aimed to elucidate whether prosthetic valve selection is an important predictor of outcome in young adult patients or whether outcome is mainly related to patient factors. Although selection of aortic valve prosthesis is predictive of the type of valve-related events that occur over time, in our study it is not an independent predictor of mortality in the first decade after the operation. This is in contradiction to a recent update of the randomized controlled trial of patients who underwent aortic valve replacement with either an autograft or allograft valve (Yacoub et al.; abstract presented at AHA Scientific sessions November 15, 2005); in this trial there was a survival advantage of patients who were randomized to autograft aortic valve replacement. However, several other (non-randomized) studies did not detect a patient survival difference between different implanted valve types.[2,3,14]

Survival after aortic valve replacement

Survival in the first decade after operation appears good in our young adult patient, but compared to mortality of the age-matched general Dutch population (10-year survival of approximately 97%), allograft and mechanical valve patients have a considerable excess mortality (84% and 92% at 10 years respectively). Survival of the autograft patients is comparable to the general population (96% at 10 years). This seems to be in contradiction with other reports of aortic valve replacement in young adults that showed no significant difference in survival between patients with mechanical and bioprostheses regarding long-term survival.[2,15] However, after we

employed multivariable Cox regression analysis, the type of implanted prosthesis was no longer predictive of survival.

Survival in the first decade after operation appears to be mainly determined by patient-related factors. Two of these factors (pre-operative impaired left ventricular function and the need for concomitant mitral valve surgery) were also predictive of mechanical prosthetic valve selection, and explain why mechanical valve patients have a higher mortality rate compared to patients who received allografts or autografts. In other studies patient-related factors like patient age, sex, diabetes mellitus and NYHA class IV[3] and concomitant CABG and preoperative left ventricular grade[2] were identified as determinants of survival in young adults.

The burden of prosthetic valve disease

The occurrence of valve related complications in our study population is comparable with other reports. Although structural failure was absent in mechanical prosthesis, the risk of reoperation –although low- was not absent. In the present study 5.2% of the mechanical prostheses were replaced after 10 years. Khan et al reported a freedom from reoperation for mechanical valves 98.7% at 10 years[3] and Ruel et al 94.6% at 10 years.[2] Also, bleeding and thrombo-embolic events were quite common (0.87%/patient year and 0.47%/patient year, respectively) but better than reported by other authors.[3,16] Khan et al[3] report a rate of valve thrombosis of 0.30% compared to 0.24% in our series.

An important advantage of the allograft is that it can be tailored to reconstruct specific endocarditis lesions and is therefore the most suitable option for surgical treatment of an infected aortic root. The allograft is durable against endocarditis, which makes it an excellent valve substitute in those patients who present with active endocarditis.[15] This is reflected by the low occurrence rates of allograft endocarditis in our series (0.55%/patient year). Unfortunately, the longevity of the allograft is disappointing especially in younger patients. This phenomenon has been reported previously[8,19] and although immune-mediated processes are hypothesized to underlie the increased failure rates observed in younger patients [20] this still needs to be clinically confirmed.

Autografts in our series have low thromboembolic event rate (0.32%/pt yr), no anticoagulation was used, no bleeding events occurred, have an excellent survival pattern and the patient can live a close to normal life. On the down side, the autograft procedure is a complex double valve operation whereby a healthy valve is replaced. A possible reoperation of the autograft and/or the valve substitute used to reconstruct the right ventricular outflow tract is complex. Thus far in our experience

the durability of the autograft procedure has been acceptable on the median term and after correction for patient age between autograft and allograft patients in our series, the autograft performs better than the allograft. However in the last few years several reports tempered the initial enthusiasm for the autograft procedure due to relatively high failure rates of autografts. In our series 9 autografts (11%) required reoperation in the study period which is comparable to other studies. [17,18]

Study limitations

This is a single center cohort study. The valve choice for this particular patient cohort may very well be different at other centers with possible other results of the influence of valve prosthesis choice on outcome after aortic valve replacement. Our results give an insight in our experience with the different aortic valve prosthesis types, but cannot be generalized to all young adults who undergo aortic valve replacement in Europe. A prospective randomized multicenter study would be the only way to answer the question whether there may be a survival advantage with a particular prosthesis in young adult patients.

It is expected that the complications related to the limited durability of the allograft and autograft valve types will increase in the second decade after the operation. This may result in an increased morbidity and mortality rate in the longer term. It is not yet possible to derive any conclusions from our study (maximum follow-up of 12.9 years) regarding the effect that valve type may have on survival beyond 10 years postoperative.

Finally, the autograft and allograft cohort were monitored in a prospective manner, while a retrospective study of the mechanical valve recipients was performed. This may have resulted in underreporting of valve-related complications in the mechanical valve cohort and an underestimation of the true burden of anticoagulation therapy.

Conclusions

In conclusion, in our center patient survival after aortic valve replacement in young adults is mainly determined by patient characteristics and not by prosthesis type. A randomized controlled trial is necessary to answer the question whether valve prosthesis type indeed plays a crucial role in improving survival in young adult patients, or whether other measures like optimizing the timing of surgery and medical therapy to provide improved myocardial protection are the key to a longer life expectancy.

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Chapter 3

Allografts For Aortic Valve Or Root Replacement: Insights From An 18-Year Single Center Prospective Follow-Up Study

Allografts for aortic valve or root replacement: insights from an 18-year single-center prospective follow-up study. Takkenberg JJM, Klieverik LMA, Bekkers JA, Kappetein AP, Roos JW, Eijkemans MJ, Bogers AJJC. *Eur J Cardiothorac Surg. 2007 May;31(5):852-60.*

Abstract

Objectives

Whether allografts are the biological valve of choice for AVR in nonelderly patients remains a topic of debate. In this light we analyzed our ongoing prospective allograft AVR cohort and compared allograft durability with other biological aortic valve substitutes.

Methods

Between 4/1987 and 10/2005, 336 patients underwent 346 allograft AVRs (95 subcoronary, 251 root replacement). Patient and perioperative characteristics, cumulative survival, freedom from reoperation and valve-related events were analysed. Using microsimulation, for adult patients age-matched actual freedom from allograft reoperation was compared to porcine and pericardial bioprostheses.

Results

Mean age was 45 years (range 1 month-83 yrs), 72% were males. Etiology was mainly endocarditis 32% (active 22%), congenital 31%, degenerative 9%, and aneurysm/dissection 12%. 27% underwent prior cardiac surgery. Hospital mortality was 5.5% (N=19). During follow-up (mean 7.4 yrs, max 18.5 yrs, 98% complete) 54 patients died, there were 57 valve-related reoperations (3 early technical, 11 non-structural, 39 structural valve deterioration (SVD), 4 endocarditis), 5 CVAs, 1 fatal bleeding, 8 endocarditis. Twelve-year cumulative survival was 71% (SE 3), freedom from reoperation for SVD 77% (SE 4); younger patient age was associated with increased SVD rates. Actual risk of allograft reoperation was comparable to porcine and pericardial bioprostheses in a simulated age-matched population.

Conclusions

The use of allografts for AVR is associated with low occurrence rates of most valve-related events but over time the risk of SVD increases, comparable to stented xenografts. It remains in our institute the preferred valve substitute only for patients with active aortic root endocarditis and for patients in whom anticoagulation should be avoided.

Keywords: aortic valve replacement, allografts, prognosis, reoperation

Introduction

There is not yet a perfect aortic valve prosthesis. In particular in non-elderly patients who have an active lifestyle and a relatively long life expectancy it can be hard to select the preferred aortic valve substitute. Choosing the optimal prosthesis requires careful weighing of the pros and cons of mechanical and biological valve substitutes for each individual patient, taking into account multiple interrelated factors like the expected lifespan of the patient, the willingness to take warfarin (and accept the associated risks) versus risking a possible reoperation for structural valve failure, major contraindications against warfarin therapy, and patient preference[1].

In our own institution we started using allografts for aortic valve replacement in the late 80's, assuming that their durability would be better compared to xenografts, their hemodynamic profile superior to mechanical prostheses and xenografts, and because they offer (in particular young adult) patients the option to live life to the full without the limitations and threats of anticoagulation that would be required after implantation of a mechanical prosthesis. We systematically and carefully follow patients over time and are now able to make statements about valve performance and patient outcome well into the second decade after operation.

The aim of this study is to assess whether allografts are indeed the biological valve substitute of choice in non-elderly patients. This is done by describing the clinical results of aortic valve and root replacement with allografts in our centre's prospective cohort study, and comparing the performance of allografts with stented porcine and pericardial bioprostheses in a simulated age-matched population.

Materials and methods

Between April 1987 and October 2005, 336 consecutive patients underwent 346 allograft aortic valve replacement or aortic root replacement procedures at Erasmus University Medical Center. All patients who receive an allograft in our center are enrolled in our ongoing prospective follow-up study[2-4]. Institutional Review Board approval was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent. Preoperative patient characteristics are displayed in Table 1.

Operation

Surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Deep hypothermia and circulatory arrest were used in 35 patients with ascending aorta or arch pathology. Early in our experience the subcoronary

Table 1. Preoperative patient characteristics

	All patients N=346	SC technique N=95	Root replacement N=251
Mean age (years (SD; range))	45 (16;0.06-83)	45 (15;14-83)	44(16; 0.06-75)
Male/female ratio	248/98	67/28	181/70
Creatinin (µmol/L,N=322,(SD;range))	103 (86;22-930)	113 (106; 48-930)	99 (76; 22-900)*
Prior cardiac surgery	27% (N=94)	20% (N=19)	30% (N=75)
Hypertension	15% (N=51)	15% (N=14)	15% (N=37)
Ischemic Heart Disease	9% (N=31)	12% (N=11)	8% (N=20)
Marfan	5% (N=18)	-	7% (N=18)#
Diabetes Mellitus	4% (N=13)	4% (N=4)	4% (N=9)
Diagnosis			
Aortic valve regurgitation (AR)	59% (N=203)	58% (N=55)	60% (N=148)#
Aortic valve stenosis (AS)	20% (N=67)	26% (N=25)	17% (N=42)
AR+AS	16% (N=61)	16% (N=15)	18% (N=46)
No AR and/or AS	4% (N=15)	-	6% (N=15)
Etiology			
Endocarditis	32% (N=102)	33% (N=31)	32% (N=80)#
Active	*N=76*	*N=13*	*N=63#*
Congenital (incl. bicuspid)	31% (N=106)	32% (N=30)	30% (N=76)
Other (mainly prosthetic valve)	10% (N=33)	9% (N=9)	10% (N=24)
Degenerative	9% (N=32)	12% (N=11)	8% (N=21)
Aneurysm	7% (N=25)	-	10% (N=25)
Rheumatic	6% (N=21)	15% (N=14)	3% (N=7)
Dissection	5% (N=18)	-	7% (N=18)
Sinus rhythm	92% (N=318)	91% (N=86)	92% (N=232)
Systolic LVF (N=343)			
Good	74% (N=255)	79% (N=75)	72% (N=180)
Impaired	18% (N=63)	17% (N=16)	19% (N=47)
Moderate/Bad	7% (N=25)	4% (N=4)	8% (N=21)
Preoperative NYHA class			
I	26% (N=89)	13% (N=12)	31% (N=77)#
II	26% (N=91)	27% (N=26)	26% (N=65)
III	30% (N=103)	48% (N=46)	23% (N=57)
IV/V	18% (N=63)	12% (N=11)	21% (N=52)
Prior CVA	5% (N=17)	8% (N=8)	4% (N=11)
Ventilation support	6% (N=21)	-	8% (N=21)#
Urgent operation (<24 hours)	11% (N=38)	2% (N=2)	14% (N=36)#

LVF = left ventricular function, NYHA = New York Heart Association, CVA = cerebrovascular accident, * statistical significant difference between the 2 surgical groups according to the unpaired T-test or Mann-Whitney U-test, # statistical significant difference between the 2 surgical groups according to the Fisher Exact test or the Chi-Square test.

technique was used, while since 1998 the root replacement technique has become the technique of choice (Figure 1).

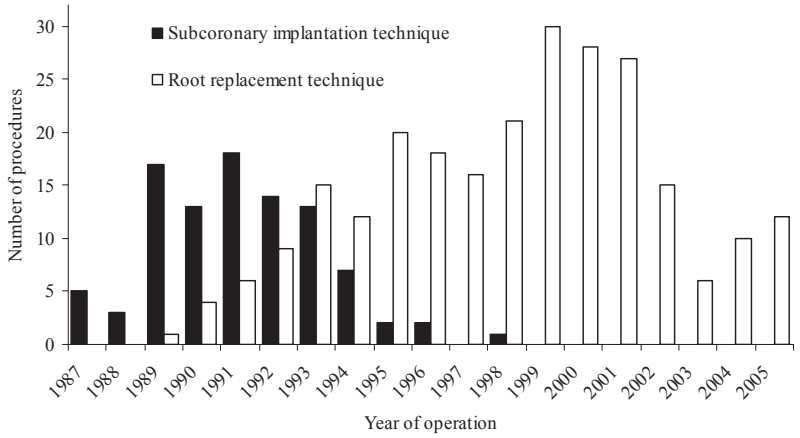

Figure 1. Number of allografts implanted with the subcoronary implantation technique and the root replacement technique by year of operation.

Subcoronary allograft implantation was done in 95 patients[5], initially with scalloping of the sinus of Valsalva (N=32) while later on the non-coronary sinus was preserved (N=63). Root replacement was performed as a freestanding root with reimplantation of the coronary arteries in 251 patients. Characteristics of implanted allografts are displayed in Table 2.

Follow-up

All patients who receive an allograft at ErasmusMC are followed prospectively by annual telephone interviews and through visits to their cardiologist. Echocardiographic follow-up at ErasmusMC is obtained at 6 months postoperative, 1 year postoperative and thereafter biennially by means of serial standardized echocardiography[3]. Valve-related complications were defined according to the 1996 guidelines for reporting morbidity and mortality after cardiac valvular operations[6].

The study database was frozen for analysis on December 1, 2005. Follow-up was 98% complete: 8 patients were lost to follow-up due to emigration. The mean follow-up duration was 7.4 years (range 0-18.5 years), with a total follow-up of 2545 patient years.

Statistical methods

Continuous data are presented as means (standard deviation; range), and comparison was done using the unpaired T-test unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances we used the Mann-Whitney U-test for comparison. Categorical data are presented as proportions, and comparison

Table 2. Allograft characteristics

	All patients N=346	SC technique N=95	Root replacement N=251
Type allograft			
Aortic	98% (N=340)	95% (N=90)	99% (N=250)#
Pulmonary	2% (N=6)	5% (N=5)	1% (N=1)
Size allograft (mm)			
Mean (SD; range; N=344)	22.7 (2.0; 14-30)	23.3 (2.3; 19-30)	22.4 (1.9; 14-28)*
≤ 24 mm	84% (N=288)	70% (N=64)	89% (N=224)#
>24 mm	16% (N=56)	30% (N=29)	11% (N=27)
Type donor (N=340)			
Heart beating	48% (N=164)	53% (N=47)	47% (N=117)
Non heart beating	33% (N=112)	15% (N=13)	39% (N=99) #
Domino	19% (N=64)	32% (N=29)	14% (N=35) #
Donor age (years N=339)			
Mean (SD; range)	40 (13; 8-62)	36 (13; 12-60)	42 (12; 8-62)*
Preservation method			
Cryopreserved	98% (N=339)	94% (N=89)	99% (N=250)
Fresh	2% (N=7)	6% (N=6)	<1% (N=1)
Origin			
Rotterdam	84% (N=291)	92% (N=87)	81% (N=2044% (N=10)
Barcelona	3% (N=10)	-	9% (N=23))#
Berlin	7% (N=25)	2% (N=2)	1% (N=3)
London	3% (N=9)	6% (N=6)	5% (N=11)
Other	3% (N=11)	-	
Quality code (N=336)			
1-2	38% (N=127)	66% (N=59)	27% (N=68)#
3-5	62% (N=209)	33% (N=29)	73% (N=180))#

* statistical significant difference between the 2 surgical groups according to the unpaired T-test or Mann-Whitney U-test, # statistical significant difference between the 2 surgical groups according to the Fisher Exact test or the Chi-Square test.

was done using the Chi-Square test or the Fisher Exact test where appropriate. All tests were 2-sided, with an α-level of 0.05. Univariate logistic regression analysis was used to study potential determinants of hospital mortality. Cumulative survival and freedom from reoperation or reintervention were analysed using the Kaplan-Meier method. The survival of a patient started at the time of aortic valve operation and ended at the time of death (event) or at the last follow-up (censoring). The analysis of allograft survival started at the time of implantation and ended with reoperation (event) or last follow-up or patient death (censoring). The Tarone-Ware test was used to compare Kaplan-Meier curves between surgical techniques (correcting for the differences in follow-up time between the groups). The Cox proportional hazards model was used for univariate and multivariate analysis of time-related events. Backwards-stepwise or forward-stepwise selection of potential predictors was employed, with criteria for entering variables: $P<0.05$.

Variables that were tested as potential risk factors for hospital and late mortality were: patient age (continuous variable expressed in years), gender, preoperative ventilation support, preoperative abnormal cardiac rhythm (any rhythm other that sinus rhythm), preoperative renal function (creatinin, continuous variable expressed in µmol/L), severe renal disease requiring either dialysis or transplantation, prior cardiac surgery, Marfan disease, ischemic heart disease, heart valve disease etiology, preoperative hypertension, systolic left ventricular function (good versus impaired/moderate/bad), prior CVA, preoperative NYHA class, emergency of the procedure, operative technique, cardiopulmonary bypass time (continuous variable expressed in minutes), and time period of operation (before 1998 versus after 1998). Factors that were tested as potential risk factors for reoperation for SVD were: patient age (continuous variable expressed in years), gender, severe renal disease requiring either dialysis or transplantation, prior cardiac surgery, heart valve disease etiology, preoperative hypertension, operative technique, surgical experience (considering the first 10 cases of an individual surgeon as inexperienced), allograft characteristics (including aortic versus pulmonary allograft, size allograft (continuous variable expressed in millimeters), type donor, donor age, donor gender, preservation method, quality code), donor-recipient sex mismatch, and time period of operation (before 1998 versus after 1998). For all analyses mentioned above SPSS 12.0 for Windows statistical software (SPSS, Chicago, Ill) was used. Using Egret, the incidence of structural valve deterioration requiring reoperation was described by a Weibull curve, which is a generalization of the exponential distribution that accommodates a changing risk over time[7-9]. An age parameter that was based on the observed relationship between patient age and structural valve deterioration was added to the Weibull model, allowing for patient age-specific calculations for structural valve deterioration[10, 11]. The age-specific Weibull model was entered into a previously developed microsimulation model [12, 13] to allow comparison of age-specific patient life time risk of reoperation for allografts, and stented porcine and pericardial bioprostheses[14]. The details of the parameters that were used for the microsimulation calculations of the CE pericardial and CE-SAV bioprostheses were previously published[14]. For each patient age group and valve type 10,000 patient lives were simulated; background mortality of the general US population was used.

Results

Early morbidity and mortality Peri-operative data are displayed for all patients and by implantation technique in Table 3. Coronary artery bypass grafting for complications related to reimplantation of the coronary arteries was necessary in 6 root replacement patients, of which 2 subsequently died. In one patient the left coronary artery button was too small, causing coronary ostium stenosis. Another patient had annular calcifications extending up to the right coronary ostium that was very thin-layered and ruptured after reimplantation. A third patient had an active endocarditis of an aortic bioprosthesis with abscesses, and the oedematous right coronary artery button ruptured after reimplantation. Another 2 patients experienced right ventricular dysfunction due to kinking of the reimplanted right coronary artery. In one patient the coronary artery buttons were very big, probably causing malperfusion of both the right and left coronary artery.

Table 3. Perioperative data

	All patients N=346	**SC technique N=95**	**Root replacement N=251**
Valve requiring operation			
Bicuspid	35% (N=121)	44% (N=42)	31% (N=79)#
Tricuspid	50% (N=173)	47% (N=45)	51% (N=128)
Quadriscuspid	1% (N=2)	-	1% (N=2)
Allograft	3% (N=9)	4% (N=4)	2% (N=5)
Prosthesis	12% (N=41)	4% (N=4)	15% (N=37)#
Concomitant procedures			
No	51% (N=176)	68% (N=65)	44% (N=111)#
Yes	49% (N=170)	32% (N=30)	56% (N=140)
Aortic cross clamp time (min (SD; range))	138 (46; 0-357)	132 (30; 79-248)	141 (51; 0-357)
Perfusion time (min (SD))	195 (76; 79-589)	176 (40; 116-316)	203 (84; 79-589)*
Circulatory arrest (min (SD; range)) (N=35)	35 (31; 5-163)	-	35 (31; 5-163)
Procedure-related CABG	2% (N=6)	-	2% (N=6)
Bleeding requiring reoperation	12% (N=41)	14% (N=13)	11% (N=28)
Permanent pacemaker	4% (N=14)	4% (N=4)	4% (N=10)
Perioperative CVA	3% (N=9)	3% (N=3)	2% (N=6)
Hospital death	5.5% (N=19)	4.2% (N=4)	6.0% (N=15)

LVOT = left ventricular outflow tract, CABG = coronary artery bypass grafting, SD = standard deviation, min = minutes, CVA = cerebrovascular accident, * statistical significant difference between the 2 surgical groups according to the unpaired T-test or Mann-Whitney U-test, # statistical significant difference between the 2 surgical groups according to the Fisher Exact test or the Chi-Square test.

During the procedure 5 patients died, and 14 more patients died during the same hospitalization or within 30 days postoperative (hospital mortality 5.5%). The 5 operative deaths were caused by persistent massive bleeding in 3 patients (1 with an active endocarditis with abscesses, 1 with an acute dissection, and 1 patient who underwent a reoperation for paravalvular leakage of a Bjork-Shiley mechanical valve), left ventricular failure in 1 patient who presented with acute endocarditis with fistula to the left atrium, and finally 1 patient with prosthetic aortic valve endocarditis with extensive tissue destruction of the left ventricular outflow tract and proximal ascending aorta with abscesses died during a salvage procedure. Causes of death in the 14 patients who died during the same hospitalization or within 30 days postoperative were registered as cardiac and not valve-related in 10 patients, 2 patients died of a major intracerebral bleeding, 1 patient of a myocardial infarction caused by a kink in the reimplanted right coronary artery, and 1 patient with an acute endocarditis as a result of a stroke caused by septic emboli. Potential risk factors for increased hospital mortality were older patient age (OR 1.07, 95% CI 1.03-1.11; p<0.001 (continuous variable expressed in years)), severe renal disease (requiring either dialysis or transplantation) (OR 11.2, 95% CI 3.4-37.2; p<0.001), longer cardiopulmonary bypass time (OR 1.008, 95% CI 1.004-1.013; p<0.001 (continuous variable expressed in minutes)), emergent procedure (within 24 hours) (OR 4.3, 95% CI 1.5-12.0; p=0.006), abnormal preoperative cardiac rhythm (OR 2.0, 95% CI 1.2-3.1; p=0.005), preoperative ventilation support (OR 4.9, 95% CI 1.5-16.2; p=0.01), NYHA class > II (OR 4.4, 95% CI 1.4-13.5; p=0.01), active endocarditis (OR 2.8, 95% CI 1.1-7.2; p=0.04), and preoperative hypertension (OR 2.9, 95% CI 1.1-8.0; p=0.04).

Late survival

During follow-up another 54 patients died (2.1%/patient year). Of these patients 36 died of non-valve-related causes. In 2 patients the cause of death could not be retrieved. Causes of valve-related death (N=16) were as follows: 9 patients died sudden unexpected and unexplained deaths, 3 patients died due to endocarditis, 2 patients who had structural allograft valve failure died of heart failure, 1 patient died after a CVA, and 1 patient died due to a major bleeding. Overall cumulative survival including early survival was 92.7% at 1 year (95% CI 90-96%), 86% at 5 years (95% CI 82-90%), and 71% at 12 years postoperative (95% CI 65-77%). In Figure 2 cumulative survival for patients operated with the subcoronary implantation technique and the root replacement technique is displayed separately (Tarone-Ware test p=0.03). Independent predictors of late mortality were older patient age

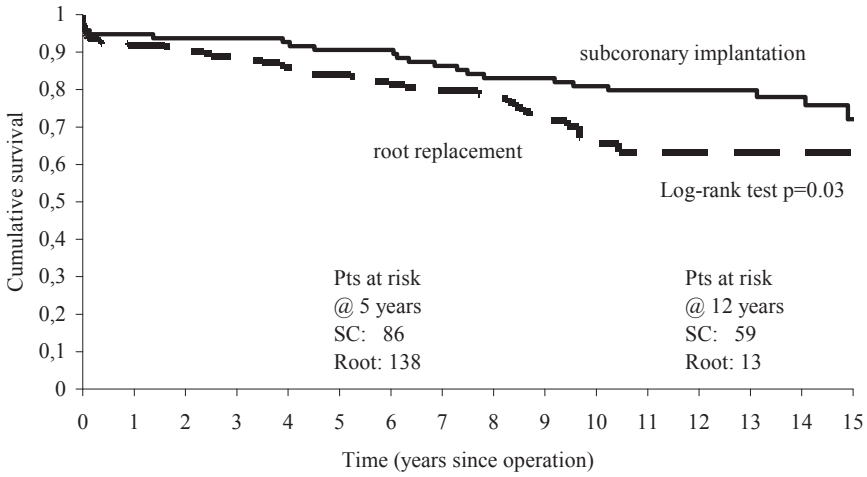

Figure 2. Cumulative survival after subcoronary implantation versus root replacement.

(HR 1.04, 95% CI 1.02-1.06; p<0.001 (continuous variable expressed in years)), preoperative ventilation support (HR 2.5, 95% CI 0.96-6.36; p=0.06), preoperative abnormal cardiac rhythm (HR 1.9, 95% CI 1.4-2.8; p<0.001), and the use of the root replacement technique (HR 2.2, 95% CI 1.2-2.4; p=0.02).

Reoperation

Reoperation for allograft related causes was necessary in 57 patients (2.2%/patient year). Reason for reoperation was structural valve deterioration in 39 patients. Non-structural or technical valve failure required reoperation in 14 patients, and persistent endocarditis in 4 patients. The allograft was replaced by a mechanical valve in 39 patients, an allograft in 10 patients, an autograft in 4 patients, and a stented bioprosthesis in 3 patients. One patient did not require replacement of the allograft: a vegetation was removed from the proximal anastomosis of the allograft 3 weeks after the initial operation for active endocarditis. Reoperative mortality was 1.7% (N=1). Freedom from reoperation for allograft-related causes was 97% at 1 year (95% CI 95-99%), 92% at 5 years (95% CI 88-95%), and 72% at 12 years (95% CI 64-79%), and worse in the subcoronary compared to root replacement technique group (Tarone-Ware test p=0.02).

Structural valve deterioration

In 39 patients structural valve deterioration caused by degeneration of the allograft was the reason for replacement of the allograft (1.5%/patient year). This occurred in 21 patients in the SC group (1.9%/patient year) and in 18 patients in the ARR group (1.3%/patient year). Freedom from reoperation for structural valve deterioration

(N=39) was 97% at 5 years (95% CI 95-99), 77% at 12 years (95% CI 69-85%). This did not differ between the subcoronary compared to the root replacement technique group (Tarone-Ware test p=ns). Using univariate Cox regression modelling the following factors were found to be potential predictors of the occurrence of reoperation for SVD: patients who received a same-sex donor valve, valves from male donors, the implantation of larger donor valves, and younger patient age (continuous variable expressed in years). Combining these 4 factors in a multivariate model proved quite tedious since most of them (with the exception of patient age) are strongly correlated. Therefore, we changed our model building strategy from backward to forward stepwise selection and started by entering the only variable that was not strongly correlated, namely patient age. Addition of same-sex donor valve to this model revealed that when corrected for patient age, same-sex donor valve was no longer a significant predictor of SVD occurrence (HR 1.9, p=0.13) and we took it out. Next, addition of donor sex to the model showed that, when corrected for patient age, male donor sex remained a significant predictor of SVD occurrence (HR 3.2; p=0.03), and we left it in the model. In the last step we added allograft diameter (continuous variable expressed in millimetres) to the model and found that, when corrected for patient age and donor sex, a larger allograft diameter was associated with increased SVD rates (HR 1.16; p=0.05) and male donor sex was no longer a significant predictor(HR 2.4; p=0.13). Therefore, in our final model independent predictors of structural valve deterioration requiring reoperation were younger patient age at the time of operation (HR 0.96; 95% CI 0.94-0.98 (age continuous variable expressed in years)), and larger allograft diameter (HR 1.2, 95% CI 1.06-1.40, diameter continuous variable expressed in millimeters)).

In Figure 3 the observed freedom from reoperation from structural valve deterioration and the Weibull function representing the effect of patient age on freedom from structural valve deterioration are displayed. For example, for a 45-year-old patient median time to reoperation for structural allograft valve deterioration was 16.5 years. The value of the age-dependent scale (σ) parameter of the Weibull model, fitted to represent allograft SVD was: $\sigma = e^{2.0755 + 0.0197 * age}$. The shape parameter ($\beta$) was estimated at 2.3856. The results of the Weibull model remained virtually unchanged when patients younger that 16 years or older than 65 years at the time of operation were excluded from the model.

Comparison with other biological valve types

Figure 4 shows patient age-specific (45-65 years) Weibull estimates of reoperation for structural valve deterioration for allografts, Carpentier Edwards pericardial

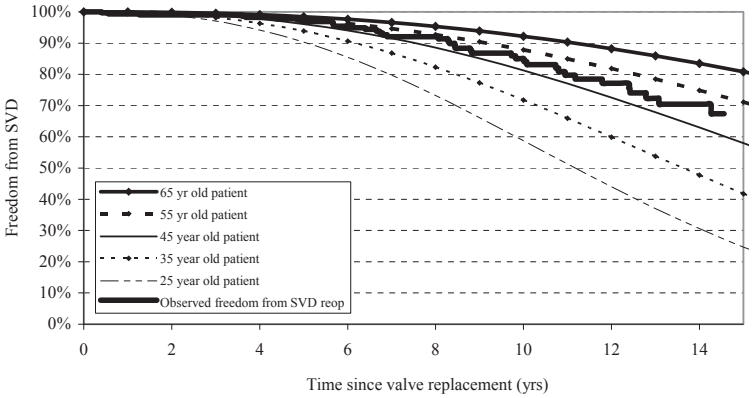

Figure 3. Observed freedom from reoperation for structural valve deterioration (SVD). Superimposed on this curve is the age-dependent Weibull estimate of age-specific freedom from reoperation for structural valve deterioration for patients aged 25 through 65 years at the time of operation.

bioprostheses and Carpentier Edwards SAV porcine bioprostheses. Figure 5 shows the microsimulation estimates of the "actual" lifetime risk of structural valve deterioration for male patients ages 35 though 65 years receiving either an allograft, a stented pericardial valve or a stented porcine bioprosthesis.

Other valve-related complications

During follow-up there were -besides the fatal CVA that was described above-: 2 non-fatal CVA's, 1 RIND and 9 TIA's. The linearized annual occurrence rate (LOR) for thrombo-embolic events was 0.5%/patient year. Besides the 4 lethal bleeding complications described above, there was 1 other major non-fatal bleeding during follow-up. The LOR for major bleeding was 0.2%/patient year. Besides the 4 endocarditis complications that required reoperation and the 4 lethal endocarditis complications, there was 1 non-fatal endocarditis that was treated with antibiotics. The LOR for endocarditis was 0.35%/patient year. No valve thrombosis or peripheral embolism was observed.

Discussion

Prosthetic valve selection in non-elderly patients who require aortic valve replacement is currently a hot topic of discussion[15, 16]. The new 2006 ACC/AHA guidelines for the management of patients with valvular heart disease only provide general recommendations for prosthetic valve selection in non-elderly patients, stating that "a mechanical prosthesis is reasonable for AVR in patients under 65

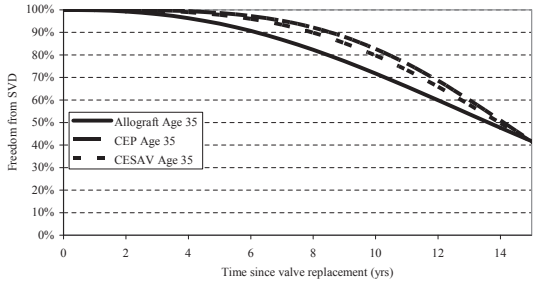

Figure 4a

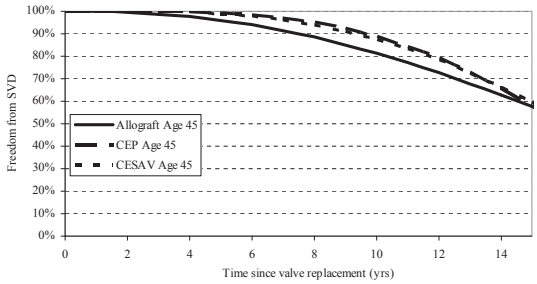

Figure 4b

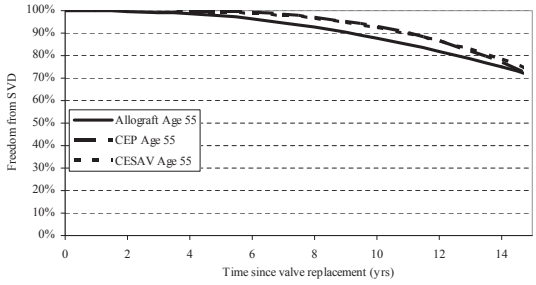

Figure 4c

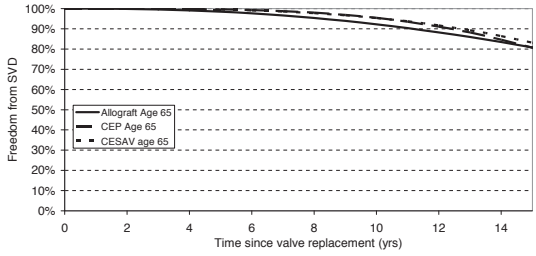

Figure 4d

Figure 4a-d. Weibull estimate of age-specific freedom from reoperation for structural valve deterioration of allografts versus CE pericardial versus CE-SAV stented bioprostheses for patients aged 35 (Figure 4a), 45 (Figure 4b), 55 (Figure 4c) and 65 years (Figure 4d) at the time of operation.

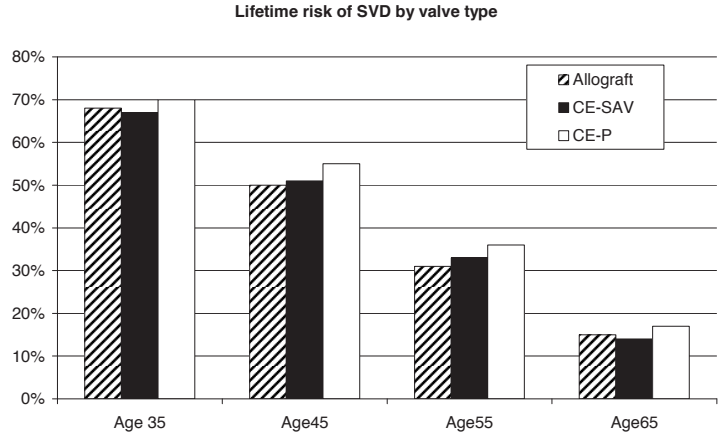

Figure 5. Age-specific microsimulation-based estimates of actual patient lifetime risk of structural valve deterioration requiring reoperation for allografts versus CE pericardial versus CE-SAV stented bioprostheses.

years who do not have a contraindication to anticoagulation. A bioprosthesis is reasonable in patients under 65 years of age who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second AVR may be necessary in the future"[1]. It is difficult to make an educated choice between these 2 completely different kinds of complication, and patient preference obviously plays an important role in the process. When a decision is made in favour of a biological valve substitute, the next question pops up: which one? We hypothesized in the late 80's that allografts would have a superior durability and hemodynamic profile compared to stented bioprostheses in non-elderly patients, but the results presented in this paper show that this hypothesis has to be rejected. What insights can be obtained from our 18-year single center prospective follow-up cohort of allograft patients? Looking back, the high expectations we had 18 years ago can only be met in part. The results show that although the use of allografts for AVR is associated with low occurrence rates of most valve-related events (in particular endocarditis), over time the risk of reoperation for structural valve deterioration increases, and is comparable to stented xenografts.

Patient survival Patient survival in our allograft cohort was comparable to other series that report survival after allograft aortic valve and root replacement[15, 17-20]. The impaired survival of patients undergoing allograft root replacement

versus the subcoronary implantation technique can be explained by the differences in patient profile (less isolated valve disease, more active endocarditis and complex root pathology) between the subcoronary implantation technique and the root replacement technique. Survival relative to the general age-matched Dutch population is markedly decreased, for example a 45-year-old male in the general Dutch population has a 12-year survival of 94%, while after allograft aortic valve or root replacement this is only 71%. This decreased relative survival has become a well-known phenomenon for patients after aortic valve replacement[21], with the exception of patients who undergo a Ross procedure[22, 23]. Whether there is patient selection or a true survival advantage in Ross patients, will remain a matter of debate until a randomized trial has been conducted.

Allograft durability This study shows that allograft durability is age-dependent in non-elderly patients and comparable to 2 commonly used stented bioprostheses in age-matched individuals who undergo aortic valve replacement. Freedom from any valve-related reoperation was better using the root replacement technique compared to the subcoronary implantation technique. This is in accordance with the observations in a recent systematic review of the effect of allograft implantation technique on reoperation rate[24]. However, when only reoperation for degenerative structural valve deterioration is studied, reoperation rates are comparable between the 2 insertion techniques. Younger patient age is associated with increased reoperation rates for structural valve deterioration in this cohort, an observation that is confirmed by several other reports[16, 18, 19]. The effect of patient age on valve durability is also comparable to CE pericardial and CE-SAV stented bioprostheses, suggesting a common pathway of degeneration. This is in accordance with a recently published study from Cleveland, Ohio, that demonstrated comparable failure rates for allografts and stented bovine pericardial prostheses for patients at all adult ages[16]. Our study adds to this the observation that stented porcine bioprostheses also have a comparable age-related valve failure occurrence. Therefore, we can conclude that durability does not play an important factor in choosing either of these 3 valve types.

Patient risk of reoperation Using microsimulation we demonstrated that the actual patient lifetime risk of structural valve deterioration requiring reoperation is comparable for all three valve types. This risk ranges from approximately 15% for a 65-year old patient to almost 70% in a 35-year old patient. These evidence-based estimates of actual patient risk of structural valve failure requiring a reoperation may provide a useful tool for patient counselling, quantifying the risks associated

with each therapeutic option. The demonstration simulation model (freeware) can be downloaded from our website (www.cardiothoracicresearch.nl) or requested by e-mail.

Reoperative mortality in our series was remarkably low, less than 2%. Although an allograft reoperation can be quite complicated, our results illustrate that it can be accomplished with a low reoperative mortality risk. Key is to closely monitor the patient over time, particularly in the second decade after operation when the risk of structural failure increases. This allows for careful planning of the reoperation, and avoids emergency reoperative procedures in decompensated patients.

Other valve-related complications Although durability of allografts is comparable to the most commonly used stented bioprostheses, the occurrence of other valve-related complications is quite low. In particular the annual occurrence rate of endocarditis is very low in our cohort, given that 22% of patients who received an allograft had an active endocarditis preoperatively. Also, thrombo-embolic and bleeding event rates are low in comparison to stented bioprostheses. However, this observed difference can at least in part be explained by the patient age difference between the allograft and stented bioprosthesis studies.

Changes in policy over time Figure 1 shows that early on in our experience we mainly used the subcoronary implantation technique while by the mid-90's the root replacement technique became the gold standard in our clinic for implanting an allograft in aortic position. As we reported previously, the subcoronary technique has a learning curve and its use resulted in our clinic in several early technical failures[4]. With the shift in surgical technique and due to the emerging disappointing durability outcomes, a change in patient profile took place: while early on in our series allograft aortic valve or root replacement was done in a broad range of patients that required aortic valve replacement, nowadays the main indication for the use of allografts is active endocarditis. Given its excellent resistance to infection, the allograft is a good solution for patients with active endocarditis, in particular when the aortic root is involved. Allograft root replacement can also be considered for patients with a (relative) contraindication for anticoagulation and patients with aortic root pathology.

Limitations Our study reports results from a single institution with a large proportion of patients with endocarditis and root pathology and may thus not be applicable to all patients who require aortic valve replacement. We were unable to study allograft mismatch as a potential risk factor for the occurrence of structural valve deterioration since we do not systematically measure the recipient annulus

at the time of operation. However, in the early postoperative phase only 1 patient had a gradient of more than 15 mmHg and therefore allograft mismatch appears uncommon in our series. Also, the microsimulation estimates that were used to calculate lifetime risks of structural valve deterioration requiring reoperation were largely based on pooled estimates of valve related complications from published reports. This may have resulted in overestimates or underestimates of complications and therefore have influenced the calculated lifetime risks. Furthermore, we assumed in the microsimulation analyses that all patients with structural valve deterioration were reoperated, while in real life this may not be the case.

Conclusions and recommendations The use of allografts for AVR is associated with low occurrence rates of most valve-related events but over time the risk of SVD increases, comparable to stented xenografts. Lifetime risk of reoperation is considerable, especially in younger patients. Careful follow-up of patients and early recognition of symptoms and signs of structural valve failure are the key to a successful reoperation. The allograft remains in our institute the preferred valve substitute only for patients with active aortic root endocarditis and for patients in whom anticoagulation should be avoided.

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Chapter 4

Surgical Treatment Of Active Native Aortic Valve Endocarditis With Allografts And Mechanical Prostheses

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Surgical Treatment of Active Native Aortic Valve Endocarditis with Allografts and Mechanical Prostheses. Klieverik LMA, Yacoub MH, Edwards SER, Bekkers JA, Roos-Hesselink JW, Kappetein AP, Takkenberg JJM, Bogers AJJC. *Submitted*

Abstract

Background

Surgery for persistent active native aortic valve endocarditis (NVE) remains challenging. No firm specific recommendations are available for use of particular valve substitute in active native aortic valve endocarditis surgery. In this regard, we analyzed our combined experience with allografts and mechanical prostheses in NVE surgery.

Methods

Between 1980 and 2002, 138 patients underwent aortic valve replacement for NVE in two centers with 106 allografts(ALLO) and 32 mechanical prostheses(MP). Patient and perioperative characteristics, early and late morbidity and mortality were analyzed.

Results

Mean age was 47 years(range 14-76), 81% were males, 34% required emergent surgery. Abscesses were more common in ALLO recipients, 38% versus 18% in MP recipients. MP patients required more often concomitant mitral valve replacement (34% versus 5%) compared with ALLO patients. Hospital mortality was 8%(n=11); 9% ALLO (n=10), 3% MP (n=1).

During follow-up(mean 8 years, range 0-25 years) 33 patients died; 22 ALLO patients(24%) and 11 MP patients(21%). Fifteen-year survival was 59%±6% for ALLO patients and 66%±9% for MP patients. Seven patients developed late recurrent endocarditis; six ALLO and one MP(p=0.29).

Overall fifteen-year freedom from reoperation was 76%±9% for ALLO and 93%±6% for MP (p=0.02).

Conclusions

This retrospective study has shown that mechanical prostheses produce comparable mid-term results both in terms of survival and freedom recurrent infection. However, this is in combination with extensive excision of destructive tissue in a specific patient subset. Furthermore, allograft reoperation rates increase with time. The influence of the choice of a valve substitute on long-term results requires further study.

Key words: Aortic valve, replacement; Endocarditis; Heart valve, allograft; Heart valve, mechanical; Outcomes

Introduction

Active aortic valve endocarditis is a life threatening disease associated with considerable morbidity and mortality. Initial treatment of active endocarditis is antibiotic therapy. If medical treatment fails, in patients with signs of peripheral emboli or heart failure, in case of extensive endocarditis, or when a prosthetic valve is involved, surgery is indicated. Surgery remains challenging in this particular patient population that often presents with acute symptoms, deteriorating haemodynamics and destruction of the aortic or other adjacent structures.

According to the ACC/AHA guidelines for management of patients with heart valve disease, surgical treatment of active native aortic valve endocarditis(NVE) should preferably consist of valve repair because of the risk of infection of prosthetic materials.[1] Thus far, there are no firm specific recommendations for use of particular valve prosthesis for surgical treatment of active NVE besides the general criteria for aortic valve selection. Currently, two commonly used substitutes to replace the infected native aortic valve are allografts and mechanical prostheses.[2]

In patients with active native aortic valve endocarditis allografts are a good option. Particularly when there is extensive destruction of the surrounding tissue, allografts can cover defects with preservation of the natural anatomy of the aortic valve and adjacent structures.[3] Furthermore, allograft patients do not require life-long anticoagulation and reinfection rate is low with a constant phase compared with mechanical prostheses and bioprostheses.[2] However, allografts have limited durability, which makes reoperation inevitable in the long-term, are not always readily available and implantation requires specific surgical training.

Mechanical prostheses, on the other hand, are designed to last a life time, are readily available and easier to implant. Furthermore, risk of endocarditis reinfection is reported to be very low.[4] On the downside, these valves are thrombogenic and require life-long anticoagulation with a high risk of bleeding and thrombo-embolic events.[5-7]

It remains a matter of debate whether there is a preferred valve substitute for active native aortic valve endocarditis treatment. In this regard, outcome of patients who underwent aortic valve replacement in two centers with an allograft or a mechanical prosthesis for active native aortic valve endocarditis were analyzed.

Material and methods

Patients

Between March 1980 and December 2002, 138 consecutive patients underwent aortic valve replacement for active NVE with allografts (n=106) or mechanical prostheses (n=32). Patients were operated by different surgeons at Erasmus University Medical Center Rotterdam, the Netherlands (n=86; 58 allografts, 28 mechanical prostheses) and by a single surgeon (MHY) at Harefield Hospital, United Kingdom (n=52; 48 allografts, 4 mechanical prostheses).

For allograft patients who were operated in Rotterdam, information on patient characteristics, perioperative details and follow-up was obtained from the ongoing prospective cohort study.[8] For mechanical prosthesis patients, these data were collected retrospectively from hospital records, correspondence with treating physicians and through the civil registry. For all patients who were operated in Harefield, all patient data was collected retrospectively in a similar fashion.

Diagnosis of endocarditis was based on clinical criteria, including signs of fever, new or altering cardiac murmurs, positive blood cultures and echocardiographic findings.[9] Endocarditis was considered active if patients underwent surgery before completing a 6 weeks course of antibiotic treatment.

Operative technique

All operations were performed on cardiopulmonary bypass with moderate hypothermia. In 2 Rotterdam patients circulatory arrest with deep hypothermia was needed because of ascending aorta and arch surgery.

Follow-up

Valve-related evens were defined according the guidelines for reporting morbidity and mortality after cardiac valvular operations.[10] The database was frozen on January 1st, 2006. Follow-up was 92.7% complete, ten patients had incomplete follow-up due to emigration.

Statistical analysis

For data analysis SPSS 12.0.1 for Windows (SPSS, Chicago, Illinois) was used.

Continuous data are displayed as mean ± 1 SD and comparison between groups were made using the unpaired T-test or the Mann-Whitney U-test where appropriate. Discrete data are presented as proportions and compared using the Chi-Square Test or Fisher's exact test.

For each patient a propensity score for receiving either an allograft or a mechanical prosthesis was calculated. First, by means of univariate logistic regression variables were identified that were potentially associated with valve substitute selection.

Variables with p<0.05 in the univariable analysis and variables that from a clinical point of view may be considered to affect prosthetic valve selection[1] were included in the multivariable model.

Variables included in the model were: age at operation (continuous variable), women at childbearing age (defined as women aged <45 years at operation), surgical center, time period, left ventricular function (LVF, defined as good: ejection fraction >50%, impaired: ejection fraction 40-50% and moderate/bad: ejection fraction <40%), presence of abscesses, emergent surgery (<24hrs after diagnosis) and concomitant mitral valve replacement. The propensity score was used as a co-variable in logistic and Cox regression models that studied mortality after operation.

Univariable and multivariable logistic regression was used to determine factors associated with hospital mortality. The following factors were analyzed: age at operation, sex, women at childbearing age, New York Heart Association Class (defined as I, II, III IV, and cardiogenic shock NYHA V), preoperative creatinin level (micromoles/L), preoperative ventilation support, preoperative atrial fibrillation, LVF, emergent surgery, presence of abscesses, type of infection causing microorganism , concomitant procedures, valve substitute used, cardiopulmonary bypass time (CPB, in minutes) and propensity score.

Cumulative survival, freedom from reoperation or reintervention or freedom from valve-related events, including reoperations, were analyzed using the Kaplan-Meier method. The Tarone-Ware test was used to compare Kaplan-Meier curves correcting for significant difference in follow-up time between allograft and mechanical prosthesis patients. Age-matched survival in the general population was calculated using the Dutch population life tables. (http://statline.cbs.nl/).

We used the life tables-method to calculate the hazard rate of structural failure for allografts over time by subdividing the follow-up period after operation into five year intervals.

The Cox proportional hazards model was used for univariable and multivariable (stepwise backward method) analysis of time-related events. The following factors were considered: age at operation, sex, women at childbearing age, surgical center, type of infection causing microorganism, presence of atrial fibrillation preoperatively, LVF, presence of abscesses, urgency of surgery, valve substitute used, concomitant procedures, CPB time and propensity score. A p-value ≤ 0.05 was considered statistically significant. All testing was two-sided.

Results

Preoperative patient characteristics by implanted valve substitute are shown in Table 1.

Table 2 displays perioperative details. Details on the 106 implanted allografts are displayed in Table 3 and causative microorganisms are shown in Table 4.

Valve selection

After univariable analysis presence of root abscesses showed a trend towards allograft selection (OR 2.6, 95% CI 1.0-6.9; p=0.05) whilst surgical center Rotterdam

Table 1. Preoperative details

	Allograft (n=106)	**Mechanical prosthesis (n=32)**
Mean age (years (SD; range))	47 (14-76)	46 (16-75)
Male gender	79% (n=84)	88% (n=28)
Women of childbearing age	8% (n=8)	3% (n=1)
Surgical center[a]		
Erasmus MC Rotterdam	55% (n=58)	88% (n=28)
Harefield Hospital	45% (n=48)	12% (n=4)[$]
Systolic LVF (n=94)		
Good	72% (n=48)	74% (n=20)
Impaired	22% (n=15)	19% (n=5)
Moderate/bad	6% (n=4)	7% (n=2)
Preoperative rhythm (n=134)		
Sinus rhythm	84% (n=87)	84% (n=26)
Atrial fibrillation	6% (n=6)	6% (n=2)
Other	9% (n=10)	10% (n=3)
Creatinin (µmol/L (range)	145 (49-900)	138 (63-364)
NYHA class (n=136)		
I	16% (n=17)	-
II	13% (n=14)	9% (n=3)
III	27% (n=28)	34% (n=11)
IV/V	43% (n=45)	57% (n=18)
Ventilation support	8% (n=9)	-
Antibiotic treatment	89% (n=94)	91% (n=29)
Type operation (n=135)		
Emergent (< 24hrs)	39% (n=40)	22% (n=7)
Urgent[a]	60% (n=62)	78% (n=25)
Elective	1% (n=1)	-

[a]p<0.05 allograft versus mechanical prosthesis

(OR 5.8, 95% CI 1.9-17.7; p=0.002), concomitant mitral valve replacement (OR 10.6, 95% CI 3.3-33.6; p<0.001) and operation performed before 1990 (HR 8.7; 95% CI 3.6-21.1; p<0.001) were potential factors for selecting mechanical

Table 2. Perioperative data

	Allograft (n=106)	**Mechanical prosthesis (n=32)**
Operative findingsa		
Abscesses/fistula[b]	38% (n=40)	18% (n=6)
Destroyed cusps	34% (n=36)	56% (n=18)
Vegetations	74% (n=78)	78% (n=25)
CPB timec(min, (range))	155 (58-483)	150 (60-375)
Cross clamp time (min, (range))	117 (25-326)	114 (43-192)
Circulatory arrest (min)	14,16 (n=2)	-
Concomitant procedures		
CABG	3% (n=3)	-
Mitral valve surgery	17% (n=18)	34% (n=11)
Mitral valve replacement[b]	*5% (n=5)*	*34% (n=11)*
Mitral valve repair	*12% (n=13)*	-
Extended root	2% (n=2)	-
Other[d]	8% (n=8)	6% (n=2)
Complications		
Rethoracotomy for bleeding	6% (n=6)	13% (n=4)
Pacemaker	5% (n=5)	6% (n=2)
Hospital death	9.4% (n=10)	3% (n=1)

[a]Overlapping categories

[b]<0.05 allograft versus mechanical prosthesis

[c]CPB= cardiopulmonary bypass time

[d]Including VSD closure, covering fistula with pericardial patches

Table 3. Allograft properties

	Rotterdam (n=58)	**Harefield** (n=48)	*p*-value
Type allograft			0.01
Pulmonary	2% (n=1)	15% (n=7)	
Aortic	98% (n=57)	85% (n=41)	
Type donor			0.17
Heart beating[a]	67% (n=39)	79% (n=38)	
Non heart beating	33% (n=19)	21% (n=10)	
Preservation method			
Cryopreserved	98% (n=57)	21% (n=10)	<0.001
Antibiotic-sterilized	*84% (n=49)*	*100% (n=10)*	0.21
Fresh	2% (n=1)	79% (n=38)	<0.001
Antibiotic-sterilized	-	*47% (n=18)*	0.35

[a]Brain death multi organ donors or heart transplant recipients

prostheses. After multivariable analysis surgical center (OR 6.1, 95% CI 1.8-20.4; p=0.03) and concomitant mitral valve replacement (OR 11.3, 95% CI 3.2-39.8; p<0.001) remained significant factors for mechanical prosthesis selection.

Table 4. Causative microorganisms

	Allograft (n=106)	**Mechanical prosthesis (n=32)**
Streptococci[a]	44% (n=47)	22% (n=7)
S.*viridans*	13% (n=14)	22% (n=7)
Pneumococci[a]	7% (n=7)	-
Enterococci	3% (n=3)	13% (n=4)
S. *aureus*	7% (n=7)	13% (n=4)
CNS[b]	10% (n=9)	-
HACEK[c]	1% (n=1)	6% (n=2)
Culture negative	16% (n=17)	19% (n=6)
Other	1% (n=1)	6% (n=2)

[a]p<0.05 allograft versus mechanical prosthesis

[b]CNS = Coagulase negative staphylococci,

[c]HACEK = *Haemophilus* species *(H parainfluenzae, H aphrophilus,* and *H paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species

Age at operation, sex, women in the childbearing age, NYHA class, stroke in history, preoperative renal failure, causing microorganism, preexisting atrial fibrillation, and urgency of surgery had no effect on valve selection.

Hospital mortality

Overall hospital mortality was 8% (n=11).Ten allograft patients (9%) and 1 mechanical prosthesis patient died (3%) (p=0.25). Three allograft patients died in theatre; one died of persistent bleeding, and two died of heart failure.

Three allograft patients died of intracranial haemorrhage 8, 9 and 10 days postoperative. One allograft patient died of a stroke 48 days postoperative and 3 allograft patients died of multi organ failure on postoperative days 5, 8, and 11. The mechanical prosthesis patient died of heart failure 1 day postoperative.

Potential risk factors for hospital mortality were female gender (OR 4.2, 95% CI 1.2-5.1; p=0.03), endocarditis caused by S. *aureus* (OR 5.6, 95% CI 1.2-25.2; p=0.03), preoperative increased creatinin (OR 1.01; 95% CI 1.01-1.02; p<0.001), NYHA class IV (OR 6.1, 95% CI 1.3-29.3; p=0.02), emergent surgery (OR 3.8, 1.05-13.7; p=0.04) and longer perfusion time (OR 1.01 95% CI 1.01-1.02; p=0.002). After multivariable analysis preoperative increased creatinin (OR 1.01 95% CI 1-003-1.02; p=0.006) and longer perfusion time (OR 1.01, 95% CI 1.003-1.02; p=0.01) were risk factors for hospital mortality. The propensity score had no effect on hospital mortality.

Follow-up and late mortality

Mean follow-up was 8.8±6.5 years, (max follow-up 25 years, 1223 patient years). Mean follow-up for allograft patients was 7.7±5.6 years (max follow-up 25

years, 820 patient years). For mechanical prosthesis patients mean follow-up was 12.5±7.8 years (max follow-up 24 years, 403 patient years). Mean follow-up time was significantly different between the 2 groups (p<0.001).

During follow-up 33 patients died (Linearized occurrence rate LOR 2.7%/patient year); 22 allograft patients (LOR 2.7%/patient year) and 11 mechanical prosthesis patients (LOR 2.7%/patient year).

Causes of death in allograft patients were recurrent endocarditis (n=3), intracranial haemorrhage (n=1) and sudden death (n=1), non valve-related death (n=17). Causes of death in mechanical prosthesis patients were sudden death (n=2) and non valve-related death (n=9).

Figure 1 shows survival for the valve substitute groups compared with 47-year old males in the general Dutch population. Overall 1 year survival was 89.6%±3.0% and 15 years survival was 61.3%±5.2%. For allograft patients 1 year survival was 89.6%±3.0% and 15 years survival was 58.7%±6.6%. For Rotterdam allograft patients 1 year survival was 91.4%±3.7% and for Harefield patients 87.3%±4.9% (p=0.43). Fifteen year survival for Rotterdam patients receiving an allograft was 64.3%±8.2% and for Harefield patients 53.8%±10.0% (p=0.76).

For mechanical prosthesis patients 1 year survival was 93.8%±4.3% and 15 years survival was 65.6%±9%. For Rotterdam mechanical prosthesis patients 1 year survival was 92.9%±4.9% and for Harefield patients 75.0%±21.7% (p=0.55). Fifteen year survival for Rotterdam mechanical prosthesis patients was 64.2%±9.7% and for Harefield patients 75.0%±21.7% (p=0.74).

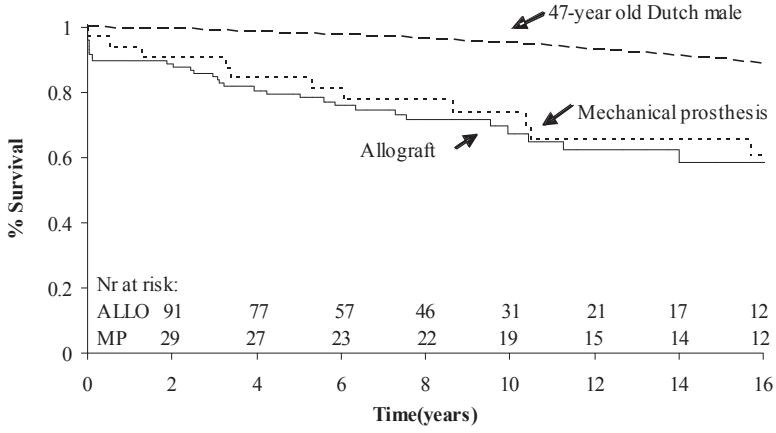

Figure 1. Survival after active NVE per valve substitute compared with the general age-matched Dutch population. ALLO=Allograft, MP=Mechanical prosthesis

Preexisting atrial fibrillation (HR 4.0, 95% CI 1.4-11.4; p=0.01) and older patient age (HR 1.05, 95% CI 1.02-10.7; p<0.001) were potential risk factors for increased late mortality. No other factors associated with increased late mortality.
After multivariable analysis preexisting atrial fibrillation (HR 4.2, 95% CI 1.4-12.6; p=0.01) and older patient age (HR 1.04, 95% CI 1.02-1.07; p=0.001) were significant risk factors for increased late mortality, even after including the propensity score in the model.
No survival differences were observed for allograft patients with root abscesses compared with patients in whom root abscesses were absent (p=0.34). Also, when comparing these patients between the two centers, no survival differences were observed (p=0.30).

Recurrent endocarditis

Six allograft patients (LOR 0.73%/patient year) and one mechanical prosthesis patient (LOR 0.25%/patient year) had recurrent endocarditis, all late episodes (range 1.5-13.5 years postoperative). Of these patients, 4 allograft patients underwent reoperation and survived. Two allograft patients and one mechanical prosthesis patient received only antibiotic treatment and died before reoperation could be performed.
One year freedom from recurrent endocarditis was 100% (Figure 2). Fifteen years freedom from recurrent endocarditis was 89.1%±4.3%. For allograft patients 15 years freedom from recurrent endocarditis was 85.9%±6.5% and for mechanical prosthesis patients 94.7%±5.1% (p=0.29). No variables were identified to be associated with recurrent endocarditis.

Reoperation

Twelve allograft (LOR 1.5%/patient year) and 1 mechanical prosthesis patient required reoperation. Reoperative mortality was 9% for allograft patients (n=1) and 0% for mechanical prosthesis patients. Reoperation causes for allograft patients were structural failure (n=5, LOR 0.61%/patient year), non-structural failure (n=2, LOR 0.24%/patient year) and endocarditis (n=5, LOR 0.61%/patient year), of which one patient had a persistent endocarditis. The mechanical prosthesis patient required reoperation due to pannus overgrowth.
The hazard rate of structural failure for allografts increased with time since operation: from 0.23%/patient year in the first 5 years after operation to 0.82%/patient year in 5-10 years after operation and 1.0%/patient year in 10-15 years after operation to finally 6.7%/patient year at 15-20 years after operation.

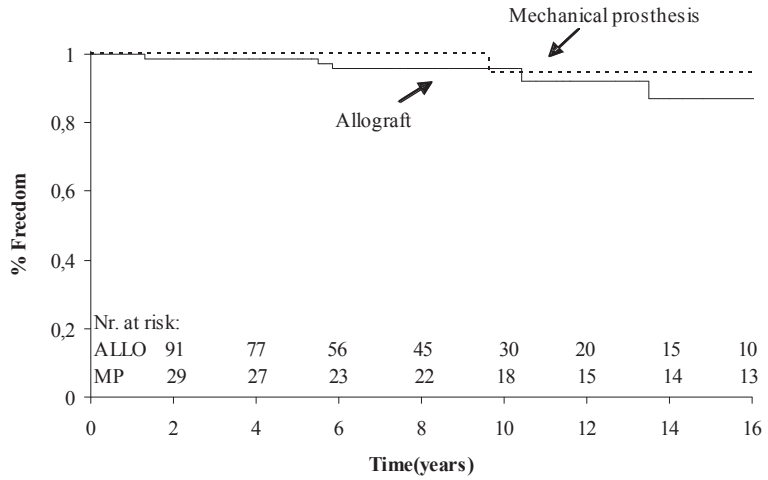

Figure 2. Freedom from recurrent endocarditis. ALLO=Allograft, MP=Mechanical prosthesis

Overall 15-year freedom from reoperation was 81.4%±6.2% (Figure 3); for allograft patients 75.8%±9.0% and for mechanical prosthesis patients 92.9%±6.9% (p=0.02). The only potential risk factor for increased reoperation rate was allograft use (HR 10.7, 95% CI 1.3-87.3, p=0.03).

Other valve-related events

One allograft patient, on anticoagulation medication, had an intracranial haemorrhage during follow-up (LOR 0.12%/patient year). No valve thrombosis or thrombo-embolic complications were observed in both groups. Overall 15 years valve-related-event-free-follow-up was 72.4%±6.5%, for allografts 67.3%±8.8% and 84.3%±8.8% for mechanical prostheses (p=0.06, Figure 4).

Comments

This study of a large cohort of patients requiring operation for active NVE provides important insights into influence of valve substitute choice on mid term survival, infection recurrence and reoperation. Early and late survival and recurrent endocarditis rates after aortic valve replacement for active NVE are comparable for allografts and mechanical prostheses, while over time allograft reoperation risk increases.

Valve selection

Selecting a valve substitute in active endocarditis seems in our study dependent on patient-related factors. A trend towards allograft selection as the preferable valve substitute in patients with root abscesses was observed. It is confirmed by

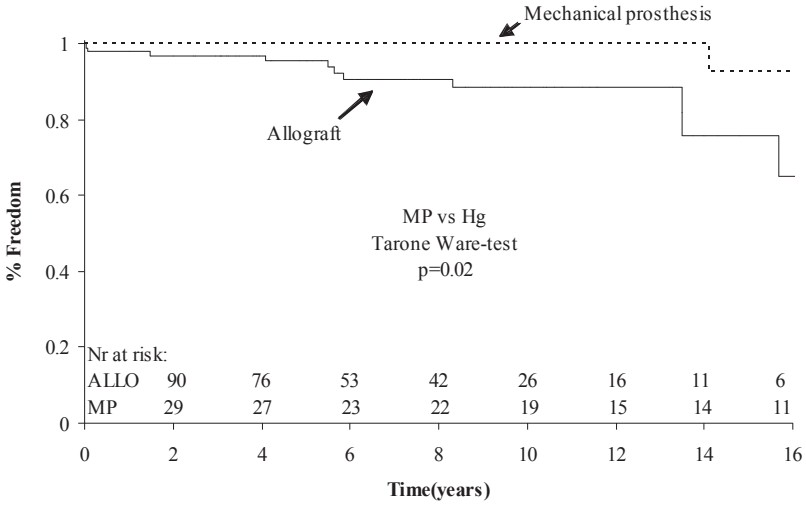

Figure 3. Freedom from reoperation. ALLO=Allograft, MP=Mechanical prosthesis

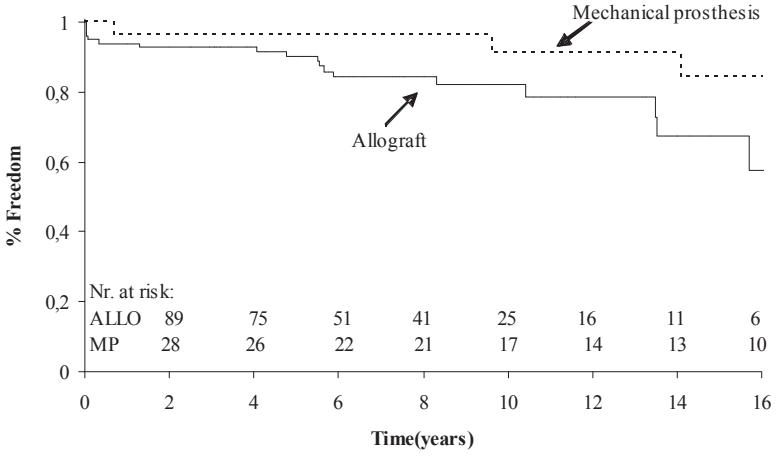

Figure 4. Freedom from valve-related events. ALLO=Allograft, MP=Mechanical prosthesis

others that extensive destruction of the left ventricular outflow tract and adjacent structures is one of the indications for allograft implanting in active NVE.[3,11] At Erasmus University Medical Center Rotterdam the decision for using allografts or mechanical prostheses in active endocarditis nowadays depends strongly on resulting anatomy after extensive debridement and excision of infected material or abscesses, fistula or annulus involvement. In the 1990's allografts were almost exclusively used in any endocarditis type, regardless of the lesion extent. This is

also reflected by the co-variable time period in our valve selection propensity score analyses. Before 1990 hardly any allograft was inserted and mechanical prostheses were valve substitutes of choice, simply because of limited experience with allografts and their scarce availability.

Furthermore, mechanical prostheses were more often used in our study patients, in whom active NVE destroyed the mitral valve, necessitating mitral valve replacement, thus warranting lifelong anticoagulation. Mechanical prostheses were implanted after extensive debridement and excision of infected material.

Although patient age is important for valve selection according the ACC/AHA guidelines[1], in our study patients it did not play a role. Moreover, our patients were relatively young patients with mean age of 47 years and according to the guidelines in these patients mechanical prostheses are the recommended valve substitute of choice, biological prostheses merely recommended in patients older than 65 years.[1]

Early mortality

Surgery for active NVE remains challenging with high operative mortality and the necessity of early surgery being reported.[2,12-16] Overall hospital mortality in this study was 8%. This is line with mortality rates described in the literature (9%-31%).[4,11,14,15]

No significant difference in early mortality between allograft patients and mechanical prosthesis patients was observed in the present report. Other factors determined in this study that potentially influenced early mortality were preoperative increased creatinin, NYHA class IV, emergent surgery, longer perfusion time and endocarditis caused by S. *aureus*. These variables were also reported by other authors to influence early mortality in active NVE.[2,4,13,15]

Late mortality

Fifteen years survival was 58.7% for allograft patients and 65.6% for mechanical prosthesis patients, which is comparable to other reports.[14,17] Furthermore, only seven patients died of valve-related causes (5 allograft patients and 2 mechanical prosthesis patients). The majority of our study patients died of non-valve related causes and only three allograft patients died of recurrent endocarditis.

Atrial fibrillation and older patient age were associated with increased late mortality risk, reflecting once again that suboptimal cardiac function and ageing play an important role in predicting late survival rates. Although there was a trend towards allograft selection in patients with root abscesses, and patients with abscesses may be more severely ill and could have adverse outcome, no differences in survival were observed between patients with presence of abscesses and without. Furthermore, no

differences in outcome were observed in these allograft patients between the two centers. Other underlying co-morbidities of patients may play a more profound role in outcome.

Recurrent endocarditis

Freedom from recurrent endocarditis after active NVE was approximately 90% and was comparable for both valve substitutes and is comparable to other series.[15,18] When our linearized rate of recurrent endocarditis for mechanical prostheses and allografts are compared with other observational studies on these valve substitutes, our results are in range with these reports.[5,13] The recurrent infection rate was lower for mechanical prostheses than for allografts in our study, and although this difference was not significant this is observed by other authors as well.[11,19]

Furthermore, Haydock and colleagues found a constant phase of recurrent endocarditis for allografts in contrast to an early peaking phase for mechanical prostheses.[2] In contrast, in our study there was no early peaking phase of recurrent endocarditis in the first year postoperative for the mechanical prosthesis (0%/patient year) and only one mechanical prosthesis patient had an episode of recurrent endocarditis. For allografts the hazard rate for recurrent endocarditis in the first five years after operation was 0.23%/patient year and increased over time to 6.7%/patient year. Although this seems to be significant it may be biased due to the small number of events that are observed and may be due to chance.

Reoperations

Allograft reoperations are perceived to be complex procedures potentially carrying high mortality and morbidity risk. In this series low reoperative mortality for allografts was found, a good result compared with other reports.[20,21] Two main causes for reoperation in our study were recurrent endocarditis and structural failure. Reoperation rates for recurrent endocarditis were 0.61%/patient year for allografts and 0% for mechanical prostheses. McGriffin and colleagues[22] studied that patients who had active NVE are more prone to have another episode of endocarditis. In the study of Tyers and colleagues, endocarditis was an important reoperation cause in mechanical prosthesis patients[23] and O'Brien and colleagues showed low reoperation rate for recurrent endocarditis after allograft implantation.[24] Although these two studies describe an incidence of reoperation for recurrent endocarditis favoring the allograft, reoperation rates for any cause are much higher in allograft patients than in mechanical prosthesis patients.[13,20,24-27] The present study confirms these results, by showing that reoperation risk for allografts

increases with time since operation, and is mainly determined by the increasing hazard of structural failure over time.

Yankah and colleagues describe also a high reoperation rate for structural failure in allograft patients, and especially in patients with undersized allografts.[3] In contradiction, in a recent report from our group a larger allograft diameter was an independent predictor for structural valve deterioration.[25]

Younger patient age is another risk factor for reoperation mentioned in the literature[2,13], which was not a significant factor in this report. This might be due to the small number of structural valve deterioration reoperations observed and limited mean follow-up duration of the study. Careful follow-up of allograft patients over time will prevent emergent reoperations in decompensated patients with degenerated allografts. Elective reoperations can be performed with good results and low mortality.[25] So, particular in active NVE patients with relatively long life expectancy reoperation is the most important limitation of allograft use, and should be considered when selecting a valve substitute.

Other valve-related complications

Bleeding complications during follow-up were rare in our study; only one allograft patient on anticoagulation medication had an intracranial haemorrhage. No events of valve thrombosis or thrombo-embolism were observed in our mechanical and allograft recipients. The low occurrence rates of valve-related events is in agreement with other reports.[14,17]

Limitations

The partially retrospective nature of study may have lead to underestimation of valve-related events during follow-up, in particular for mechanical prosthesis patients. Moreover, follow-up is slightly over 92% complete, leaving possible valve-related events during follow-up of approximately 8% of patients unresolved, which might have influenced our results.

This study is a combined series involving two centers with different policies for allograft and mechanical prosthesis use, and may not apply to other centers.

Furthermore, question remains whether all patients were eligible for an allograft or a mechanical prosthesis and vice versa. Patient selection bias can occur due to different treatment policies and due to the fact that implanting allografts remains difficult and requires specific surgical skills.

On the other hand, not all allograft patients could have been treated with a mechanical prosthesis, especially those with extensive destruction of the aortic root. A case controlled study or a randomized trial could give a better insight in which

valve best to implant in active aortic valve endocarditis, although the last mentioned is hardly achievable. Finally, timing of surgery after antibiotic treatment was not profoundly analyzed in this study and this may have an influence on the outcomes we observed.

Conclusions

Our study indicates that in this two center study both the allografts and mechanical prostheses provide a good solution in active native aortic valve endocarditis in terms of survival and recurrent endocarditis. However, when it comes to inserting a mechanical prosthesis in active endocarditis, this should be combined with extensive excision of infected tissue and done in patients without presence of aortic root abscesses. More reoperations for structural valve deterioration can be expected for the allograft in the second decade after operation given the increasing reoperation hazard with time. Whether the choice for a particular valve substitute in active aortic valve endocarditis has an influence on long-term results requires further study.

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Chapter 5

Autograft Or Allograft Aortic Valve Replacement In Young Adult Patients With Congenital Aortic Valve Disease

Autograft or Allograft Aortic Valve Replacement in Young Adult Patients with Congenital Aortic Valve Disease. Klieverik LMA, Bekkers JA, Roos-Hesselink JW, Bol Raap G, Bogers AJJC, Takkenberg JJM. *Submitted*

Abstract

Aims

We analyzed outcome of young adults with congenital aortic valve disease who underwent allograft or autograft aortic valve or root replacement in our institution and evaluated whether there is a preference for either valve substitute.

Methods and results

Between 1987 and 2007, 169 consecutive patients with congenital aortic valve disease aged 16-55 years, participating in our ongoing prospective follow-up study, underwent 63 autograft and 106 allograft aortic valve replacements. Mean age was 35 years(SD 10.8), 71% were males. Etiology was 71% bicuspid valve(BV), 14% other congenital, and 15% BV endocarditis. 22% underwent previous cardiac surgery; 11% had an ascending aorta aneurysm. Two patients died in hospital. During follow-up 6 more patients died and 45 patients required valve-related reoperations. Thirteen-year survival was 97% for autograft and 93% for allograft recipients; 13-year freedom from valve-related reoperation was 63% for autograft patients and 69% for allograft patients.

Conclusions

In patients with congenital aortic valve disease autograft and allograft AVR show comparable satisfactory early and long-term results, with the increasing reoperation risk in the second decade after operation remaining a major concern.

Introduction

Prosthetic valve selection for patients who require aortic valve replacement remains a delicate and complicated topic of discussion, as evidenced by the major criteria for aortic valve selection in ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease.[1] For young adult patients with congenital aortic valve stenosis this is particularly true. The guidelines state that "although the Ross operation, homograft, heterograft, and valve repair each appear to offer an attractive alternative to a mechanical valve for those with a relative contraindication to warfarin for anticoagulation (e.g., athletes or women desiring pregnancy), in the absence of long-term results, it is not believed that the indications for surgery with the Ross operation, heterograft, or homograft differ from those for mechanical valve replacement at this time".[1]

In our own institution we started using autografts and allografts for aortic valve replacement in the late eighties, assuming that their durability would be better compared to bioprostheses, their haemodynamic profile superior to mechanical prostheses and bioprostheses, and because they offer (in particular young adult) patients the option of an active life without the limitations of anticoagulation that would be required after implantation of a mechanical prosthesis. We systematically and carefully followed patients over time[2-4] and are now able to present reliable observations on valve performance and patient outcome well into the second decade after operation.

The aim of this study is to analyze the clinical results of aortic valve and root replacement with autografts versus allografts in young adult patients with congenital aortic valve disease that are participating in our center's prospective cohort study and assess whether there is a preference for one of these valve substitutes in this particular patient population.

Materials and Methods

Patients

Between April 1987 and January 2007, 499 consecutive patients underwent autograft or allograft aortic valve or root replacement at Erasmus University Medical Center Rotterdam. All patients who received an autograft or allograft in aortic position in our center are enrolled in our ongoing prospective follow-up study[2-4]. Institutional Review Board approval was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent.

For the purpose of this study we selected out of the 499 patients those patients with congenital aortic valve disease, no previous aortic valve replacement, and an age at operation between 16 and 55 years. Congenital aortic valve disease was defined as: bicuspid aortic valve or discrete subaortic obstruction, resulting in subvalvular or valvular aortic stenosis, aortic regurgitation, or a prolapse of one of the aortic cusps into a ventricular septal defect causing aortic regurgitation.[1] The enrollment was based on the presence of congenital aortic valve disease, either determined on preoperative echocardiography or based on the abnormalities seen at operation.
A total of 330 patients were excluded. Of these patients 70 patients were younger than 16 years of age and 106 were older than 55 years. These patients were excluded

Table 1. Preoperative patient characteristics

	Autograft n=63	Allograft n=106	p-value
Mean age (years (SD; range))	29 (9; 16-52)	38 (10; 16-55)	<0.001
Male/female ratio	35/28	85/21	0.001
Prior cardiac surgery*	27% (n=17)	20% (n=21)	0.28
Left ventricular outflow tract	22% (n=14)	7% (n=7)	0.003
Coarctectomy	5% (n=3)	9% (n=10)	0.27
Prior aortic valve balloon dilatation	8% (n=5)	3% (n=3)	NS
Actual diagnosis			
Aortic valve regurgitation (AR)	22% (n=14)	39% (n=41)	0.03
Aortic valve stenosis (AS)	38% (n=24)	29% (n=31)	0.24
AR + AS	35% (n=22)	31% (n=33)	0.61
AS + Subvalvular AS	5% (n=3)	1% (n=1)	0.11
Etiology			
Bicuspid valve	78% (n=49)	67% (n=71)	0.14
Other congenital	19% (n=12)	11% (n=12)	0.16
Endocarditis on bicuspid valve	3% (n=2)	22% (n=23)	0.005
Active endocarditis	-	*11%*	0.006
Aneurysm ascending aorta	6% (n=4)	13% (n=14)	0.17
Sinus rhythm	100% (n=63)	97% (n=103)	0.18
Creatinin (µmol/L, (SD;range))	72 (16; 38-121)	92 (36; 39-371)	<0.001
Systolic LVF (1 missing)			
Good	91% (n=57)	78% (n=83)	0.04
Impaired	9% (n=5)	22% (n=23)	0.02
NYHA class			
I/II	80% (n=50)	70% (n=74)	0.18
III/IV	20% (n=13)	30% (n=32)	0.18
Type operation			
Emergency	-	4% (n=4)	0.12
Urgent	10% (n=6)	18% (n=19)	0.14
Elective	90% (n=57)	77% (n=83)	0.04
Ventilatory support	-	2% (n=2)	0.27

LVF = left ventricular function measured by angiography or 2D-echocardiography, NYHA class = New York Heart Association classification, * = overlapping categories

because they did not fit the age criteria. Furthermore, 154 patients were between 16 and 55 years of age, but were excluded because these patients required surgery for another etiology than congenital aortic valve disease. Other etiologies were rheumatic disease (n=21), endocarditis (n=44), senile degeneration of a tricuspid valve (n=20), aneurysm (n=15), dissection (n=13) or reoperation (n=41).
This selection resulted in 169 patients: 63 autograft patients and 106 allograft patients. Preoperative patient characteristics are displayed in Table 1. Overall mean patient age was 35.0 years (SD 10, range 16-55 years).

Operation

Root replacement was performed as a freestanding root with reimplantation of the coronary arteries in 61 autograft patients and 66 allograft patients. In 2 autograft patients an inclusion cylinder aortic root replacement was done [5] and 40 allograft patients underwent subcoronary allograft implantation.[6] The autograft or allograft root was placed in the left ventricular outflow tract and annulus with a short rim of right ventricular muscle, which was kept to a minimum and no measures were taken to reinforce the aortic root or sinotubular junction. Either continuous or interrupted sutures were used for the proximal anastomosis, depending on the surgeon's preference. Initially in this series the autograft was placed on the annulus, in more recent years particular attention was paid to place the autograft inside the annulus. During the autograft procedure reconstruction of the right ventricular outflow tract

Table 2a. Characteristics of allografts used in the RVOT at pulmonary autograft procedure

	RVOT allograft n=63
Type allograft	
Pulmonary	100% (n=63)
Aortic	-
Size allograft (mm)	
Mean (SD; range)	25 (2; 19-30)
≤ 24 mm	63% (n=40)
>24 mm	37% (n=23)
Type donor (4 missing)	
Heart beating	44% (n=28)
Non heart beating	54% (n=34)
Domino	2% (n=1)
Donor age	
Mean (SD; range)	43 (11;10-59)
Donor sex (7 missing)	42 male/ 21 female
Preservation method	
Cryopreserved	100% (n=63)
Fresh	-

Table 2b. Allograft characteristics

	Allograft n=106
Type allograft	
Pulmonary	2% (n=2)
Aortic	98% (n=104)
Size allograft (mm)	
Mean (SD; range)	23 (2; 20-28)
≤ 24 mm	80% (n=85)
>24 mm	20% (n=21)
Type donor (4 missing)	
Heart beating	51% (n=54)
Non heart beating	31% (n=33)
Domino	14% (n=15)
Donor age	
Mean (SD; range)	40 (12; 15-62)
Donor sex (7 missing)	65 male/ 34 female
Preservation method	
Cryopreserved	96% (n=102)
Fresh	4% (n=4)

(RVOT) was done using an allograft. Details on these allografts are displayed in Table 2a and Table 2b. Surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection.

Follow-up

All patients who received an autograft or allograft at Erasmus MC are followed prospectively by annual telephone interviews and through visits to their cardiologist. Echocardiographic follow-up is obtained at 6 months postoperative, 1 year postoperative and thereafter biennially by means of serial standardized echocardiography.[2-4] Valve-related complications were defined according to the 1996 guidelines for reporting morbidity and mortality after cardiac valvular operations.[7] The mode of autograft and allograft failure was determined at time of reoperation or death.

The study database was frozen for analysis on April 1st, 2007. Follow-up was 96.5% complete.[8] Overall median follow-up duration was 10.1 years (interquartile range 6.9 years), with total follow-up of 1743 patient years, for autograft patient mean follow-up was 10.3 years (SD 3.8, range 0-18.4 years) with 650 patient years and for allograft patients mean follow-up was 10.3 years (SD 4.9, range 0.1-19.8 years) with 1093 patient years.

Statistical methods

Continuous data are presented as mean ± 1 standard deviation, and compared with the unpaired T-test or the Mann-Whitney U-test. Categorical data are presented as proportions, and compared with the Fisher's exact test or the Chi-Square test. To account for the inflation of the experiment wise Type I error due to multiple testing we used the Bonferroni post-hoc test in case of comparison of more than 2 categories.

Univariable logistic regression was used to determine factors associated with the different valve substitute groups. The following factors were analyzed: age at operation (continuous variable expressed in years), sex, previous surgery on the left ventricular outflow tract (LVOT), New York Heart Association Class (defined as I, II, III and IV), preoperative creatinin level (micromoles/L), preoperative ventilation support, abnormal cardiac rhythm preoperative (other preoperative rhythm than sinus rhythm), left ventricular function (defined qualitatively as good or impaired on either angiography or echocardiography), active endocarditis (operated on before completing a standard course of antibiotics) and preoperative haemodynamic diagnosis.

Cumulative survival and freedom from reoperation or reintervention were analyzed using the Kaplan-Meier method. Survival curves were compared using the Log-rank test. Univariable Cox regression was used for analysis of time-related events. The following factors were analyzed as potential risk factors for reoperation for structural failure:

Patient age, gender, previous cardiac surgery, endocarditis as the etiology for operation and allograft characteristics (as mentioned in Table 2).

Age-matched survival in the general population was calculated using the Dutch population life tables. (http://statline.cbs.nl/).A p-value of ≤ 0.05 was considered statistical significant. All testing was performed 2-sided.

For all analyses SPSS 12.0 for Windows statistical software (SPSS, Chicago, Ill) was used.

Using Egret, the incidence of structural valve deterioration requiring reoperation was described by a Weibull curve, which is a generalization of the exponential distribution that accommodates a changing risk over time.[9,10]

Results

Valve selection

Patients who received an autograft were younger at the time of operation (OR 1.09, 95% CI 1.06-1.14; p<0.001), were more often females (OR 3.2, 95% CI 1.6-6.5; p=0.001), had more previous surgery on the LVOT (OR 4.0, 95% CI 1.5-10.7; p=0.005), underwent more commonly elective surgery (OR 2.6, 95% CI 1.01-6.6; p=0.05) and had a good preoperative left ventricular function (OR 2.6, 95% CI 1.01-6.9; p=0.05). On the other hand, endocarditis on a bicuspid valve (OR 8.5, 95% CI 1.9-37.2; p=0.005), increased preoperative serum creatinin level (OR 1.05, 1.03-1.08; p<0.001) and aortic regurgitation as the haemodynamic diagnosis (OR 2.2., 95% CI 1.1-4.5; p=0.03) were more common in allograft recipients.

Two allograft patients received a pulmonary allograft in the aortic position (see Table 2b). One of the patients required a reoperation within 2 weeks after initial implantation of the pulmonary allograft and received a new aortic allograft. Six

Table 3. Perioperative data

	Autograft n=63	Allograft n=106	p-value
Concomitant procedures*			
CABG (planned)	-	8% (n=8)	0.04
CABG (unplanned)	3% (n=2)	3% (n=3)	0.90
Replacement ascending aorta	1% (n=1)	11% (n=12)	0.02
LVOT enlargement	1% (n=1)	3% (n=3)	0.61
Mitral valve surgery	1% (n=1)	6% (n=6)	0.20
Tailoring ascending aorta	1% (n=1)	2% (n=2)	0.90
Closure VSD	-	1% (n=1)	0.44
Aortic cross clamp time (min (SD; range))	145 (30; 90-225)	123 (29; 68-217)	<0.001
CPB time (min (SD; range))	206 (76; 114-685)	165 (42; 79-344)	<0.001
Circulatory arrest	2% (n=1)	4% (n=4)	0.42
Bleeding requiring reoperation	18% (n=11)	7% (n=7)	0.02
Permanent pacemaker for AV block	-	2% (n=2)	0.28
Reoperation paravalvular leak	-	2% (n=2)	
Stroke	-	1% (n=1)	0.44
Perioperative myocardial infarction	2% (n=2)	2% (n=2)	0.59
Hospital death	3.2% (n=2)	-	0.07
Postoperative hospital stay (days)			
Mean (SD)	11 (4)	13 (10)	0.07
Median	10	10	
Range	6-39	6-56	

CABG= coronary artery bypass grafting, LVOT = left ventricular outflow tract, VSD = ventricular septal defect, CPB = cardiopulmonary bypass, SD = standard deviation, min = minutes, AV = atrioventricular, * = overlapping categories

years after this allograft implantation this patient required another reoperation and received a mechanical prosthesis. This patient is alive today.
The other pulmonary allograft patients required a reoperation 6 years after allograft implantation. Unfortunately, this patient died 3 years after the reoperation due to an intracerebral bleeding.

Early morbidity and mortality

Perioperative details are displayed in Table 3. Two patients, both autograft recipients, died in hospital (3.2%). One patient died during a long and complicated autograft procedure due to low output failure (see details below). The other autograft patient died on the 13th postoperative day due to mediastinitis and sepsis.
Five patients, two autograft patients and three allograft patients (all root replacements), required coronary artery bypass grafting due to procedural complications. Furthermore, 11 autograft patients required a rethoracotomy for persistent bleeding. Circulatory arrest was employed in 4 allograft root replacement patients because additional replacement of the ascending aorta with a vascular prosthesis was required, and in 1 autograft patient because the ascending aorta perforated during sternotomy.

Follow-up and survival

During follow-up 6 more patients died (3.6%), all allograft recipients (linearized occurrence rate (LOR) 0.55%/patient year). Causes of death were: Stroke (n=1), sudden unexplained death (n=5) and non-valve related death (n=1)
Overall cumulative survival was 94.6%±2.1 at 13 years, for autograft recipients 96.8%±2.2% and 92.7%±3.3% for allograft recipients (p=0.45). Figure 1 shows overall survival for autograft and allograft recipients compared with 35-year old males in the general Dutch population.

Reoperation

During follow-up 45 valve-related reoperation were required: 37 for structural valve deterioration, 7 for non-structural valve deterioration and 1 for recurrent endocarditis.
Sixteen autograft recipients (LOR 2.5%/patient year) and 21allograft recipients (LOR 1.9%/patient year) required reoperation for structural valve deterioration. Structural valve deterioration in autografts was caused by progressive dilatation of the neo-aortic root and subsequent aortic regurgitation, while in allografts it was characterized by degeneration and calcification. In 4 of the 10 autograft reoperations a degenerated pulmonary allograft was concomitantly replaced with

another cryopreserved pulmonary allograft. One autograft patient underwent an isolated pulmonary allograft replacement with a cryopreserved allograft.
The 7 reoperations for non-structural valve deterioration or technical valve failure occurred all in allografts that were implanted using the subcoronary technique (LOR 0.64%/patient year).

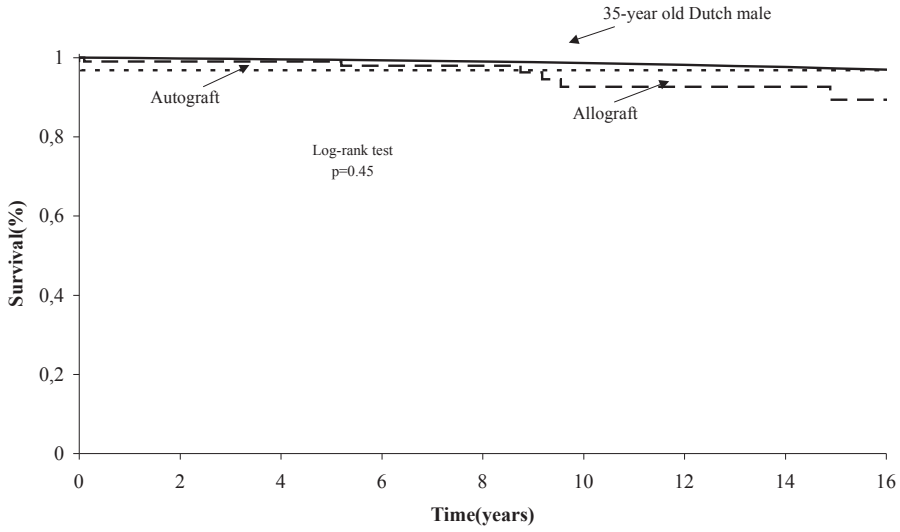

Figure 1 Survival after allograft or autograft operation compared with 35-year old males in the general Dutch population.
ALLO= allograft, AUTO= pulmonary autograft, 95% C.I.= 95% confidence interval

Table 4 . Details on reoperations

	Autograft (n=16)	**Allograft (n=29)**
Total patient years	650	1093
Cause for aortic valve reoperation		
Structural failure	n=16	n=21
Non-structural valve deterioration	-	n=7
Endocarditis	-	n=1
Valve substitute inserted at reoperation		
Mechanical prosthesis	-	n=15
Bentall procedure	n=13	n=6
Autograft	-	n=4
Allograft	n=2	n=3*
Stentless bioprosthesis	n=1	n=1
Mean CPB time (minutes; range)	237 (129-389)	182 (79-321)
Mean clamp time (minutes; range)	151 (96-271)	120 (59-196)

* subcoronary allografts

Finally, one patient with a subcoronary allograft required a reoperation for recurrent endocarditis (LOR 0.09%/patient year). See Table 4 for details on reoperations.
There was no reoperative mortality. One autograft patient who received a mechanical valve conduit had a major stroke in the immediate postoperative period.
Overall freedom from aortic valve reoperation was 94.5%±1.8% at 5 years and 61.4%±5.5% at 13 years. For autograft patients freedom from aortic valve reoperation was 100% at 5 years and 63.4%±9.6% at 13 years, for allograft patients 91.2%±2.8% at 5 years 59.8%±6.8% at 13 years (p=0.48). See also Figure 2.
Freedom from aortic valve reoperation for structural valve deterioration for all valves was 98.8%±0.9% at 5 years and 67.2%±5.2% at 13 years, for autograft patients 100% at 5 years and 63.4%±9.6% at 13 years and for allograft patients 98.0%±1.4% at 5 years and 68.8%±6.3% at 13 years (p=0.44). No factors were found to be associated with an increased risk on reoperation for structural failure in both the allograft and autograft group. Figure 3 shows the observed freedom from reoperation from structural valve deterioration and the corresponding Weibull functions representing the increasing hazard with time of structural valve deterioration for both allografts and autografts.

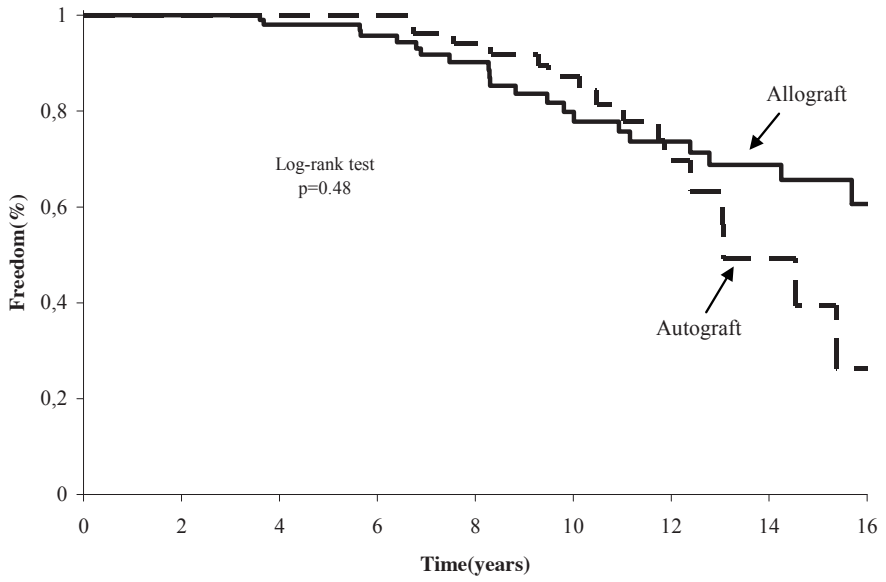

Figure 2 Freedom from reoperation for any cause
ALLO= allograft, AUTO= pulmonary autograft, 95% C.I.= 95% confidence interval

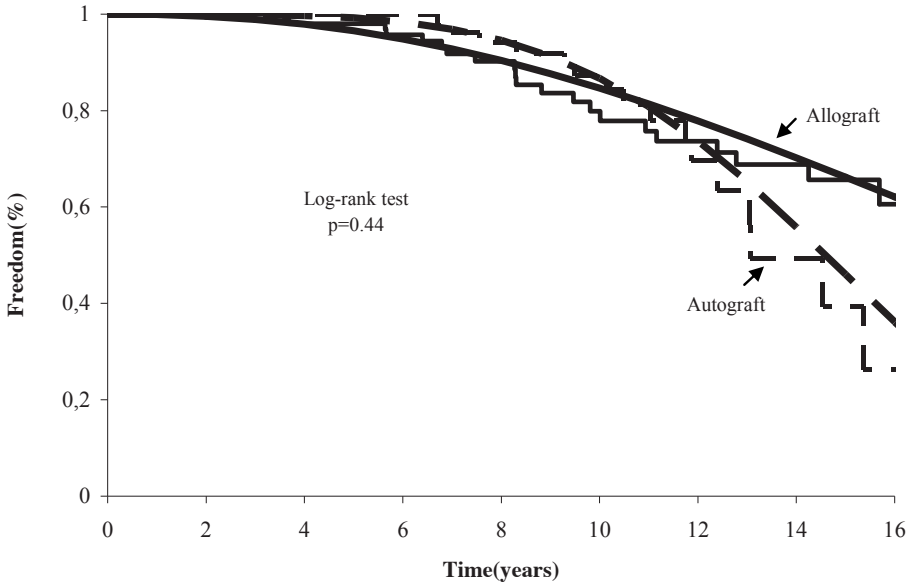

Figure 3 Freedom from reoperation for structural failure
ALLO= allograft, AUTO= pulmonary autograft, 95% C.I.= 95% confidence interval

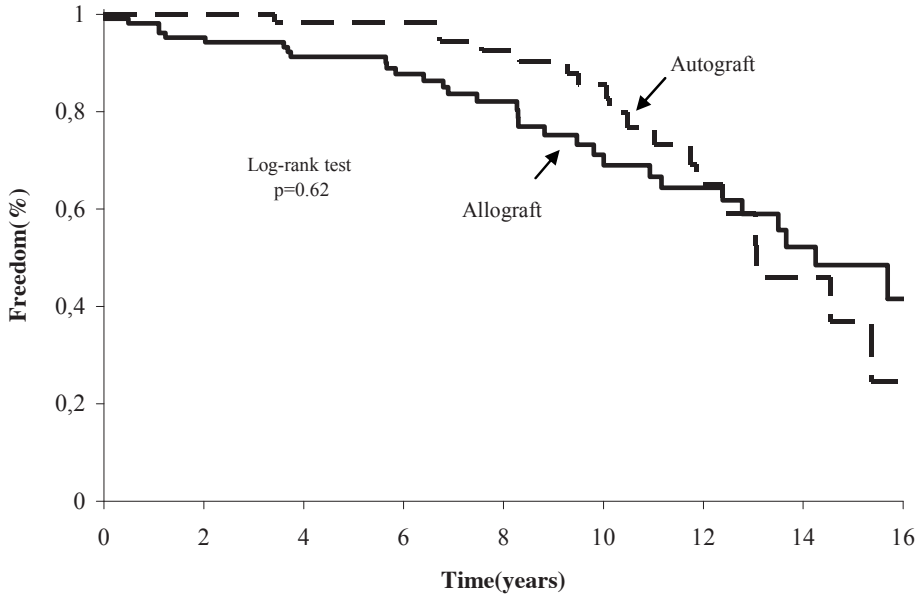

Figure 4 Freedom from any valve-related event
ALLO= allograft, AUTO= pulmonary autograft, 95% C.I.= 95% confidence interval

Other valve-related events

In the autograft patient group, one patient had a recurrent episode of endocarditis (0.15%/patient year), and one patient had a pulmonary embolism (0.15%/ patient year). In the allograft patients group, one patient had a recurrent episode of endocarditis (0.09%/patient year) and two allograft patients had a TIA (LOR 0.18%/ patient year). Figure 4 shows the freedom from any valve-related event. Overall freedom from any valve-related event at 13 years was 59.1%±5.5%, for autograft patients 59.2%±9.5% and for allograft patients 59.0%±6.8% (p=0.62).

Functional and echocardiographic status at last follow-up.

Table 5 shows aortic regurgitation for both allograft and autograft patients, pulmonary regurgitation for autograft patients at echocardiography and NYHA class at last follow-up. Echocardiographic measurements of patients who underwent reoperation or died during follow-up were excluded. Autograft patients had a larger aortic annulus at last follow-up compared with allograft patients ($p<0.001$) and no differences were observed in functional exercise capacity.

Discussion

Our study shows satisfactory results on early and long-term survival for both the autograft and the allograft in patients with congenital aortic valve disease. On the other hand, it also shows that durability of both procedures is limited and the majority of patients will require a reoperation later in life.

Early morbidity and mortality

Aortic valve replacement with an autograft or allograft is a complex operation illustrated by the long cardiopulmonary bypass and cross-clamp times. Still, this can safely be performed evidenced by the low hospital mortality of 3% for autograft patients and no hospital mortality for allograft patients.

Survival

No differences were observed in late survival between both valve substitutes and late survival was comparable to that of the general age-matched Dutch population. Allograft patients more often underwent aortic valve replacement for endocarditis on the aortic valve or valve prosthesis, a factor that may have affected long-term survival. However, only 1 of the 6 late deaths was in a patient with endocarditis etiology, and all other late deaths were in patients who did not have a previous AVR for endocarditis. On the other hand, a survival difference between the autograft and allograft in favour of the autograft is observed in a randomized controlled study of Aklog and colleagues, although survival differences between the two valve

Table 5. Echocardiographic and functional outcome at last follow-up visit

	Autograft	Allograft	p-value
AR	*n=42*	*n=72*	
Grade 0-0.5+	21% (n=9)	28% (n=20)	0.44
Grade 1+	41% (n=17)	39% (n=28)	0.90
Grade 2+	26% (n=11)	29% (n=21)	0.71
Grade 3+	10% (n=4)	4% (n=3)	0.26
Grade 4+	2% (n=1)	-	0.19
PR	*n=44*		-
Grade 0-0.5+	86% (n=38)	-	-
Grade 1+	12% (n=5)	-	-
Grade 2+	2% (n=1)	-	-
Grade 3+	-	-	-
Grade 4+	-	-	-
Diameter aortic annulus (mm)	*n=38*	*n=65*	
< 30	13% (n=5)	20% (n=13)	0.38
30 -< 40	41% (n=16)	74% (n=48)	0.001
40 -< 50	41% (n=16)	6% (n=4)	<0.001
> 50	5% (n=2)	-	0.19
Mean diameter aortic annulus (mm, (range))	37 (26-52)	33 (21-44)	<0.01
NYHA class	*n=45*	*n=73*	0.18
I/II	98% (n=44)	92% (n=67)	
III/V	2% (n=1)	8% (n=6)	

AR = aortic regurgitation, PR = pulmonary regurgitation

substitutes were not significant.[11] When comparing patient survival after aortic valve replacement with an autograft or allograft to the patient survival of other valve substitutes available in patients under 55 years of age, long-term survival rates for autograft and allograft patients are better than other valve substitutes in this patient population.[12-14] Whether this is due to patient selection or the haemodynamic superiority of human tissue valves is a question that requires further exploration.

Reoperation

Although freedom from reoperation for any cause was comparable for both the allograft and autograft, causes for reoperation differed considerable between the valve types. Indications for reoperation for allograft patients were endocarditis, perivalvular leakage and structural failure. Structural allograft failure was characterized by degeneration and calcification, an observation that is confirmed by several other institutions.[15-17]

Indication for autograft patients to return for reoperation was solely structural failure. The autograft failed due to progressive dilatation of the neo-artic root with subsequent

aortic regurgitation. No age-dependency was observed for autograft structural valve failure in this study.

In the present study the autograft roots were placed in the left ventricular outflow tract and annulus with a short rim of right ventricular muscle, which was kept to a minimum and no measures were taken to reinforce the aortic root or sinotubular junction. Minimization of the length of the autograft root may result in less dilatation and may produce better durability. Furthermore, reinforcement of the aortic root or sinotubular junction may enhance durability as well.

The majority of our study patients have a bicuspid valve, the most common congenital valvular abnormality, which comprises 1% of the general population. It remains debatable if presence of a bicuspid valve is a risk factor for reoperation after the pulmonary autograft procedure.[18-22] A bicuspid valve is reported to be associated with a high incidence of aortic root dilatation due to aortic wall abnormalities.[23] Moreover, Schoof and coworkers observed in a recent autograft explant study that there was no association between bicuspid valve disease and histological changes in explanted pulmonary autografts.[24]

The necessity for reoperation will increase for both valves in the second decade after operation and this increase seems larger for autograft patients. This trend is already to some extent seen in Figure 3 and is also reported in other series.[5,25-27] Structural failure is the main disadvantage of allografts and autografts compared to mechanical prostheses, which have an unlimited durability.[14] Comparing allografts with stented biological prostheses a comparable age-dependent structural failure rate is observed in adult patients,[28] which is not observed in adult autograft patients.[29] This suggests an advantage of the autograft in younger patients and of a biological prosthesis or allograft in older patients. However, Svensson and colleagues provided an overview of different surgical strategies in young adult patients and compared the available valve substitutes. They concluded that the structural failure rate of biological valves is much higher and of mechanical prostheses much lower in young adults compared with the allograft or autograft and would therefore be not a good solution in young adults.[30] Yet, the main disadvantage of the mechanical prostheses remains the anticoagulation use and the related complications, such as bleeding events and higher thrombo-embolic event rates.[31]

Furthermore, reoperation on a calcified homograft takes a lot more effort than on a dilated pulmonary autograft. The dilated autograft root allows the surgeon a clear view of the insufficient autograft and its dilated annulus, on which an anastomosis is

easier to perform. The calcified aortic allograft on the other hand is rigid causing a smaller operation field.

Valve-related events

Occurrence rates of valve-related events other than reoperations are low in our study population.

Concha and colleagues compared the pulmonary autograft to the mechanical prosthesis regarding early and long-term results and observed no other valve-related events than pulmonary stenosis in the pulmonary autograft group compared with major bleeding, thromboembolic complications related to coumarin, and prosthetic valve endocarditis in mechanical prosthesis group.[32] Other reports comparing the allograft to the mechanical prosthesis show similar results, suggesting that these human tissue valves provide a superior valve substitute in this regard compared with mechanical prostheses.[11,12,33]

Conclusions

In young adult patients with congenital aortic valve disease, our study shows that both the allograft and autograft are valve substitutes with satisfactory results regarding early and long-term patient survival, with late survival even comparable with the general age-matched population. These patients comprise a young patient population with little co-morbidity, who have an active lifestyle with a long life-expectancy and in whom preferably anticoagulation treatment should be avoided. However, the major limitation of human tissue valves is the increasing high incidence of reoperations for structural valve deterioration in the second decade after operation.

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Chapter 6

Aortic Valve Replacement With Human Tissue Valves In Young Women: Outcome And Effects Of Pregnancy

Aortic Valve Replacement with Human Tissue Valves in Young Women: Outcome and Effects of Pregnancy. Klieverik LMA, Yap SC, Roos-Hesselink JW, Bogers AJJC, Takkenberg JJM. *Submitted*

Short abstract

We studied outcome of 98 female patients younger than 45 years who underwent aortic valve replacement with either a pulmonary autograft or an allograft at our institution between 1987 and 2007 and were part of our ongoing prospective follow-up study. Furthermore, we evaluated whether there was an influence of pregnancy on the durability of these tissue valve substitutes. During follow-up 7 patients died and 18 required a reoperation. Twenty-three patients contemplated 37 pregnancies and pregnancy had no effect on valve durability. In young female patients contemplating pregnancy within the next decade, human tissue valves provide good valve substitutes.

Abstract

Objectives

We studied outcome of aortic valve replacement in young female patients who received human tissue valves and the effect of pregnancy on the durability of these valve substitutes.

Background

Young women with congenital heart valve disease remain a special group regarding valve selection due to their potential desire to have children.

Methods

Between 1988 and 2007, 98 women younger than 45 years underwent aortic valve replacement with an autograft (n=50) or allograft (n=48) in our center. Patient characteristics, early and long term outcome of patients and characteristics of pregnancies were analyzed.

Results

Mean age at operation was 25 years (0-44 years), haemodynamic diagnosis was aortic stenosis in 37%, aortic regurgitation in 37% and mixed lesions in 28%. Sixty-two percent had congenital etiology, including bicuspid valve. Hospital mortality was 5% (n=5).

During follow up (94% complete, mean 9.2, max 18 years) 7 patients died (2 autografts, 5 allografts). Overall 15-year survival was 80.5%±6.7%, for autograft patients 89.8%±4.3% and 67.6%±13.8% for allograft patients (p=0.41). Twenty-three patients completed 37 pregnancies.

There were 18 valve-related reoperations for structural failure (LOR 2.0%/patient year). Overall 15-years freedom from reoperation for structural failure was 69.3%±9.9% for autograft patients and 61.3%±15.4% for allograft (p=0.91). Pregnancy had no effect on durability of the allograft or autograft (p=0.60).

Conclusions

In young women who underwent aortic valve replacement with autografts or allografts, a considerable proportion had pregnancies without complications. Pregnancy had no influence on valve durability. Therefore, in young female patients contemplating pregnancy within the next decade, human tissue valves provide good valve substitutes.

Key words: pregnancy, aortic valve replacement, allograft, autograft, outcome

Introduction

The introduction of paediatric cardiothoracic surgery has resulted in a dramatic improvement of survival in children with congenital heart disease. However, at adolescent or adult age these patients may encounter particular problems related to their previous heart surgery. Especially, young girls and women of childbearing age who have undergone AVR are a patient population that requires special attention, due to their potential desire to have children.

Aortic valve replacement is not without consequences, irrespective of the valve substitute used. The pulmonary autograft procedure is presumably the most suitable valve substitute in children and young adults, because of diameter increase along with somatic growth and the absence of anticoagulation treatment.(1,2) The pulmonary autograft is normally situated in the right ventricular outflow tract and is transplanted in the left ventricular outflow tract, a high pressure system. The exact mechanism of pulmonary autograft adaptation to the high pressure system of the LVOT is not well understood, but in recent years an increasing number of reoperations due to autograft root dilatation is observed.(3-5)

The allograft can also be applied in children with aortic valve disease. No anticoagulation treatment is required, and good haemodynamic performance is observed. On the down side, allografts do not grow or increase in diameter with the growing child, and valve degeneration rate is inversely correlated with patient age. For these reasons, in children allografts have become a less favourable option to replace the aortic valve or root.(6,7)

During pregnancy significant haemodynamic changes occur with an important demand on cardiac function.(8,9) There is an increase in cardiac output, heart rate and blood volume and a decrease in systemic vascular resistance resulting in a lower blood pressure, despite the increase in cardiac output. These cardiac changes may have an influence on progressive deterioration of the pulmonary autograft and allograft.(8)

The aim of this study was to analyze outcome of young female patients who received a human tissue valve in aortic position and evaluate the influence of pregnancy on the durability of these tissue valve substitutes and patient outcome after pregnancy. To achieve this, we studied all young female patients who underwent aortic valve replacement with either an autograft or an allograft in our institution and were annually followed according to a prospective predefined protocol.

Methods

Patients

Between April 1987 and January 2007, 486 patients underwent 501 consecutive autograft or allograft aortic valve or root replacement in Erasmus University Medical Center. All patients who receive an autograft or allograft in aortic position in our center are enrolled in our ongoing prospective follow-up study.(10-12) Approval from the Institutional Review Board was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent.

For the purpose of this study we selected out of the total of 501 procedures all operations in female patients who were less than 45 years of age at time of operation.

Operation

Root replacement was performed as a freestanding root with reimplantation of the coronary arteries in 48 autograft patients and in 35 allograft patient. In 2 autograft patients an inclusion cylinder aortic root replacement was done(3) and 14 patients underwent a subcoronary allograft implantation.(13) Surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Eight patient required circulatory arrest due to surgery on the ascending aorta or arch.

Follow-up

All patients were followed prospectively and annually contacted and interviewed by telephone. Echocardiographic follow-up at Erasmus MC is obtained at 6 months postoperative, 1 year postoperative and thereafter biennially by means of serial standardized echocardiography.(10-12)

In case of suspected complications the attending physician was contacted for verification. Valve-related events were defined according to the guidelines for reporting morbidity and mortality after cardiac valvular operations.(14) Failure of the autograft or pulmonary allograft was determined at time of reoperation or death. Patient survival started at time of the Ross operation and ended at time of death or at last follow-up. Survival of the autograft or pulmonary allograft started at time of operation and ended when a reoperation or reintervention was done, when the patient died or at last follow-up.

Pregnancy

To obtain information on pregnancy after operation, all patients were contacted by telephone after obtaining informed consent and subjected to a structured questionnaire. If a patient could not be reached by telephone, a questionnaire was sent

to the patient. The patient had to complete a questionnaire with detailed information on every completed pregnancy. Even when a patient had not been pregnant during follow-up, the questionnaire was completed with information on the reason why the patient remained childless after operation. The questionnaires consisted of questions regarding the occurrence of cardiac and obstetric complications during pregnancy. Part of the questionnaire was according to the ZAHARA protocol, with minor adjustments for the purpose of our study.(15) ZAHARA is a Dutch collaboration of cardiologists that analysed pregnancy and delivery in women with congenital heart disease (CHD) by reviewing cardiologic hospital records and interviewing all Dutch women with CHD aged 20-45 years that enrolled in the CONCOR database (= national registry of adult CHD patients, www.concor.net)

Cardiac complications that were documented: clinically significant symptomatic arrhythmia or symptomatic heart failure requiring treatment (according to attending cardiologist); NYHA class deterioration (as evaluated by their cardiologist during trimesters and comparison of pre-pregnancy and post-partum).

Obstetric complications: pregnancy-induced hypertension (PIH, new onset hypertension after 20 weeks of gestation: blood pressure (140 mmHg systolic or 90 mmHg diastolic without significant proteinuria); pre-eclampsia (PIH criteria and .0.3 g of proteinuria/ 24 h); eclampsia (pre-eclampsia with grand mal seizures); haemolysis elevated liver enzymes low platelets (HELLP) syndrome; thrombo-embolic complications; stroke; and gestational diabetes. Obstetric complications: assisted delivery (forceps/vacuum/caesarean); premature rupture of membranes (membrane rupture before the onset of uterine contractions); prolongation of second stage of delivery (according to the gynaecological guidelines); premature delivery (spontaneous onset of delivery < 37 weeks gestation).

Neonatal complications: premature birth (delivery < 37 weeks of gestation); small for gestational age birth weight (<10th percentile); recurrence of CHD; and neonatal death (within the first year after birth).

Statistical methods

For data analysis SPSS 12.0.1 for Windows (SPSS, Chicago, Illinois) was used. Continuous data are displayed as mean ± 1 standard deviation and compared using the unpaired T-test or the Mann-Whitney U-test. Discrete data are presented as proportions and compared using the Chi-square test or Fisher's exact test. Cumulative survival and freedom from reoperation or reintervention were analysed using the Kaplan-Meier method. The log-rank test was used to compare Kaplan-Meier curves. The Cox proportional hazards model was used for univariate and

multivariate analysis (stepwise backwards method) of time-related events. A p-value of ≤ 0.05 was considered statistical significant. All testing was performed 2-sided.

Results

A total of 96 female patients underwent 98 aortic valve replacements with a tissue valve and were young than 45 years of age at time of operation. Preoperative and operative details are displayed in Table 1. One subcoronary allograft patient underwent a reoperation due to structural failure 4.8 years after operation and received another subcoronary allograft and one autograft patient underwent a reoperation due to structural failure 7.0 years after the initial procedure and received an allograft root. Both patients were included twice in the study and did not become pregnant during follow-up.

Early morbidity and mortality

Hospital mortality was 5.1% (n=5). Three autograft patients and 2 allograft patients died.

Two autograft patients died during operation. One autograft patient had a lesion to the main stem of the left coronary artery and died in theatre due to low output failure despite revascularization. The other patient, a child, died in theatre due to heart failure.

The third autograft patient died due to mediastinitis and sepsis on the 13th day postoperative.

Of the 2 allograft patients who died in hospital, one died due to a major intracerebral bleeding on the 9th day after operation. This patient was on anticoagulation treatment, required for a dialysis shunt. The other patient died of a stroke caused by septic emboli as a result of an acute persistent endocarditis on postoperative day 21.

Nine patients required rethoracotomy for persistent bleeding, six autograft patients and three allograft patients. Furthermore, two allograft patients had a non-lethal stroke postoperatively and one allograft patient had a non-lethal intracranial haemorrhage.

Follow-up

The database was frozen on May 1st, 2007. Mean follow-up duration was 9.2 years (range 0-18.6 years) with a total of 886 patient years and was 94.2% complete. (16) Mean follow-up duration for autograft patients was 9.5 years (range 0.02-18.4 years) with a total of 478 patient years. Mean follow-up duration for allograft patients was 8.8 years (range 0.02-18.6 years) with a total of 408 patient years.

Table 1. Preoperative details

	Autograft (n=50)	**Allograft (n=48)**
Mean age (years, (range))	22.5 (0.1-44.9)	28.6 (4.9-44.7)
Previous cardiac surgery		
Valvulotomy	20% (n=10)	6% (n=3)
Aortic valve replacement	6% (n=3)	8% (n=4)
Haemodynamic diagnosis		
Aortic valve regurgitation (AR)	26% (n=13)	52% (n=25)
Aortic valve stenosis (AS)	46% (n=23)	29% (n=14)
AR + AS	28% (n=14)	15% (n=7)
None	-	4% (n=2)
Etiology		
Rheumatic	4% (n=2)	15% (n=7)
Congenital (incl. bicuspid valve)	82% (n=41)	42% (n=20)
Endocarditis	6% (n=3)	13% (n=6)
Active	-	*8% (n=4)*
Senile native valve degeneration	2% (n=1)	4% (n=2)
Aneurysm/Dissection	6% (n=3)	15% (n=7)
Other	-	10% (n=5)
NYHA class		
I/II	62% (n=31)	56% (n=26)
III/IV	37% (n=19)	44% (n=21)
Left ventricular function (6 missing)		
Good	87% (n=41)	87% (n=39)
Impaired	13% (n=6)	13% (n=6)
Sinus rhythm	100% (n=50)	92% (n=44)
Creatinin (μmol/L)	62 (28-121)	89 (22-634)
Type operation		
Emergent	-	10% (n=5)
Urgent	20% (n=10)	15% (n=7)
Elective	80% (n=40)	75% (n=36)
Concomitant procedures		
CABG	6% (n=3)	4% (n=2)
Mitral valve surgery	2% (n=1)	15% (n=7)
Extended Ross	12% (n=6)	-
Extended root	2% (n=1)	13% (n=6)
Other*	6% (n=3)	21% (n=10)
Mean CPB time (min)	225 (114-685)	181 (79-435)
Mean cross clamp time (min)	146 (90-240)	127 (68-247)
Circulatory arrest	n=2	n=6
(min, (range))	(15,64)	70 (5-163)
Rethoracotomy for persistent blood loss	12% (n=6)	6% (n=3)
Hospital death	6% (n=3)	4.2% (n=2)

* Including surgery for discrete subaortic stenosis, closure patent ductus arteriosus, closure ventricular septal defects and tailoring ascending aorta

Survival

During follow-up 7 patients died (0.79%/patient year), 2 autograft patients and 5 allograft patients.

One 12 year old autograft patient had severe juvenile rheumatic disease causing severe aortic valve regurgitation and mitral valve incompetence resulting in progressive heart failure and death 6 months after operation. The other autograft patient, a 1.5 year old girl, died of a septic shock caused by Candida Albicans 51 days after operation. Although we are aware that these two patients were too young to contemplate pregnancy at time of death, for completeness of the study they were described.

One allograft patient with an abnormal functioning allograft died a sudden unexplained death 9.5 years after operation just before reoperation and one allograft patient died of heart failure 14.3 years after operation with a normal functioning allograft.

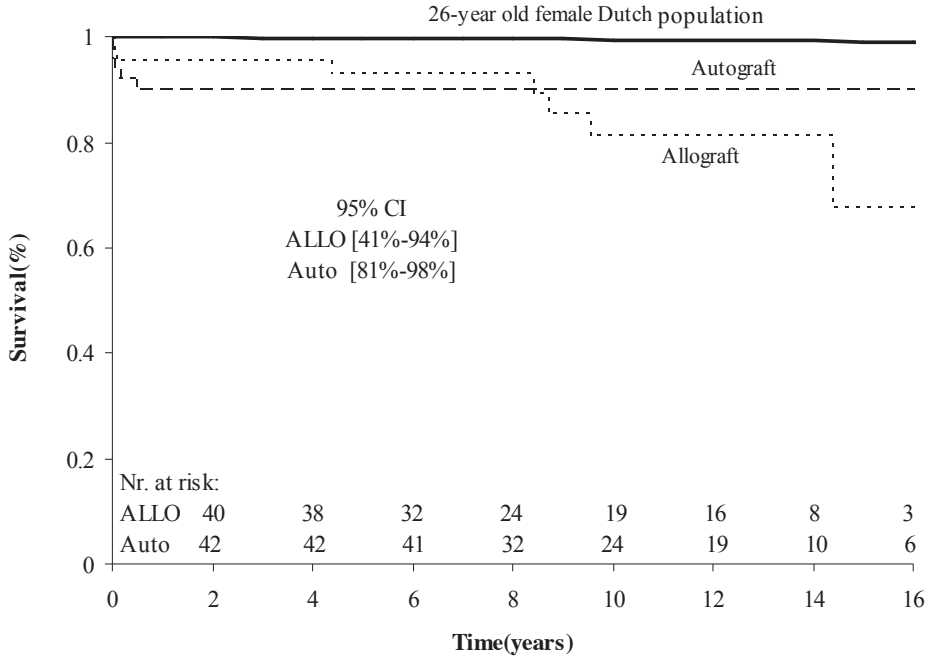

Figure 1. Survival of female patients after operation with autograft or allograft
95% CI= 95% confidence interval, ALLO = allografts, Auto= autografts

Finally, three allograft patients died of non-valve related causes 4.3, 8.3 and 8.7 years after operation, respectively. For these patients who died during follow-up no pregnancies were reported in the annual follow-up records.

Overall 15-year survival was 80.5%±6.7%, for autograft patients 89.8%±4.3% and for allograft patients 67.6%±13.8% (p=0.41). Figure 1 shows overall survival for autograft and allograft patients compared with 26-year old females in the general Dutch population.

Reoperations

During follow-up there were 18 valve-related reoperations, all for structural failure (LOR 2.0%/patient year). Ten autograft patients required reoperation due to dilatation of the neo aortic root and 8 allograft patients for a calcified and degenerated allograft. Of these 18 patients, 7 patients had been pregnant during follow-up. Mean time after the first pregnancy until reoperation was 5.9 years (range 0.4 – 11.5 years).

Ten autograft patients requiring reoperation (2.1%/patient year), of which 5 had been pregnant. Autografts were replaced by a mechanical valve conduit in 7 patients, a bioprosthesis in one patient and an allograft in one patient. In 3 autograft patients a degenerated pulmonary allograft was concomitantly replaced with another cryopreserved pulmonary allograft. One autograft patient underwent an isolated pulmonary allograft replacement with a cryopreserved allograft.

One autograft patient underwent an aortic valve sparing reoperation before her pregnancy.

Out of the 8 allograft patients requiring reoperation (1.96%/patient year), 2 had been pregnant. Allografts were replaced by mechanical valves in 6 patients, an aortic valve conduit in 1 patient and another allograft in one patient.

Figures 2 and Figure 3 display the freedom from reoperation for structural failure for the autograft and the allograft patients. Overall freedom from reoperation for structural failure at 15 years for autograft patients was 69.3%±9.9%. Freedom from reoperation for structural failure at 15 years for autograft patients who had been pregnant was 53.6%±18.9% and for non-pregnant autograft patients 78.3%±10.5% (p=0.36).

Overall freedom from reoperation for structural failure at 15 years for allograft patients was 61.3%±15.4%. Freedom from reoperation for structural failure at 15 years for allograft patients who had been pregnant was 75.0%±21.7% and for non-pregnant allograft patients 57.0%±18.1% (p=0.48).

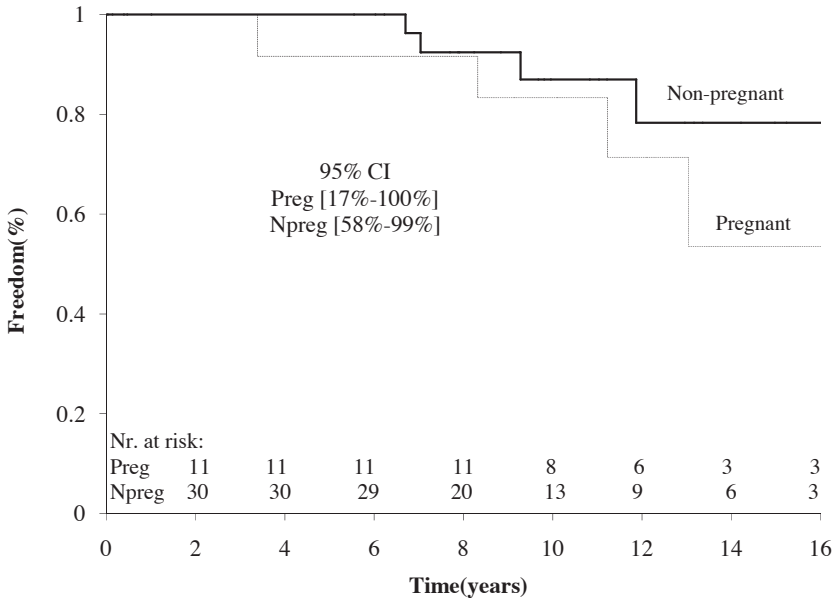

Figure 2. Freedom from reoperation for structural failure for autograft patients
95% CI= 95% confidence interval, Preg = pregnant, Npreg = non-pregnant

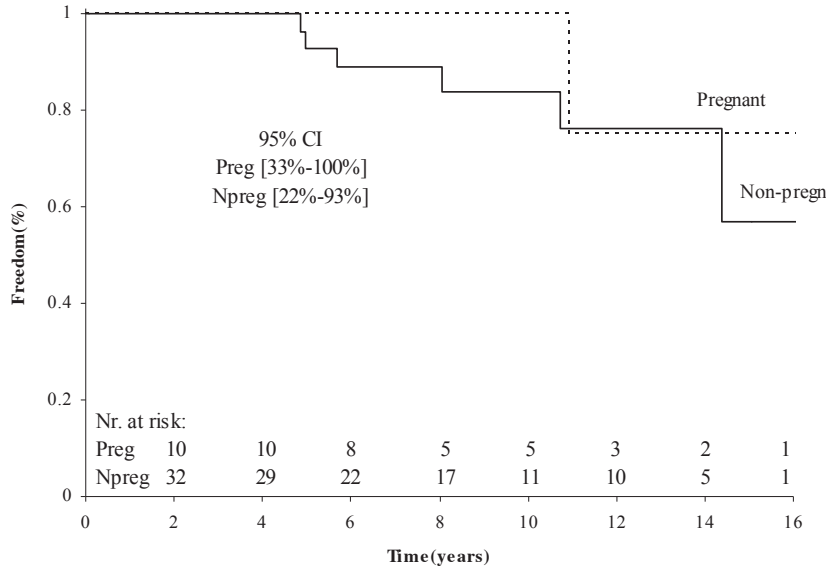

Figure 3. Freedom from reoperation for structural failure for allograft patients
95% CI= 95% confidence interval, Preg = pregnant, Npreg = non-pregnant

Valve related events

One autograft patient had a recurrent episode of endocarditis, 3 years postoperative, and was treated medically (LOR 0.21%/patient year). Another autograft patient had a recurrent episode of rheumatic disease 0.4 years after operation and died (LOR 0.21%/patient year, see details described above). Two autografts patients had supravalvular pulmonary stenosis; one underwent enlargement of the pulmonary outflow tract and the other underwent balloonvalvuloplasty of the pulmonary outflow tract (LOR 0.42%/patient year). One allograft patient had a stroke 2.5 years after operation (LOR 0.23%/patient year) and 3 patients a TIA, 0.3, 3.7 and 5.8 years after operative, respectively (LOR 0.70%/patient year). No valve thrombosis or bleeding events were observed.

Pregnancies

Sixty-eight patients, of the 84 patients that were still alive, returned 84 completed questionnaires (81%). Reasons for not responding were: 3 patients did not want to participate, 3 patients were lost to follow up due to emigration and in 10 patients unknown.

Seventeen patients reported to have had children before the initial operation with no intent to become pregnant after operation. Twenty-seven patients reported to have remained childless after operation. Reasons were: too old age (n=1), too young age (n=15), Marfan's disease (n=1), regurgitant aortic valve (allograft) (n=1), decision to have no children to avoid potential congenital heart disease in offspring (n=1), recent aortic valve surgery (n=1), previous hysterectomy (n=1), mentally retarded (n=1), systemic lupus erythematodes (n=1), social factors (n=4).

Twenty-three patients completed 37 pregnancies. Three patients were still pregnant at time of the questionnaire. Two autograft patients had an elective abortion and one autograft patient had a spontaneous miscarriage. Twelve autograft patients completed 19 pregnancies and 11 allograft patients 18 pregnancies. Table 2 displays details of these pregnancies.

Mean maternal age at first delivery was 29.3 years (range 23-35 years). Mean time interval between operation and first pregnancy was 5.0 years (range 0.1-16.3 years) and mean pregnancy duration was 37.9 weeks (range 27-42 weeks).

Cardiac complications during pregnancy: 5 patients (14%) developed cardiac complications during pregnancy. Two patients reported episodes of arrhythmias; one patient had an episode of idiopathic tachycardia and one patient had episodes of atrioventricular reentry tachycardias. Two patients had an episode of chest pain; one patient was suspect for pulmonary embolism and one had angina pectoris. One

Table 2 Maternal and perinatal outcome

	Autograft	Allograft
Number of pregnancies	n=21	n=19
Number of completed pregnancies (n=37)	n=19	n=18
1	63% (n=12)	61% (n=11)
2	32% (n=6)	28% (n=5)
3	5% (n=1)	11% (n=2)
Mean maternal age at the time of delivery (years, (range))	30.7 (24.9-38.0)	29.7 (23.1-34.5)
Interval between operation - 1st pregnancy (years, (range))	6.6 (1.4-16.3)	3.9 (0.2-8.9)
Mean duration pregnancy (weeks, (range))	37 (29-42)	38 (27-41)
Cardiac complications during pregnancy		
Arrhythmias	11% (n=2)	-
Angina pectoris	-	6% (n=1)
Heart failure	5% (n=1)*	-
Obstetric complications		
Hypertension	11% (n=2)	28% (n=5)
Deep venous thrombosis	5% (n=1)*	-
Pre-eclampsia	5% (n=1)	11% (n=2)
Premature rupture of membranes	5% (n=1)#	-
Vaginal blood loss	5% (n=1)	-
Prolongation of second stage of delivery	21% (n=4)	11% (n=2)
Bleeding in placenta	5% (n=1)#	-
Delivery (1 missing)		
Vaginal	79% (n=14)	83% (n=15)
Caesarean section	21% (n=4)	17% (n=3)
Premature delivery (< 37 wks)	26% (n=5)	6% (n=1)
Instrumental use at delivery based on maternal cardiac status		
Epidural analgesia	11% (n=2)	11% (n=2)
Artificial rupture of membranes	-	17% (n=3)
Vacuum extraction	5% (n=1)	-
Birth weight (gram, (range))	2544 (700-3590)	2992 (580-4200)
Small for gestational age	21% (n=4)	22% (n=4)
Neonatal mortality	5% (n=1)	-

*post partum, # same patient

autograft patient developed heart failure after delivery, this was initially ascribed to the pregnancy, but turned out to be caused by severe pulmonary regurgitation, for which the patient underwent a pulmonary allograft reoperation 1.6 years after delivery.

Pregnancy complications Seven patients (19%; 2 with an autograft and 5 with an allograft) developed hypertension during pregnancy, in range from week 21 to week 40, which was treated medically and additionally 5 of these patients required hospital admission. In 3 of these 5 patients hypertension was a reason of induction of labor.

Two allograft (5%) and one autograft patient (3%) developed pre-eclampsia during pregnancy. In one allograft patient medication was started in week 37 and the patient delivered a healthy girl at 38 weeks. The other allograft patient developed pre-eclampsia at 21 week with haemolysis, elevated liver enzymes and low platelets (suspected for HELLP syndrome), for which medication was started. However, the patient required a caesarian section at 27 weeks, and gave birth to a girl weighting only 580 grams. The child was born with a patent arterial duct and bronchial pulmonary dysplasia but survived.

One autograft patient required low-molecular heparin due to previous deep venous thrombosis after the first pregnancy. During the 2nd pregnancy the patient had premature rupture of membranes in the 18th week of pregnancy. Due to premature rupture of membranes and emboli present in the placenta, insufficient oxygen supply and obstruction of the blood flow occurred, resulting in intrauterine growth retardation and premature delivery. At 30 weeks the patient gave birth to a girl weighting only 700 grams. Unfortunately, this child died 11 hours after delivery due to a pneumothorax and cardiac arrest.

Another autograft patient was admitted at 26 weeks of pregnancy for vaginal blood loss suspected for a solutio placenta. At 29 weeks an emergency caesarian section was performed and a boy was delivered with a birth weight of 1380 grams.

Seven patients required a caesarian section, 4 autograft patients and 3 allograft patients. In 1 allograft and 3 autograft patients the indication for the caesarian section was maternal congenital heart disease. One of the 37 newborns was diagnosed to have congenital heart disease (see details above).

Discussion

This study shows that young female patients who underwent aortic valve replacement with an autograft or an allograft in our institution have a good prognosis, and considerable proportion of patients was able to start a family. However, these pregnancies were not without complications, and compared to the general population, pregnancy duration was shorter and birth weight was lower. Although the incidence rate of reoperations increases with time since operation, and more reoperations should be anticipated, there was no difference between autograft and allograft patients, and pregnancy was not a factor associated with increased reoperation rates.

Survival

Hospital mortality was 5% in our study population, and this is high compared with other studies on aortic valve replacement at a young age. This can partly be explained by the fact that women have a higher risk on operative mortality.(17) Furthermore, these female patients were all young patients with congenital heart disease, and 3 of the patients who died had a previous operation. These patients had severe co-morbidities, such as renal failure, a factor that is also predictive of increased hospital mortality.(18,19) Also, during operations complications occurred during reimplantation of the coronary arteries, emphasizing the complexity of the operation.

Fifteen-year survival was 80% for the total study population and appears to be slightly better for the autograft patients compared with the allograft patients, although this difference was not significant. Furthermore, the autograft patients had a late survival that was comparable to the general age-matched population, in contrast to patients that received an allograft. Patient-related factors, such as patient age or etiology may be associated difference in survival between the two groups.

Reoperations

There was no difference in reoperation rate between autograft and allograft patients, neither was there any difference between female patients that had become pregnant and those who had not. Pregnancy theoretically may have an adverse effect on durability of the human tissue valves due to haemodynamic changes that occur during pregnancy and delivery, and this concern is also mentioned in the literature. (20,21) However, our findings support other reports that also describe that pregnancy has no effect on the durability of both the autograft and the allograft.(8,22) Of note, the sample size of our study is small and we only investigated reoperation for structural valve deterioration as an endpoint for durability. Larger clinical and echocardiographic outcome studies are necessary to investigate the potential effect of pregnancy on human tissue valve durability.

Valve-related events

Thrombo-embolic events during follow-up did not occur in autograft patients and only in a small number of allograft patients. However, the occurrence rate of thrombo-embolic events in allografts is still much lower when compared with the mechanical prostheses in young adult patients (23,24) and also in female patients who became pregnant.(22)

Due to the absence of anticoagulation treatment, no bleeding events or valve thrombosis during follow-up were observed in our study. This is a major advantage

of the tissue valves, especially for these female patients who have a desire to have children, or those who want to become pregnant again. Pregnancy is a thrombogenic state and patients with a mechanical prosthesis are at high risk of developing complications. Anticoagulation treatment used in pregnancy will decrease this risk for the female patient, but may have adverse effects on the outcome of the foetus. Warfarin is known to be teratogenic in the first trimester and associated with increased risk of foetal intracerebral haemorrhage. Heparin is much safer for the foetus, but has an increased risk of events for the mother due to the adequate adjustment of the INR levels.(8)

Pregnancies

Although the majority of patients that became pregnant delivered healthy children, these pregnancies were not all uneventful. In 5 of the 37 pregnancies cardiac complications occurred, necessitating reoperation on the pulmonary allograft 1.6 years after delivery in one autograft patient. Due to intensified cardiologist monitoring during pregnancy in female patients with a known (congenital) heart disease and the improved medical treatment, with less foetal side-effects, these complications can be reduced to a minimum. Pregnancy duration was observed to be shorter than average in our study patients compared with normal healthy pregnant women, which may be caused by placental insufficiency.(25)

Furthermore, adverse foetal outcome was present in one newborn. This newborn was delivered prematurely but had fatal co-morbidity and died several hours after delivery

Also, eight newborns were too small for gestational age. This phenomenon is more often observed in women that underwent aortic valve replacement. (25-27) The incidence of adverse outcome is much higher in mechanical prosthesis and mainly related to the use of anticoagulation.(28-30)

Limitations

Unfortunately, not all patients returned a completed questionnaire, which may have influenced the results of the study.

Conclusions

With the growing experience in our center with implantation of autografts and allografts it has become clear that although patient survival is good, the durability of both human tissue valves is limited. In this particular study in young females, the implantation of human tissue valves allowed a considerable proportion of patients to have pregnancies that were not complicated by anticoagulant use. Nevertheless, these pregnancies were not uneventful. Pregnancy did however not influence valve

durability. Therefore, in young female patients who have plans to start a family within the next decade, human tissue valves provide an adequate valve substitute at the cost of a reoperation later in life.

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Chapter 7

An Evaluation Of The Ross Operation In Adults

An evaluation of the Ross operation in adults. Yacoub MH, Klieverik LMA, Melina G, Edwards SER, Sarathchandra P, Bogers AJJC, Squarcia U, Sani G, van Herwerden LA, Takkenberg JJM. *J Heart Valve Dis. 2006 Jul;15(4):531-9.*

Short abstract

The Ross procedure remains controversial in adults. We studied 264 consecutive adult patients who underwent the Ross operation in 2 institutions and were followed for 1634 patient years. Etiology was mainly congenital and degenerative. Thirty-day mortality was 2.3%. Cumulative survival was 95.4% at 10 years, and comparable to the general population. Freedom from any reoperation was 89.7% at 10 years; for pulmonary homograft reoperation 94.9 and for autograft reoperation 92.9% respectively. The question whether the excellent survival rates are due to patient selection or to the potential advantages of the Ross procedure should be addressed in a randomized trial.

Abstract

Background and aim of the study

Pulmonary autograft replacement of the aortic valve (the Ross operation) is the operation of choice in infants and children. Although this procedure can offer theoretical advantages at any age, its use in adults remains controversial. We studied 264 consecutive patients above the age of 18 years (18-66, mean 35) who underwent the Ross operation in 2 institutions and were followed for 1634 patient years.

Methods

There were 203 males and 61 females, mean age was 36.9 years (SD 12.4). The etiology was mainly congenital (52%), degenerative (22%), and rheumatic (8%). Twenty-one percent of patients underwent prior aortic valve replacement.

Results

Thirty-day mortality was 2.3% (N=6) and 4 more patients died during follow-up (mean follow-up 6.2 years, range 0-15.4). Cumulative survival at 5 years was 96.8% and at 10 years 95.4%. Eleven patients underwent re-operation on the aortic valve, due to progressive dilatation and aortic regurgitation in 10, and dissection of the arterial wall of the autograft in one. Overall freedom from pulmonary homograft reoperation was 94.9% at 10 years; for autograft reoperation 92.9%. Estimated freedom from autograft reoperation in Harefield was 98.6% at 5 and 10 years, in Rotterdam 96.0% at 5 years and 88.2% at 10 years (p=0.10, Tarone-Ware). No risk factors for early and late mortality and reoperation were detected.

Conclusions

In this combined series the Ross operation in adult patients resulted in excellent survival and acceptable reoperation rates. A prospective randomized trial is proposed to study whether this observation truly reflects the potential advantages of the Ross procedure or whether it is caused by patient selection.

Introduction

Although aortic valve replacement has been shown to improve the course and prognosis of patients with severe aortic valve disease(1), the choice of a valve substitute may influence both the early and long term outcome after aortic valve replacement. Furthermore, the pattern of survival after aortic valve replacement appears to be inferior to age matched controls from the general population(2). This can be attributed at least in part to the valve substitute. There is increasing realization that the normal aortic valve performs many sophisticated functions which depend on the biological properties of its living components(3). The Ross operation is the only operation that provides, in the longer term, a living valve substitute capable of reproducing most or all the sophisticated function of the normal aortic valve(4,5). We theorize that this might have implications to survival and quality of life. There are, however, several legitimate concerns about the use of the Ross operation particularly in adults where there are many alternatives with a fairly long track record. These concerns include the perceived complexity of the operation that requires longer cardiopulmonary bypass and thus could increase the risks of the operation in the older patients. In addition, progressive dilatation of the neoaortic root resulting in valve malfunction requiring reoperations has been reported in adults(6-9). Other complications relate to the use of a pulmonary homograft in the right ventricular outflow tract(7,9,10). Furthermore, dissection of the autologous pulmonary valve necessitates dividing normal myocardial tissue in the right ventricular outflow tract and endangers the first septal arteries which, at least in theory, could compromise right ventricular function and possibly predispose to ventricular arrhythmias and/or sudden death. In an attempt to clarify some of these issues, we have reviewed our two center experience with 264 consecutive adult patients (over the age of 18 years) who had their aortic valve replaced by a pulmonary autograft root (Ross) and followed up for up to 15 years (1634 patient years). In this study we analyzed the pattern of survival, the incidence and severity of early and late complications, particularly those related to aortic and/or pulmonary valve dysfunction and their possible determinants.

Material and methods

Patients

Between November 1988 and May 2004 264 consecutive adult patients (aged 18 years and older at the time of operation) underwent pulmonary autograft replacement of the aortic root in 2 institutions (in Harefield 178 patients, in

Rotterdam 86 patients). Indications for the Ross operation were similar in both centers: severe aortic valve or root disease in patients with an expected long life expectancy and a normal pulmonary valve. All patients were operated according to the recommendations for aortic valve replacement in the AHA/ACC Guidelines for the management of patients with valvular heart disease(11). Their pre-operative characteristics are displayed in Table 1.

Table 1. Patient characteristics at the time of autograft aortic root replacement

	N=264
Mean age (years (SD; range))	35 (11.5; 18-66)
Males (%)	76.9%
Previous cardiac surgery	39%
Previous aortic valve surgery	31%
Valve replacement	21.5%
Valve repair or valvotomy	9.5%
Hemodynamic diagnosis	
Aortic valve regurgitation (AR)	44%
Aortic valve stenosis (AS)	16%
AR+AS	36%
unknown	4%
Etiology (N=248)	
Congenital	52%
Degenerative	22%
Bacterial endocarditis	5%
Rheumatic	8%
Other	7%
Unknown	6%
Valve requiring replacement	
Native valve	81%
Homograft	11%
Mechanical valve	4%
Bioprosthesis	3%
Dura valve	<1%
Pre-operative NYHA-class (N=238)	
I	31%
II	45%
III	21%
IV	3%
Urgency (N=252)	
Elective	92%
Urgent	5%
Emergent	3%

Figure 1 displays the patient age distribution in the 2 centers. The Harefield patients were older compared to the Rotterdam patients (mean age 36.9 years (SD 12.4; median 35.0) versus 31.7 years (SD 8.5; median 29.9); $p<0.001$), and the proportion

of male patients was higher in Harefield compared to Rotterdam (84% versus 61%; p<0.001).

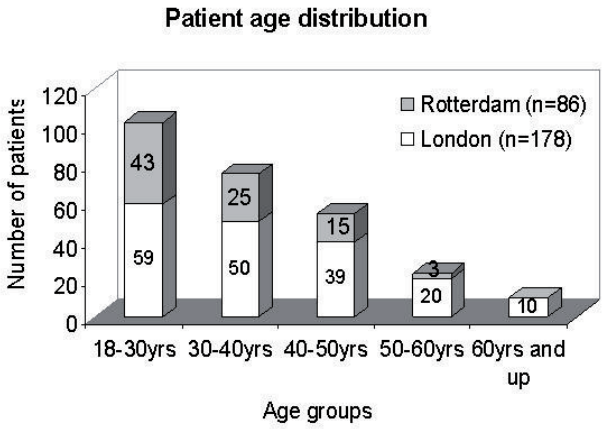

Figure 1. Distribution of patient age at the time of the autograft procedure in the 2 centers.

Operation

All surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. In Harefield either blood or crystalloid cardioplegia were used, while in Rotterdam crystalloid cardioplegia and topical cooling were used for myocardial protection. In Harefield one surgeon operated all patients, while; In Rotterdam 6 different surgeons performed the procedure. In Harefield this resulted in a more consistent implantation technique. The autograft root was placed in the left ventricular outflow tract and annulus with a short rim of right ventricular muscle, which was kept to a minimum. No attempts were made to wrap the autograft or reinforce the base of the autograft.

In the Harefield series, the lower end of the autograft was scalloped to a level of 2 mm below the attachment of the cusps. Then the autograft was inserted by a series of interrupted sutures placed outside the attachment of the autograft cusps and inside the aortic annulus of the patient thus providing support for the area of cusp attachment of the autograft and the lower part of the sinus of Valsalva that are lined by RV outflow muscle (Figure 2).

In the Rotterdam series either a straight rim of muscle was left intact below the autograft valve or scalloping was performed to reduce the muscle rim to a minimum of approximately 3-4 mm. Then either continuous (N=65) or interrupted sutures (N=21) were used to insert the autograft in aortic position, depending on the

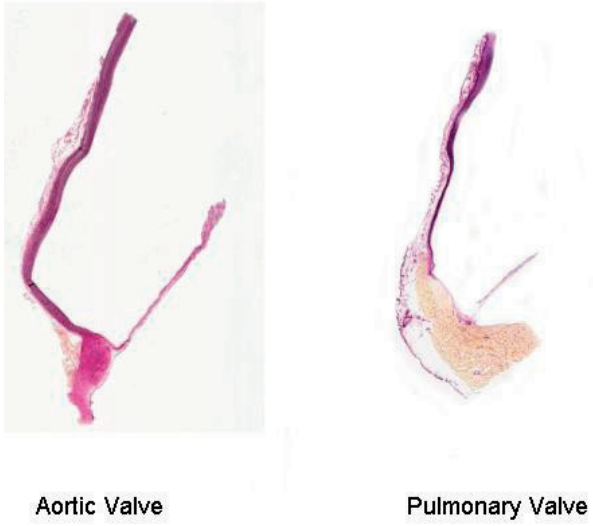

Figure 2. Microphotographs of a normal aortic and pulmonary valve illustrating the distinct differences in the mode of attachment of the valve leaflets.

surgeon's preference. In Rotterdam 6 autografts were implanted using the inclusion root cylinder technique, and in 2 patients the proximal suture line was supported by an autologous pericardial strip.

Table 2. Peri-operative details

	N=264
Concomitant procedures (n=31)	
CABG	2.7%
Mitral valve repair	3.4%
Aortic arch replacement	1%
Other	4.9%
Cross-clamp time (minutes (SD))	125 (33)
Cardiopulmonary bypass time (minutes (SD))	183 (65)
Hospital death	2.3% (n=6)
Complications	
Bleeding/tamponade	14%
Infection	4.2%
Permanent pacemaker	1.9%
CVA/TIA	1.5%
Procedure-related CABG	0.8%
Acute myocardial infarction	0.4%

The pulmonary root was replaced by a homograft in all patients. Thirty-seven (14%) patients required a resternotomy because of persistent bleeding or tamponade. Two patients (0.8%) required coronary artery bypass grafting due to impaired perfusion of a coronary artery after reinsertion. Table 2 displays peri-operative characteristics.

Follow-up

Patients who receive an autograft in Harefield Hospital are prospectively followed by visits to Harefield outpatients including yearly echocardiography. All patients who receive an autograft at ErasmusMC are followed prospectively by annual telephone interviews and through visits to their cardiologist. Echocardiographic follow-up at ErasmusMC is obtained at 6 months postoperative, 1 year postoperative and thereafter every other year by means of serial standardized echocardiography(12). Valve-related complications were defined according to the 1996 guidelines for reporting morbidity and mortality after cardiac valvular operations(13). Autograft and pulmonary homograft failure were determined at the time of reoperation or death. Indications for reoperation of the autograft due to structural failure were moderate to severe aortic regurgitation causing left ventricular dilatation and/or dilatation of the autograft root > 50 millimeters and/or symptoms. Indications for pulmonary homograft reoperation due to structural failure were allograft stenosis resulting in a right ventricular pressure >50% of systemic pressure and/or moderate to severe allograft regurgitation with gross right ventricular dilatation. The study database was frozen for analysis on October 1, 2004. Follow-up was 96.1% complete until at least 1 January 2004 (93.4% for Harefield, 100% for Rotterdam) (14). The mean follow-up duration was 6.4 years (range 0-15.4 years, SD 3.1), with a total follow-up of 1634 patient years. Mean follow-up for Harefield was 5.6 years, (range 0.02-11.0 years, SD 2.8) and total number of patient years of 951. For Rotterdam mean follow-up was 7.9 years (range 0.0-15.4 years, SD 3.3) and a total number of patient years of 683.

Statistical methods

Continuous data are presented as mean ± 1 standard deviation, and comparison was done using the unpaired T-test. Categorical data are presented as proportions, and comparison was done using the Fisher Exact test or the Chi-Square test. Cumulative survival and freedom from reoperation or re-intervention were analyzed using the Kaplan-Meier method. The Tarone-Ware test (correcting for the difference in follow-up duration between the 2 centers) was used to study possible differences in Kaplan-Meier survival estimates. Cox regression analysis was used to assess potential risk factors for reoperation over time. For all analyses mentioned

above SPSS 11.0 for Windows statistical software (SPSS, Chicago, Ill) was used. Using microsimulation(15) survival estimates were obtained for the age-matched general population in the United Kingdom, age-matched patients after aortic valve replacement with a SJM mechanical prosthesis(16) and age-matched patients after cryopreserved homograft aortic root replacement(17).

Results

Early and late survival

In total ten patients died. Six died in hospital (2.3% early mortality) and 4 more patients died during follow-up. Causes of death are described below by study center. Figure 2 shows that overall 10-year survival was 95.4% (S.E. 2.9%). No potential risk factors for death were detected. Microsimulation estimates of survival were 98.4% at 10 year for age-matched individuals in the general population and after homograft and mechanical prosthesis implantation 84.8% and 84.4%, respectively (see Figure 3).

Harefield Three patients died in hospital. All died of multi-organ failure between the 6th and 16th day postoperative. Late death occurred in another 3 patients: two

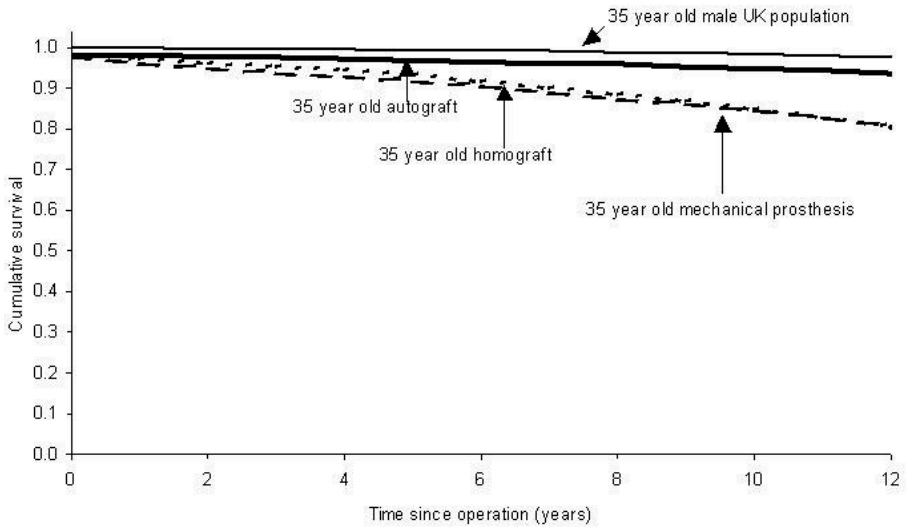

Figure 3. Cumulative survival after autograft aortic root replacement, survival of a 35-year-old male in the UK population, and microsimulation-based survival estimates of 35-year-old patient with a cryopreserved homograft or bileaflet mechanical prosthesis.

patients died suddenly 0.5 and 6.6 years after operation. Another patient died of motor neuron disease 4.9 years after operation.

Rotterdam Three patients died in hospital. Causes of death were low output failure in 2 patients (of which 1 myocardial infarction due to malperfusion of a reinserted right coronary artery; this patient died shortly after the operation). The third patient died due to pulmonary emboli in on the day of operation.

Late death occurred in 1 patient. This patient died of an acute myocardial infarction 4.7 years after the initial Ross operation and 2.5 months after replacement of the autograft with a mechanical valve conduit for progressive neo-aortic root dilatation and aortic regurgitation.

Reoperation for autograft failure

The autograft required reoperation in 11 patients. Two were reoperated in Harefield and nine in Rotterdam. Progressive dilatation of the neo-aortic root and neo-aortic

Table 3. Reoperations on the autograft

Patient	Sex	Age at Ross operation	Implantation technique	Years to Redo	Center	Replacement valve	Indication	Result
1	M	53	Freestanding root	0,8	H	Homograft	RD, AR	Alive
2	M	26	Freestanding root	3,2	H	Homograft	Dissection	Died 3.4 years postop
3	F	26	Freestanding root	11,7	R	Mechanical	RD, AR	Alive
4	M	28	Freestanding root	4,5	R	Mechanical	RD, AR	Died 2.5 months postop
5	F	27	Freestanding root	6,7	R	Mechanical	RD, AR	Alive
6	F	29	Freestanding root	8,3	R	Mechanical	RD, AR	Alive
7	M	20	Freestanding root	5,7	R	Mechanical	RD, AR	Alive
8	M	34	Freestanding root	7,3	R	Mechanical	RD, AR	Alive
9	M	28	Freestanding root	6,7	R	Homograft	RD, AR	Alive
10	M	26	Freestanding root	3,1	R	Mechanical	Reiter's disease, RD, AR	Alive
11	F	21	Freestanding root	11,2	R	Mechanical	RD, AR	Alive

M = male, F= female, H = Harefield, R = Rotterdam, RD = Root dilatation, AR= aortic regurgitation

regurgitation was the main cause in ten patients. One patient in Harefield was reoperated for a dissection of arterial wall of the autograft. This dissection was located in the non-coronary sinus of the autograft and did not extend to any of the suture lines. One patient in Rotterdam who received a Ross operation for severe aortic regurgitation resulting from aortic valve damage caused by Reiter's disease following a Shigella dysenteria, required autograft reoperation for regurgitation and dilatation of the autograft following a recurrent attack of Reiter's disease. Details on the autograft reoperations are displayed in Table 3.

Reoperation for pulmonary homograft failure

The homograft failed in 9 patients. Six were operated in Harefield, three in Rotterdam. Main causes for homograft failure were pulmonary stenosis (7 patients), pulmonary insufficiency (1 patient) and bacterial endocarditis (1 patient). All failing pulmonary homografts were replaced by another pulmonary homograft. Two pulmonary homografts were replaced concomitantly with a failing autograft.

Freedom from reoperation and possible determinants

Overall freedom from any reoperation was 95.4% (S.E. 1.4%) at 5 years and 89.7% (S.E. 2.7%) at 10 years. For the Harefield cohort freedom from any reoperation was 95.1% (S.E. 1.8%) at 5 years and 94.0% (S.E. 2.1%) at 10 years. For the Rotterdam cohort the freedom from any reoperation was 96.1% (S.E. 2.2%) at 5 years and 86.9% (S.E. 4.5%) at 10 years (p=0.85).

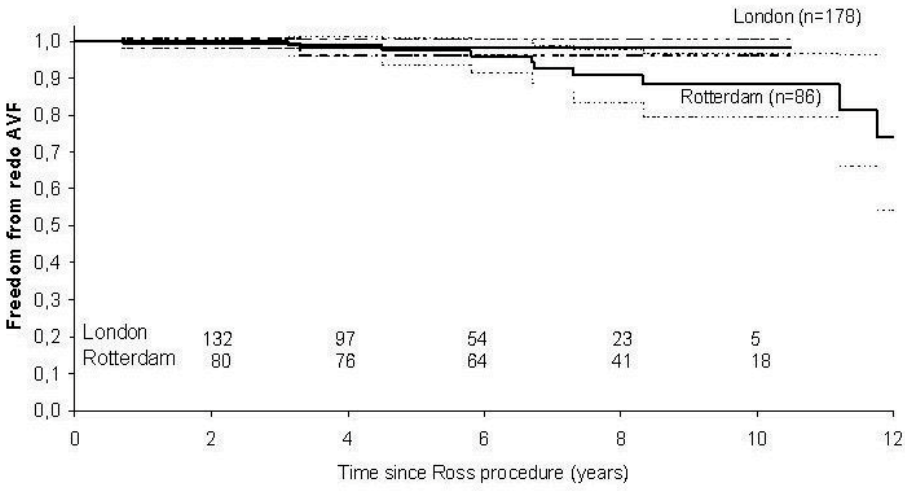

Figure 4. Estimated freedom from reoperation comparing the Harefield and Rotterdam population.

Overall estimated freedom from autograft reoperation was 98.1% (S.E. 1.0%) at 5 years and 92.9% (S.E. 2.5%) at 10 years respectively. For Harefield the freedom from autograft reoperation was 98.6% (S.E. 1.0%) at 5 years and 10 years respectively. For Rotterdam the freedom from autograft reoperation was 96.0% (S.E. 2.3%) at 5 years and 88.2% (S.E. 4.4%) at 10 years (Figure 4; p=0.10).

Univariate Cox regression analysis failed to identify any risk factors for autograft reoperation. In particular patient age (HR 0.96, 95% CI 0.90-1.03; p=0.26), hemodynamic diagnosis aortic regurgitation (HR 1.6, 95% CI 0.5-5.3; p=0.45), originally bicuspid valve disease (HR 0.4, 95% CI 0.1-1.4; p=0.15), prior aortic valve surgery (HR 0.44, 95% CI 0.1-2.0; p=0.28), rheumatic valve disease (HR 0.05, 95% CI 0-20699; p=0.64), and Harefield center (HR 0.24, 95% CI 0.05-1.18; p=0.08) were not predictive of autograft reoperation.

The overall estimated freedom from pulmonary homograft reoperation was 96.4% (S.E. 1.3%) at 5 years and 94.9% (S.E. 1.9%) at 10 years. The freedom from pulmonary homograft reoperation was for Harefield 96.7% (S.E. 1.4%) at 5 years and at 95.7% (S.E. 1.8%) at 10 years. The freedom from pulmonary homograft reoperation was for Rotterdam 97.5% (S.E. 1.8%) at 5 years and 95.0% (S.E. 3.0%) at 10 years (p=0.63). Univariate Cox regression analysis did not reveal any potential risk factors for pulmonary homograft reoperation. In particular patient age (HR 0.97, 95% CI 0.3-5.7; p=0.65), donor age (HR 0.98, 95% CI 0.93-1.04; p=0.47), and fresh versus cryopreserved homografts (HR 0.64, 95% CI 0.17-2.40; p=0.51) were not predictive of pulmonary homograft reoperation.

Other valve-related events

One patient developed postoperative supravalvular pulmonary stenosis for which balloon dilatation was performed. Two years later this same patient underwent a reoperation to enlarge the pulmonary artery at the distal anastomosis of the pulmonary homograft. Two patients had a transient ischemic attack early postoperatively and two patients had cerebrovascular accidents, one shortly after operation and one 3.4 years after operation (linearized occurrence rate 0.2%/patient year). No autograft endocarditis, valve thrombosis or non-structural valve deterioration was observed.

Functional and echocardiographic status at last follow-up

At last follow-up it was possible to determine functional status for 216 patients. Of these patients 89.3% (N=193) was in NYHA class I, 9.3% (N=20) was in NYHA class II, and 1.4% was in NYHA class III. For 190 patients aortic regurgitation was measured at last follow-up by means of 2D-echocardiography: 37% had no or trivial aortic regurgitation, 59% mild aortic regurgitation, 3% moderate aortic

regurgitation and 1% severe aortic regurgitation. Seven out of the 8 patients who had moderate to severe aortic regurgitation at last follow-up were from Rotterdam.

Comments

This study serves to define further the mid term results of the Ross root replacement in adults with special emphasis on the pattern of survival, the function of the aortic and pulmonary roots and factors which could influence them. Although the autograft procedure is technically demanding, especially with regard to coronary translocation, the pulmonary autograft is currently the only valve substitute which continues to be living and therefore, arguably, can reproduce most or all the sophisticated functions of the normal aortic valve. These include capacity to change in shape and size during the cardiac cycle, growth and response to various hemodynamic and humoral stimuli as well as specific molecular cues(3). These unique features should translate into clinical benefit, however, there are continuing concerns about the complexity of this technically demanding operation, regarding the capacity of the autograft to withstand the systemic pressure in adults, as well as the complications which may arise from removing the native pulmonary valve and inserting a foreign substitute.

Analysis of the pattern of survival in our combined series showed an actuarial survival of 95.4% (SE 2.9%) at 10 years, which is equivalent to age-matched controls from the normal population of the UK and superior to survival after other types of valve replacement(16,17). This is a remarkable observation since in particular young adult patients who undergo aortic valve replacement show a considerable excess mortality rate relative to the age-matched general population(2,15). Other investigators have reported excellent survival after the Ross operation in their selected series(7,9,18). The early mortality in our series was 2.3%, which is acceptable considering the inclusion of elderly patients with advanced disease and those requiring emergency operation in addition; approximately 21% of the patients had had previous valve replacement. Taken together, these data suggest that the Ross operation as described in this combined series may produce better survival compared to other types of valve. This finding needs to be validated.

The perceived complexity of the operation is due largely to lack of familiarity and can be circumvented by definable attention to detail, particularly with regard to the technique of explantation of the pulmonary valve, positioning of the autograft and avoiding tension, kinking or torsion of the relocated coronary arteries, which are all achievable. One of the most important concerns about the use of the Ross operation

as a root replacement is the occurrence of progressive aneurismal dilatation of the root resulting in severe aortic valve malfunction requiring reoperations(6,7,9). The incidence of this complication is different in different series. The increasing number of reoperations in Rotterdam for dilatation and regurgitation were an important reason for combining the Harefield and Rotterdam experience, and allowed for analysis of potential determinants of this complication. In the current study, the freedom from reoperations on the aortic root was 92.9% (SE 2.5%) at 10 years in the whole series (98.6% (SE 1.0%) in the Harefield series and 88.2% (SE 4.4%) in the Rotterdam series). In a recently reported series from Kouchoukos and co-workers(7), the freedom from reoperations for this complication was 75% at 10 years. The causes for these differences are not clear, however, several factors could be responsible. Although the aortic and pulmonary valves share many characteristics, there are several fundamental differences in the structure of the 2 valves due to both developmental and acquired factors (Figure 2). One of the most important differences that may be relevant to the Ross operation is the mode of attachment of the pulmonary valve leaflets, which are fixed to muscular tissue of the right ventricular outflow tract (19). The muscle extends along the proximal part of each cusp as well as outside the lowest parts of the sinuses of the pulmonary root. In contrast, the aortic leaflets are attached to a well-defined crown shaped fibrous annulus (Figure 2). As the infundibular muscle attached to the pulmonary autograft is rendered acutely ischemic during mobilization of the valve, its support to the region of the attachment of the cusp and sinuses of Valsalva may be lost and could contribute at least in part, for the later dilatation of the root. We therefore believe that the technique of insertion of the autograft should take account of these points by scalloping the lower end of the autograft leaving minimal amount of muscular tissue and inserting this region inside the annulus of the aortic valve. Another potential factor relates to the structure of the pulmonary wall. Although at birth the media of the pulmonary arterial wall is identical in structure to that of the aortic wall, the elastic fibers in the pulmonary arterial wall undergo progressive fragmentation during the first 3-6 months of life (20). Furthermore, the media of the pulmonary wall is significantly thinner than that of the aortic wall in both children and adults. These differences render the pulmonary arterial wall, less capable of withstanding excessive degrees of high distending pressures during the early post-operative period after Ross root replacement(5). However, as the pulmonary arterial wall is living and autologous, it is potentially capable of adapting to the increased pressure by progressive deposition of collagenous tissue in adventia (Figure 5), which renders

the vessel wall of adequate strength and prevents progressive dilatation. Changes in the stress-strain relationship of the pulmonary arterial wall after relocation in the aortic position have been documented after the Ross operation in humans(5). We believe, however, that this process of adaptation requires several weeks. For this reason in Harefield particular attention is paid not to subject the newly inserted pulmonary arterial wall to systolic arterial pressures higher than 110 mmHg during the first three months. This did however thus far not result in a difference in the autograft reoperation rates between the two centers. Another undesirable effect of overstretching the pulmonary arterial wall before full adaptation is the possibility of producing an intimal or medial tear that can progress to acute or chronic dissection and predispose to massive dilation of the autograft root. This complication was encountered in one patient in Harefield. In the current series unlike reports from other institutions, age, sex, etiology of valve disease and presence of a bicuspid

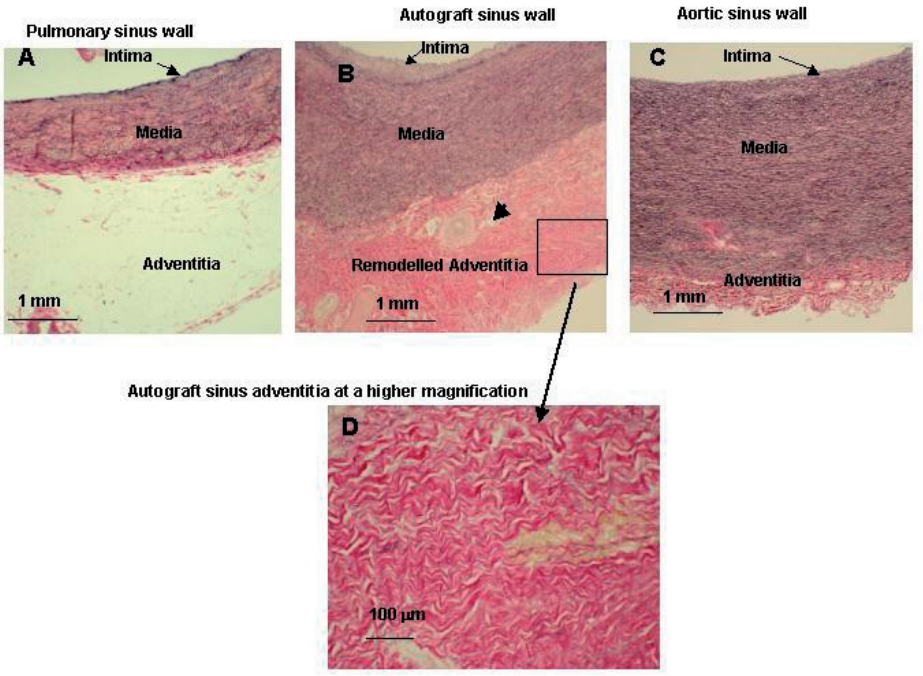

Figure 5. Photomicrographs of the sectors of normal human pulmonary arterial sinus with a thin almost areolar media (Fig.5A), the pulmonary autograft sinus wall (10 years after insertion; Fig. 5B) showing increased elastic content in the media and development of thick vascular neo-adventitia formed of mature fibrous tissue (see insert), and a normal aortic root showing a thick media with unfragmented elastic lamina (Fig 5C). All photomicrographs were stained with Elastic Van Giesson stain and are shown at the same magnification.

valve did not influence the incidence of progressive dilatation(6,8,21). It is hoped that the technical and management strategies suggested above, coupled with further understanding of the causes of this complication will reduce the incidence or prevent this complication.

The reoperation of a dilated autograft root (although thus far without reoperative mortality) is not just a reoperation. It is found to be a risk-carrying and demanding procedure where the aneurysmatic ascending aorta may be attached to the sternum, and the pulmonary homograft may be compressed by and attached to the dilated autograft root. Also, the coronary buttons may pose problems when they are removed from the autograft and reimplanted in a new root. The complexity of these reoperations should be taken into account when the original choice for an autograft is made, and every attempt at their prevention should be made as mentioned above.

The other important late complication of the Ross operation is the development of malfunction of the valve conduit inserted in the right ventricular outflow tract usually a pulmonary homograft. In the current series, the freedom from reoperations from pulmonary dysfunction was 94.9% (SE 1.9%) at 10 years. This is comparable to previous reports(7,9,18,22). Multivariate analysis showed no association between several patient and graft related variables and the incidence of this complication. The exact cause of homograft stenosis is still unknown. Although an allogenic immune response has been suggested to be a contributing factor(23), a previous study failed to show correlation between the development of HLA antibodies and homograft stenosis(10). The use of decellularized homografts has been shown to reduce the frequency of postoperative anti-HLA antibodies(24). However, the effect of decellularization on homograft stenosis and/or calcification still needs to be tested in a prospective randomized trial. An intriguing aspect of homograft stenosis is that it tends to develop during the first 18 months after operation with marked reduction in the instantaneous hazard function of the developing the complication after that(10). A previous MRI study from Harefield showed compression of the homograft by mediastinal mass which proved to be dense fibrous tissue with chronic inflammatory cells(10). In an attempt to reduce this complication, the Harefield center initiated a policy of using anti-inflammatory drugs during the first 6 months after operation and in addition recommended the use of the largest pulmonary homograft available with the use of interrupted sutures for the upper suture line of the homograft. This did however thus far not result in a difference in pulmonary homograft events between the two centers. Future development of a tissue engineered pulmonary valve may offer further steps towards a definite solution to this problem(1).

In the current study, the incidence of other valve-related complications was very low. The extremely low occurrence rates of thrombo-embolic complications and pulmonary homograft endocarditis, the absence of any other valve-related complications and the fact that almost all patients live a life without physical impairment further illustrate the superiority of the autograft procedure.

In conclusion, this study strongly suggests that the Ross root replacement in adults may be associated with a decrease in excess mortality when compared to other valve substitutes. This however, needs to be confirmed in larger series followed up for longer periods and, importantly, in prospective randomized trials. The optimal surgical technique should be meticulously applied and progressive dilatation in neo-aortic root warrants periodical close observation of all autograft patients. Homograft degeneration in the right ventricular outflow tract continues to be a problem but does not appear to undermine the overall value of the operation.

Acknowledgements

We thank Marijke Rozema-Botermans for her excellent secretarial assistance in pursuing a complete follow-up of this patient cohort.

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Chapter 8

The Ross Procedure: A Systematic Review

Discussion paper emerging from an expert meeting on the clinical, surgical/technical, and histological factors that may affect autograft durability, Rotterdam, the Netherlands, November 3, 2005.

The Ross Procedure: A systematic Review. Takkenberg JJM, Klieverik LMA, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Yacoub MH, Bogers AJJC. *Submitted*

Abstract

Background

To give a systematic review of outcome after the Ross procedure, and discuss the patient-related factors, surgical-technical considerations and histological aspects of the procedure to improve insight into potential determinants of success for this special operation.

Methods and results

A systematic review of reports published between 01/2000 and 08/2006 on outcome after the Ross procedure was done. Twenty-six papers met the inclusion criteria and were allocated to 3 partially overlapping categories of (1) consecutive series, (2) pediatric patient series and (3) adult patient series. Using straight pooling linearized occurrence rates of morbidity and mortality were obtained.

Pooled mortality rates were excellent (0.39, 0.44 and 0.45%/patient year for consecutive, pediatric and adult patients series respectively), and occurrence rate of most valve-related complications low. Reintervention rates for structural valve deterioration of the autograft were 1.1%, 1.2% and 0.6%/patient year respectively: and for pulmonary allograft 0.44%, 0.79%, and 0.41%/patient year respectively. Patient-related, surgical and histological factors were discussed in relation to the observed results of the systematic review.

Conclusions

The Ross procedure provides both children and young adults with satisfactory results, but has several limitations that become apparent by the end of the first decade after operation. Whether these limitations may at least in part be addressed by the surgical details and postoperative measures discussed in this paper remains to be determined.

Keywords: epidemiology, prognosis, surgery, survival, valves

Introduction

The autograft or Ross procedure, developed in Norman Shumway's research laboratory[1] and was introduced in clinical practice by Donald Ross in 1967[2] . In this operation the pulmonary root is used to replace the diseased aortic valve or root, the pulmonary root being replaced with a substitute, often an allograft. Potential advantages are the use of the patient's own living valve with favourable haemodynamic characteristics, low endocarditis risk, low thrombogenicity, avoidance of anticoagulant therapy, and autograft size increase in children. The autograft is the only valve substitute which guarantees long-term viability of most components of the valve. This could allow the valve to respond and/or adapt to environmental factors. However, the Ross procedure is a technically demanding operation and the autograft in aortic position and the valve substitute in the right ventricular outflow tract (RVOT) may develop structural failure over time.

With the growing clinical experience with the Ross procedure in young adult patients, the notion arises that results with this procedure vary widely among implanting centers. Although survival of young adult patients after this procedure is almost uniformly excellent and comparable with the general population, durability of the autograft valve is in some centers clearly superior to other biological valve conduits while other centers report worrisome autograft reoperation rates comparable to other bioprostheses. It remains unclear why these individual results diverge so much and whether there are keys to success for a durable result.

Reviews are essential tools for health care workers and researchers to keep up with the accumulating evidence in their field. They are also required to identify areas –such as outcome after the Ross procedure- where the available evidence is insufficient. Systematic reviews allow for a more objective appraisal of the evidence than traditional narrative reviews and may thus contribute to resolve uncertainty when original research, reviews and editorials disagree[3]. The goal of this discussion paper is to give a systematic review of reported outcome after the Ross procedure, and discuss patient-related factors, surgical-technical considerations and histological aspects of the Ross procedure in order to improve insight into potential determinants of success for this special operation.

Methods

Systematic review of reported outcome after the Ross procedure

On October 1, 2006 we performed a literature search of the MEDLINE database using the PubMed search engine for studies published between January 1, 2000

and July 31, 2006, to obtain the most recent reports with the longest follow-up. MeSH terms and text words used for the search were "autograft" and "aortic valve replacement", limited to English publications. The search resulted in 120 publications. All titles and abstracts were screened for study design (reports of clinical experience with autograft aortic valve or root replacement), and completeness of follow-up (>90%), study size (N>39, reflecting the center's experience). References of selected papers were crosschecked for other potentially relevant studies. In case of multiple publications on the same patient population, the most recent report was selected. Ninety-four papers were excluded from the review for the following reasons: case report, review or comment (N=33), echocardiographic, MRI or other imaging studies (N=16), different subject (N=14), overlap with other publications (N=14), study size too small (N=13), <90% completeness of follow-up (N=3), unable to retrieve publication (N=1). The remaining 26 papers were reviewed and patient characteristics and results of each study were tabulated in a spreadsheet.

After review, we allocated the papers to 3 partially overlapping categories: (1) consecutive series without selection criteria (N=15);[4-18] (2) series reporting on outcome after the Ross procedure mostly in children (including children < 1 year at the time of the procedure) (N=6);[9, 19-23] and (3) series reporting on outcome after the Ross procedure mainly in adults and/or children ages 10 and older at the time of the procedure (N=10).[6, 12, 15, 17, 24-29] Events and outcomes in all studies were registered according to the guidelines for reporting morbidity and mortality after cardiac valvular operations.[30] Structural and non-structural valve deterioration were defined as diagnosed either at reoperation or autopsy. In case the total number of patient years was not provided in the selected papers, we calculated it by multiplying the number of patients in the study with the mean follow-up duration of that study. Estimates of survival, freedom from autograft reintervention and freedom from RVOT reintervention were extracted from the selected papers. If these estimates were not provided (for survival in 1 paper, for freedom from autograft and/or RVOT reintervention in 9 papers), we either extracted them from the survival figures in that paper or calculated an estimate using the following formula: Freedom from event at x years = 1-((number of events/ the number of accumulated patient years) x follow-up years with more than 10% of the original population still at risk). Linearized occurrence rates of valve-related complications were calculated using straight pooling (pooled number of events/pooled number of patient years). When a particular valve-related event was not specified in the methods section and/or its occurrence was not mentioned in the results section of a study, then this study

Table 1. Overview of selected cohort studies in the systematic review

First author	Year of publication	Operative period	Number of patients	Surgical technique	Study type	Mean follow-up (years)	Mean age (yrs; range)
Consecutive series of pediatric and/or adult patients							
Moidl[11]	2000	1991-…..	109	root/sc	prospective	2.8	32 (6-59)
Sharoni[16]	2000	1996-1999	40	root	retrospective	1.0	? (0-41)
Laudito[9]	2001	1993-2000	72	root/RK	retrospective	……	9 (0-40)
Paparella[12]	2001	1990-1999	155	root/ic/sc	retrospective	3.8	35 (17-57)
Pessotto[13]	2001	1992-1999	111	root/sc	retrospective	median 3.6	16 (0-67)
Takkenberg[18]	2002	1988-2000	343	root/ic/sc	retrospective	4.0	26 (0-58)
Concha[5]	2003	1991-2002	169	root	prospective#	3.0	30 (0-54)
Fullerton[6]	2003	1997-2002	44	root	retrospective	3.2	49 (19-71)
Sakaguchi[14]	2003	1986-2000	399	root/ic/sc	retrospective	4.5	? (0-59)
Kouchoukos[7]	2004	1989-2002	119	root	retrospective	…..	31 (5-56)
Kumar[8]	2005	1993-2003	153	root	retrospective	6.4	28 (0-65)
Luciani[10]	2005	1994-2004	112	root/ic/sc	retrospective	5.1	29 (6-49)
Settepani[15]	2005	1991-2003	103	root	retrospective	6.0	35 (17-65)
Brown[4]	2006	1994-2002	167	root/RK	retrospective	5.1	25 (0-61)
Sievers[17]	2006	1994-2005	347	sc	prospective	3.8	44 (14-71)
Pediatric patient series							
Elkins[20]	2001	1986-2001	178	root/ic	retrospective	5.5	10 (0-18)
Laudito[9]	2001	1993-2000	72	root/RK	retrospective	……	9 (0-40)
Al-Halees[19]	2002	1990-2000	53	root	retrospective	4.0	8 (0-18)
Hazekamp[21]	2005	1994-2003	53	root	retrospective	5.5	9 (0-18)
Takkenberg[23]	2005	1988-2003	47	root	prospective	6.1	8 (0-15)
Ruzmetov[22]	2006	1993-……	81	root/ic	retrospective	6.8	?
Adult patient series							
Knott-Craig[27]	2000	1986-1999	154	root	retrospective	3.0	36 (16-62)
Paparella[12]	2001	1990-1999	155	root/ic/sc	retrospective	3.8	35 (17-57)
Fullerton[6]	2003	1997-2002	44	root	retrospective	3.2	49 (19-71)
Concha[24]	2005	1997-2003	63	root	prospective	2.5	35 (20-50)
Khwaja[26]	2005	1992-……	53	root?	retrospective	5.8	14 (10-21)
Duebener[25]*	2005	1990-2004	351	root	prospective	3.9	43 (16-67)
Settepani[15]	2005	1991-2003	103	root	retrospective	6.0	35 (17-65)
Kumar[28]	2006	1993-2003	81	root	retrospective	7.7	30 (11-56)
Sievers[17]	2006	1994-2005	347	sc	prospective	3.8	44 (14-71)
Yacoub[27]	2006	1988-2004	264	root/ic	prospective	6.4	35 (18-66)

* Only information on the root replacement patients was included, since there was a more recent publication[17] on the subcoronary patients); # prospective since 1998; Surgical technique: root=freestanding root replacement, sc= subcoronary, ic=inclusion cylinder, RK=Ross-Konno procedure

was excluded from analysis of the pooled occurrence rate of that particular valve-related event. This applied to the following valve-related events: thrombo-embolism (10 studies excluded), bleeding (15 studies excluded), valve thrombosis (15 studies excluded), endocarditis autograft (8 studies excluded), endocarditis RVOT (9 studies excluded).
Table 1 provides an overview of the publications obtained by the systematic review. Table 2 displays observed morbidity and mortality after the Ross procedure by category.
Figure 1A shows observed survival, Figure 1B displays freedom from autograft reoperation, Figure 1C freedom from RVOT reintervention, and Figure 1D freedom from autograft and/or RVOT reintervention.

Discussion

This systematic review shows that a considerable experience with the Ross procedure has accumulated worldwide. Unfortunately, follow-up duration is still too limited to make projections of prognosis beyond the first decade after operation. It also illustrates that the Ross operation is almost exclusively employed in children and young adults, in an age range where its advantages of avoidance of anticoagulant therapy, superior haemodynamics and size increase are very important.
Early mortality risk is acceptable, considering that the Ross procedure is a double valve procedure. In children early mortality is slightly higher compared to adults. This is mainly caused by increased mortality risk in infants with complex congenital lesions requiring a Ross-Konno procedure. Late survival is excellent (Figure 1A) and resembles in most series survival observed in the age-matched general population.
The occurrence of thrombo-embolic complications, bleeding, non-structural valve failure and endocarditis is low compared to other aortic valve substitutes.[31-33] One randomized trial that compares outcome after allograft versus autograft aortic valve replacement shows no difference in freedom from valve-related complications.[34] An update of this trial (Circulation 110 (17): 672-672 3117 Suppl. S, 2004) shows that autograft durability is superior to the allograft, freedom from reintervention is comparable and that overall survival of autograft patients is significantly better. With time both the autograft and the valve substitute in the RVOT (usually an allograft) show limited durability, and autograft reoperation and RVOT reintervention for structural valve deterioration are the most common valve-related complications both for adult and pediatric patients. Noteworthy in this review is the large variation in freedom from autograft reoperation between the different reports.

Table 2. Pooled mortality and morbidity after the Ross procedure

	Consecutive series (adult and/or pediatric)		Pediatric patient series		Adult patient series	
Patients (N)	2,443		484		1,615	
Patient years (N)	10,025		2,528		7,160	
Pooled mean follow-up	4.1 yrs (median 4.0)		5.2 yrs (median 5.5)		4.4 yrs (median 3.9)	
	N	**% or LOR (range)**	**N**	**% or LOR (range)**	**N**	**% or LOR (range)**
Early mortality	54	2.2% (0-6.8%)	15	3.1% (0-5.6%)	28	1.7% (0-6.8%)
Late mortality	39	0.39 (0-0.9)	11	0.44 (0-1.1)	32	0.45 (0-1.3)
SUUD	7	0.07 (0-0.5)	2	0.08 0-0.3)	7	0.10 (0-0.4)
Thrombo-embolism	12	0.18 (0-0.5)	-	-	20	0.30 (0-0.5)
(Patient years)	*(6,663)*		*(1,257)*		*(6,711)*	
Bleeding	3	0.06 (0-0.1)	-	-	1	0.02 (0-0.1)
(Patient years)	*(4,920)*		*(284)*		*(4,136)*	
Valve thrombosis	-	-	-	-	-	-
(Patient years)	*(4,920)*		*(284)*		*(4,136)*	
SVD autograft						
Reoperation	108	1.1 (0-3.2)	31	1.2 (0-3.2)	41	0.6 (0-1.3)
Death	3	0.03 (0-0.2)	-	-	2	0.03 (0-0.4)
SVD RVOT						
Reintervention	44	0.44 (0-0.9)	20	0.79 (0-1.1)	29	0.41 (0-1.1)
Death	-	-	1	0.04 (0-0.3)	-	-
NSVD autograft						
Reoperation	4	0.04 (0-0.3)	-	-	3	0.04 (0-0.3)
Death	1	0.01 (0-0.2)	-	-	-	-
NSVD RVOT						
Reintervention	-	-	-	-	-	-
Death	-	-	-	-	-	-
Endocarditis autograft	13	0.19 (0-0.7)	2	0.14 (0-0.5)	11	0.16 (0-0.7)
Reoperation	6	0.09 (0-0.7)	1	0.07 (0-0.5)	6	0.09 (0-0.7)
Death	5	0.07 (0-0.4)	-		1	0.01 (0-0.2)
(Patient years)	*(6,804)*		*(1,469)*		*(6,853)*	
Endocarditis RVOT	10	0.15 (0-0.7)	2	0.16 (0-0.4)	7	0.10 (0-0.3)
Reoperation	6	0.09 (0-0.3)	-	-	5	0.07 (0-0.3)
Death	1	0.02 (0-0.2)	-	-	2	0.03 (0-0.2)
(Patient years)	*(6,804)*		*(1,257)*		*(6,853)*	

* LOR = Linearized occurrence rate (%/patient year); SUUD = sudden unexpected unexplained death, RVOT= right ventricular outflow tract, SVD = structural valvular deterioration, NSVD = non-structural valvular deterioration. For those events that were not reported in all studies, the patient years are displayed in parentheses).

Patient factors

Patient age, etiology of valve disease, and preoperative aortic regurgitation and dilatation are the most commonly reported patient-related determinants of durability of the autograft valve. Most studies are unable to determine any risk

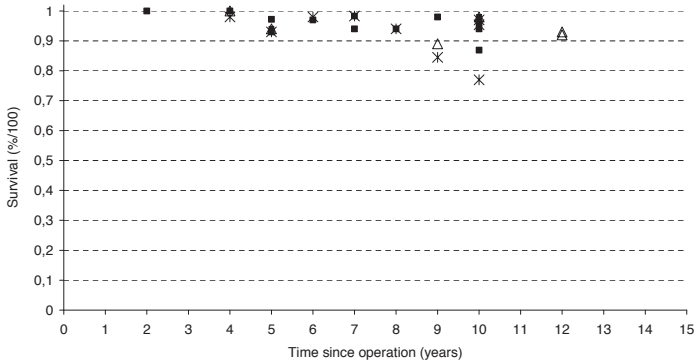

Figure 1A. Overview of reported survival in the consecutive series (■), pediatric patient series (Δ), and adult patient series (ж)

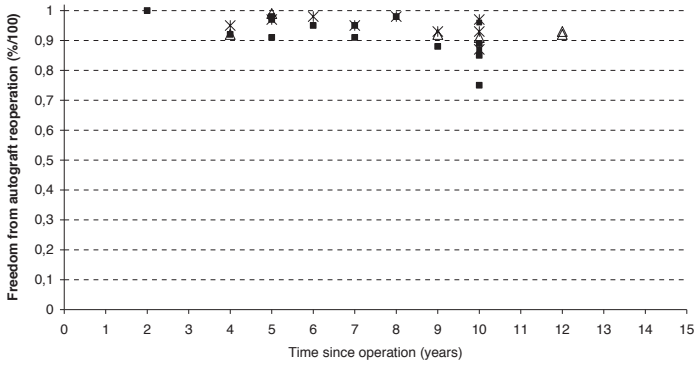

Figure 1B. Reported freedom from autograft reoperation in the consecutive series (■), pediatric patient series (Δ), and adult patient series (ж)

factors, hampered by limited numbers of patients, follow-up duration and number of autograft failures. From the 26 reports in this systematic review, only a few could determine (potential) patient-related determinants of autograft durability.

Younger patient age was previously implicated to be associated with increased autograft dilatation, but not with late autograft dysfunction.[10] In contrast, in another recent report freedom from reoperation for autograft valve failure is better in pediatric patients versus adults (92% versus 57% at 13 years postoperative; p=0.02).[35] From Table 2 it appears that the reoperation rate for autograft structural failure is higher in children compared to adults (1.2 versus 0.6%/patient year). The pediatric reports in this systematic review have a considerably longer follow-up duration compared to the adult patient series. Since the hazard of autograft

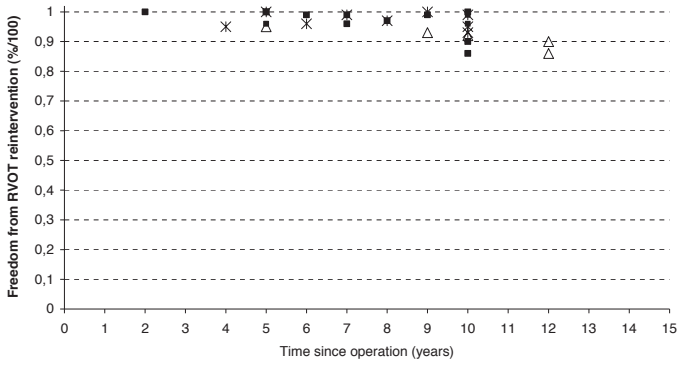

Figure 1C. Reported freedom from RVOT reintervention in the consecutive series (■), pediatric patient series (Δ), and adult patient series (ж)

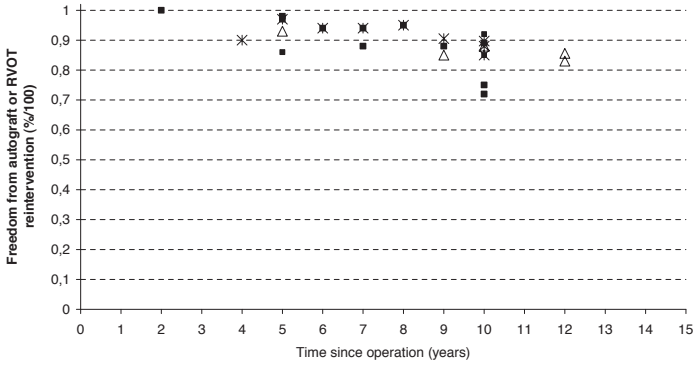

Figure 1D. Reported freedom from autograft and/or RVOT reintervention in the consecutive series (■), pediatric patient series (Δ), and adult patient series (ж)

failure increases with time since operation it therefore appears from Table 2 that children are at higher risk of autograft failure. However, Figure 1B shows that at 10 years postoperative freedom from autograft reoperation does not differ between children and adults. The next few years will reveal whether patient age is indeed a determinant of autograft durability and whether the observed increased autograft dilatation in children will translate to increased autograft failure.

Congenital aortic valve disease (predominantly bicuspid valve disease) was previously suggested to be associated with increased risk of dilatation of the autograft root over time.[36] Although in our systematic review several reports studied the association between bicuspid valve disease and autograft durability, only one study found a possible association between bicuspid aortic valve and an increased occurrence

of aortic regurgitation during follow-up.[15] In addition, a recent prospective serial echocardiography study failed to find an association between bicuspid valve disease and (increase in) aortic regurgitation and neo-aortic dimensions over time.[37] Therefore, the influence of bicuspid valve disease on autograft durability remains highly debatable.[38]

Rheumatic valve disease is another etiology reported to be associated with impaired autograft survival. Two overlapping reports in the systematic review showed an association between rheumatic valve disease in young patients and increased autograft dysfunction.[8, 28] With increasing patient age recurrence of rheumatic fever (and risk of subsequent involvement of the autograft valve) becomes infrequent; this explains why in particular young rheumatics are at risk for autograft dysfunction.

Two pediatric studies in the systematic review report an association between preoperative aortic regurgitation and autograft failure.[9, 20] Both studies hypothesize that annular dilatation associated with aortic regurgitation may be a factor, and one of the studies suggests a role for altered geometry and tissue characteristics of the subvalvular left ventricular outflow tract (LVOT) resulting from chronic aortic regurgitation. In another study from the systematic review in 90 patients aged 6-49 years, preoperative aortic root dilatation was predictive of autograft dilatation.[10] The latter paper therefore recommends resection of the dilated aorta rather than tailoring the ascending aorta, to prevent dilatation.

Surgical-technical considerations

The variability in durability results of the autograft procedure may also partly be explained by the surgical technique and by individual variation of the application of the root replacement technique.

The subcoronary implantation technique, as originally employed by Ross, was abandoned by most centers for multiple reasons including its technical complexity and the attractive option of the root replacement technique that preserves the geometry of the autograft valve apparatus. In the systematic review there is only one series that reports solely on results with the subcoronary implantation technique. Thus far these results are excellent and offer hope for true believers of the Ross procedure who are currently discouraged by the disappointing root replacement durability results.

Most patients in the systematic review received an autograft using the freestanding root replacement technique with reimplantation of the coronary arteries. This surgical technique can be applied in a variety of ways. The autograft can be inserted on the annulus or below the annulus and scalloping of the muscle rim can be done

to a minimum below the valve cusps. Also, either continuous or interrupted sutures can be used for the proximal suture line. Another option is to employ support to the proximal suture line using for example a strip of pericardium. Finally, the autograft root length can be varied. Some surgeons keep the neo-aortic root as short as possible above the sinotubular junction while others preserve its complete length distally. The variability in autograft durability results (Figure 1B) could be explained by the non-uniform application of the root replacement technique. In theory, supra-annular placement of the proximal suture line may predispose to dilatation and regurgitation. However, supra-annular positioning is not associated with dysfunction or poor autograft durability in children. Also, echocardiographic follow-up studies show that dilatation is most pronounced at the sinus and sino-tubular junction level, and to a lesser extent at the level of the annulus.[7, 36] These observations imply that minimization of the autograft root length may result in less dilatation and may produce better durability.

Probably the ascending aorta diameter should not exceed the autograft diameter at the outflow anastomosis. Most surgeons will match the size of the aortic annulus and receiving aorta to the dimensions of the pulmonary autograft when indicated. In patients with ascending aorta aneurysm the replacing Dacron graft may have a stabilizing effect on the aorta-pulmonary junction. In addition, the convexity of the autograft (anterior pulmonary root) should preferably come on the right side in aortic position (former ascending aortic convexity). The unsupported facing sinus of the pulmonary valve should be placed in the left coronary position where it derives support from surrounding tissues.

The third surgical technique used to insert the autograft is the inclusion cylinder technique. It is infrequently used: in 7.7% in the consecutive series, 7.9% in the pediatric patient series and 5.2% in the adult patient series in this review. The inclusion cylinder technique prevents dilatation of the neo-aortic root,[12, 36] but its application requires an intact anatomy of the ascending aorta and aortic root and is limited by several technical challenges, including distortion of the reinserted coronary arteries.[39]

Another measure that may potentially increase autograft root durability is postoperative antihypertensive treatment. It was reported that the physical properties of the pulmonary root change after being in the aortic position for a short time.[40] Since the autograft will be subject to significantly increased mechanical stress, blood pressure control may result in improved valve longevity. Whether this treatment is effective and whether it should be restricted to the early postoperative period[29] or

for a prolonged period of time, has not yet been studied systematically. One can argue that prolonged use of beta blockers or other antihypertensive drugs defeats the purpose of the Ross operation, and may seriously impair quality of life in this young patient population.

The allograft is the valve substitute used to reconstruct the RVOT is in most patients in this review. A small proportion of patients received a bioprosthesis, mostly a bovine jugular vein conduit. The durability of the valve substitute in the RVOT is thus far quite good. From Table 2 it appears that structural valve deterioration of the valve substitute in the RVOT is more common in children compared to adults (0.79 versus 0.41 %/patient year), but there is no apparent difference between the pediatric and adult patient reports from Figure 1C. However, 2 of the larger studies did find an association between younger patient age and increased occurrence of structural failure of allografts implanted in the RVOT,[17, 18] suggesting that patient age affects allograft durability. Measures to improve durability of the allograft in the RVOT are the use of pulmonary allografts[41] and prescription of anti-inflammatory drugs to suppress the specific immune response of the recipient to the allograft.[42] Reintervention for allograft stenosis usually is a minor, elective procedure, associated with very little mortality, as shown in Table 2. Hopefully, with further development of tissue engineered valved conduits a more durable solution will be found for RVOT reconstruction.[43] Also, the emergence of percutaneous pulmonary valve re-replacement, offers patients with degenerated RVOT allografts a less invasive reintervention.[44]

Histological aspects

Rabkin-Aikawa *et al.* reported that explanted autografts are viable and have a near-normal trilaminar cuspal structure and collagen architecture, but autograft walls are damaged, with focal loss of normal smooth muscle cells, elastin, and collagen.[45] More recently, the centers participating in the Dutch Ross registry[18], reported their histological findings in 30 explanted autografts.[46] This report illustrated that compared to normal pulmonary and aortic valves, explanted autograft valves also have an intact laminar architecture and cellularity, but apposition of fibrous tissue on the ventricular surface increases overall valve thickness, as can be seen in longstanding valvular insufficiency. The autograft wall typically shows severe aneurysm formation with intimal hyperplasia, and medial degeneration characterized by elastin loss and fragmentation, hypertrophy of smooth muscle cells and adventitial fibrosis containing functional vasa vasorum.

An important question arising from the observed histological features of autograft valves and walls is: do they represent appropriate repair with the adapted neo-aorta

as a functional and stable end product? The majority of explants was removed for clinical failure and thus proved unstable. Therefore one can argue that the observed changes, the result of adaptive remodelling, are pathologic and should be classified as degenerative. The mode of adaptation conceivably differs between normal aorta and pulmonary root which each having their own typical functional design. Consequently, the pulmonary root has a different stress-strain curve than the aortic root with a greater extensibility at lower strain levels. One can therefore expect the neo-aortic root to stretch beyond its normal transitional point of high to low extensibility. This is supported by in vitro analysis of pulmonary root dynamics.[47] The theoretical consequence of this stretch is compliance loss and root stiffening, a mechanism supported by clinical MRI study, confirming distensibility loss of the pulmonary autograft in adult patients.[48] Adding to this the thin walled and dilated neo-aortic root, it is plausible that the autograft is subject to significantly elevated stresses, and that observed histological changes of elastin loss (distensibility) and collagen increase (integrity) are conceivable modes of adaptation where functional priority is shifted to integrity maintenance. Despite this adaptation, as in any aneurysm, excess wall stress may induce intimal tearing causing a localized chronic dissection, which was indeed observed in two of our explants.

Obviously, changes in root geometry and dynamics influence valve function and durability. The failure of adaptation may be seated in the inability of the anatomic pulmonary root to adequately adapt to systemic pressures which are way off the limits of normal physiology. Remodelling without establishing a new steady state may become sustained activity that may eventually exhaust wall structure, clinically translating into autograft failure.

To further elucidate the mechanisms of autograft remodelling, more experimental studies are necessary, including immunohistochemical, biochemical, and molecular studies, uniform quantification of observed histological changes, including proliferation, apoptosis and senescence of the autograft, and testing of mechanical properties

Limitations

Selection bias is likely in this systematic review of published cohort studies, due to the selection criteria employed and since unpublished data, abstracts and presentations were not included. Moreover, the occurrence of valve-related complications is probably underestimated since most of the studies had a retrospective design. Also, valve degeneration requiring reintervention is described in this paper using linearized occurrence rates. Valve degeneration has an increasing hazard with time

since implantation and may better be described using a Weibull distribution, which accommodates a changing hazard over time.[49] However, since follow-up duration of most studies is limited to the first postoperative decade, and no increasing hazard was yet observed, we chose to depict only linearized rates. In our own experience progressive aortic regurgitation and dilatation after autograft aortic root replacement shows a linear pattern over time[37], but in the second decade there appears to be a worrisome increasing hazard with time for autograft valve reoperation due to progressive dilatation and aortic regurgitation.[35]

We did not study echocardiographical valve performance in this review. It is extremely difficult to obtain this type of information since it is infrequently, incompletely and inconsistently reported in most included studies. Another factor complicating the assessment of the degree of aortic regurgitation and aortic dilatation is the fact that these are not hard endpoints but longitudinal outcomes, "snapshots" of autograft function, which may be taken repeatedly at prospectively specified follow-up intervals, cross-sectionally, or opportunistically. These snapshots are subject to many biases, and precision of the measurements is very important and dependent on multiple factors, related to the haemodynamic status of the patient, and technical factors. In our opinion, the correct way to measure this type of longitudinal outcome, is to estimate the average outcome pattern over time and its variability in the patient group, and requires multiple serial echocardiographic measurements, that are analyzed using hierarchical models[37].

Conclusions

From the considerable experience with the Ross procedure that has accumulated worldwide we can conclude that it provides both children and young adults an adequate biological solution in the first decade after the operation. On the downside, it is a double valve procedure with several limitations that become apparent by the end of the first decade after the procedure, as evidenced by Figure 1D. Whether these limitations may at least in part be addressed by surgical details and postoperative measures discussed in this paper remains to be determined.

The pulmonary autograft is a valve designed for a low pressure environment. Its durability in aortic position depends on the appropriate surgical technique applied in a systematic fashion and tailored to the individual patient. Only in this setting the ingenious concept developed by Donald Ross 40 years ago, will continue to provide young patients with aortic valve disease a solution that meets their needs and standards of living.

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Chapter 9

The Ross Operation: A Trojan Horse?

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The Ross operation: a Trojan horse? Klieverik LMA, Takkenberg JJM, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJJC. *Eur Heart J. 2007 Aug;28(16):1993-2000.*

Abstract

Aims

The Ross operation is the operation of choice for children who require aortic valve replacement (AVR) and may also provide a good option in selected adult patients. Although the autograft does not require anticoagulation and has a superior haemodynamic profile, concern regarding autograft and allograft longevity has risen. In this light, we report the 13-year results of our prospective autograft cohort study.

Methods and Results

Between 1988 and 2005 146 consecutive patients underwent AVR with a pulmonary autograft at Erasmus Medical Center Rotterdam. Mean age was 22 years (SD 13; range 4 months – 52 years), 66% were male. Hospital mortality was 2.7% (N=4), during follow-up 4 more patients died. 13-year survival was 94%±2%. Over time, 22 patients required autograft reoperation for progressive neo-aortic root dilatation. Additionally, 8 patients required allograft reoperation. Freedom from autograft reoperation at 13 years was 69%±7%. Freedom from allograft reoperation for structural failure at 13 years was 87%±6%. Risk factors for autograft reoperation were previous AVR and adult patient age.

Conclusions

Although survival of the Rotterdam autograft cohort is excellent, over time a worrisome increase in reoperation rate is observed. Given the progressive autograft dilatation careful follow-up of these patients is warranted in the second decade after operation.

Key words: Ross operation, prospective study, survival, autograft dilatation, reoperation

Introduction

The autograft procedure was introduced by Donald Ross in 1967.[1] Ross initially used the scalloped subcoronary implantation technique to insert the pulmonary valve into the left ventricular outflow tract with encouraging results.[2] It became a worldwide-accepted procedure for aortic valve replacement despite the need for specific surgical expertise to perform this complicated operation on both the aortic and pulmonary valve.

Initially, the Ross operation was employed using the subcoronary implantation technique but over the years most centers shifted towards the root replacement technique, nowadays the most commonly used implantation technique. Conservation of the autograft root appeared to be more versatile and associated with a decreased incidence of early and late failure compared to the other techniques.[3,4]

Several studies reported satisfactory midterm and long-term results of the Ross operation.[5-8]

The pulmonary autograft has excellent haemodynamic adaptation, there is no need for anticoagulation, patients can live an active lifestyle and patient survival seems to be superior compared with survival of patients with other valve substitutes.[2,5,9] However, in recent years the number of reports on the reoperation rate after the Ross operation using root replacement is becoming more and more extensive[8,10-12] thus questioning the durability of the autograft.

The Ross operation has previously been claimed to be the next best thing to nature, but at present serious drawbacks are shown, raising the question whether or not this operation may turn out to be a Trojan Horse. In this regard we evaluated our prospective cohort study of the Ross operation with emphasis on patient survival, durability of the autograft and pulmonary allograft and the incidence of and potential risk factors for reoperation after the Ross operation in children and adult patients.

Methods

Patients

From 1988 until 2005 146 consecutive patients underwent the Ross operation at our institution. Preoperative patient characteristics are shown in Table 1. Twelve patients underwent previous aortic valve replacement: 6 subcoronary homografts, 3 biological prostheses and 3 mechanical prostheses were used. Approval from the Institutional Review Board was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent.

Table 1. Preoperative patient characteristics

	All patients N=146	Patients <16 yrs N=52	Patients ≥ 16 yrs N=94
Mean age (years (SD; range))	22.4 (13.4; 0.3-52)	8.0 (5.4; 0.3-15)	30.4 (9.1; 16-52)
Male gender	66% (n=96)	67% (n=35)	65% (n=61)
Prior cardiac surgery*	33% (n=48)	44% (n=23)	27% (n=25)
Prior aortic valve replacement	8% (n=12)	-	13% (n=12)
Prior valvulotomy	18% (n=26)	31% (n=16)	11% (n=10)
Prior balloon dilatation	20% (n=29)	46% (n=24)	5% (n=5)
Aetiology			
Endocarditis	5% (n=8)	6% (n=3)	5% (n=5)
Congenital (incl. bicuspid)	74% (n=108)	90% (n=47)	65% (n=61)
Other (mainly prosthetic valve)	13% (n=18)	2% (n=1)	19% (n=17)
Degenerative/Rheumatic	8% (n=11)	2% (n=1)	11% (n=10)
Aneurysm/Dissection	1% (n=1)	-	1% (n=1)
Diagnosis			
Aortic valve regurgitation (AR)	30% (n=44)	17% (n=9)	37% (n=35)
Aortic valve stenosis (AS)	32% (n=47)	33% (n=17)	32% (n=30)
AR+AS	38% (n=55)	50% (n=26)	31% (n=29)
Systolic LVF§ (n=140)			
Good (EF >50%)	83% (n=116)	83% (n=39)	82% (n=77)
Impaired (EF 40-50%)	11% (n=16)	17% (n=8)	9% (n=8)
Moderate/bad (EF <40%)	6% (n=8)	-	9% (n=8)
Sinus rhythm	100%	100%	100%
Creatinin (µmol/L (SD; range), n=145)	63 (24; 12-157)	40 (13; 12-71)	75 (18; 38-157)
NYHA class (n=143)			
I	42% (n=61)	56% (n=29)	34% (n=32)
II	36% (n=53)	21% (n=11)	45% (n=42)
III	15% (n=22)	8% (n=4)	19% (n=18)
IV/V	5% (n=7)	11% (n=5)	2% (n=2)
Ventilation support	2% (n=3)	4% (n=2)	1% (n=1)
Type operation			
Emergency (<24 hrs)	1% (n=1)	-	1% (n=1)
Urgent	13% (n=20)	23% (n=12)	9% (n=8)
Elective	86% (n=125)	77% (n=40)	90% (n=85)

*Some patients had other prior cardiac surgery, i.e. VSD closure, subvalvular membrane resection

§ Systolic left ventricular function based on echocardiographic estimations, EF = ejection fraction.

Operation

Perioperative data are shown in Table 2. All surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia, in 3 patients additional deep hypothermia with total circulatory arrest was needed for surgery on the aortic arch. Crystalloid cardioplegia and topical cooling were used for myocardial protection. In most patients the root replacement technique was employed, and the pulmonary autograft was inserted at the level of the annulus while care was taken to reduce

the subannular muscular rim of the autograft to 3-4 mm. The proximal suture line of the autograft was constructed with interrupted sutures in 21% (n=30) of the procedures, with running sutures in the remainder. In 2 patients an autologous pericardial strip supported the proximal suture line.

In all patients the right ventricular outflow tract (RVOT) was reconstructed using an allograft, in 98% a pulmonary allograft was used and 99% of the allografts used were cryopreserved. Three patients required concomitant coronary artery bypass grafting (CABG) due to a procedural complication.

Table 2. Perioperative details

	All patients n=146	**Patients <16 yrs n=52**	**Patients ≥ 16 yrs n=94**
Aortic valve			
Bicuspid	61% (n=89)	69% (n=36)	56% (n=53)
Tricuspid	32% (n=46)	31% (n=16)	32% (n=30)
Prosthesis	7% (n=11)	-	12% (n=11)
Surgical technique			
Autograft root replacement	96% (n=140)	100%	94% (n=88)
Inlay autograft	4% (n=6)	-	6% (n=6)
Concomitant procedures			
CABG	2% (n=3)	-	3% (n=3)
LVOT enlargement	10% (n=14)	21% (n=11)	3% (n=3)
Mitral valve surgery	1% (n=1)	-	2% (n=1)
Other*	11% (n=17)	14% (n=8)	10% (n=9)
CPB time (min)	202 (114-685)	179 (118-465)	215 (114-685)
Cross-clamp time (min)	141 (90-240)	125 (90-240)	150 (90-238)
Circulatory arrest (N=3, min)	30 (11-64)	15 (n=1)	37 (11-64, n=2))
Complications			
Bleeding/Tamponade	13% (n=19)	2% (n=1)	19% (n=18)
Pacemaker	1% (n=1)	2% (n=1)	-
Perioperative MI	1% (n=1)	-	1% (n=1)
Early mortality	2.7% (n=4)	2% (n=1)	3% (n=3)

*Includes patients requiring tailoring of the ascending aorta or subvalvular membrane resection

Follow-up

All patients were followed prospectively and annually contacted and interviewed by telephone. Patients over 16 years underwent standardized echocardiography biannually.[13]

In case of suspected complications the attending physician was contacted for verification. Valve-related events were defined according the guidelines for reporting morbidity and mortality after cardiac valvular operations.[14] Hospital mortality and morbidity were registered and the causes of death were documented. Hospital

mortality was defined as death of the patient within any time interval of operation if the patient was not discharged from the hospital. Failure of the autograft or pulmonary allograft was determined at time of reoperation or death. Patient survival started at time of the Ross operation and ended at time of death or at last follow-up. Survival of the autograft or pulmonary allograft started at time of operation and ended when a reoperation or reintervention was done, when the patient died or at last follow-up. Two patients moved abroad and were lost to follow-up. Echocardiographic measurements were obtained for patients who did not die or did not require reoperation related to the Ross operation during follow-up.

The database was frozen on October 1st, 2005. Total follow-up was 1269 patient years and was 99.3% complete.[15] Mean follow-up duration was 8.7 years (range 0-17.1 years).

Statistical methods

Descriptive statistical analysis of perioperative data was done. Continuous data are displayed as mean ± 1 standard deviation and were compared using the unpaired T-test. Discrete data are presented as proportions and were compared using the Chi-square Test or Fisher exact Test. Cumulative survival and freedom from reoperation or reintervention were analysed using the Kaplan-Meier method. Survival is displayed as a proportion ± standard error. Age-matched survival in the general population was calculated using the Dutch population life tables (http://statline.cbs.nl/). The log-rank test was used to compare Kaplan-Meier curves.

The Cox proportional hazards regression analysis was used to evaluate the following variables as predictors for autograft reoperation over time: previous aortic valve replacement, patient age, bicuspid valve disease, the surgical technique used (root replacement versus inclusion cylinder technique) and haemodynamic diagnosis (regurgitation versus stenosis versus combined regurgitation and stenosis). First, all variables were entered into a univariable analysis. Next, all variables that were significant in the univariable analysis or showed a tendency towards significance ($P \leq 0.20$) were forced into the multivariable Cox regression analysis (enter method); The proportional hazards assumption was assessed for each variable through graphical inspection of the log minus log survival and the linearity assumption for continuous variables though the partial residuals. There was no indication of violation of the assumptions. A p-value of ≤ 0.05 was considered statistical significant. All testing was performed 2-sided. For all data analysis SPSS 12.0.1 for Windows (SPSS, Chicago, Illinois) was used.

Results

Hospital mortality and late survival

Hospital mortality was 2.7% (4 patients). Two patients, both female, died perioperatively. One 40-year-old patient died due to low output failure and the other patient, 4 months old, died of heart failure and severe arrhythmias.

One 26-year-old male patient died due to massive pulmonary emboli shortly after the operation Finally, one 24-year-old female patient with Turner syndrome and extreme left ventricular hypertrophy died due to mediastinitis and sepsis 13 days after surgery.

During follow-up 4 more patients died. There were 1 valve-related and 3 non-valve related deaths. The valve-related death was a 12-year-old girl with severe juvenile rheumatic disease and severe aortic valve regurgitation and mitral valve incompetence resulting in progressive heart failure. She died 6 months after operation.[16]

Causes of the non-valve related deaths included septic shock (Candida Albicans) in one infant 51 days after autograft operation, heart failure resulting in cardiogenic shock in another infant 1.7 years after autograft operation and an acute myocardial infarction in an adult patient 4.7 years after autograft operation. The latter patient died 2 months after autograft reoperation for structural valve deterioration with implantation of a mechanical prosthesis.

Overall 13-year survival was 94.4%±1.9% (Figure 1). For patients younger than 16 years the 13-year survival was 92.0%±3.8%; for patients older than 16 years 95.7%±2.1% (Log-rank test p=0.35).

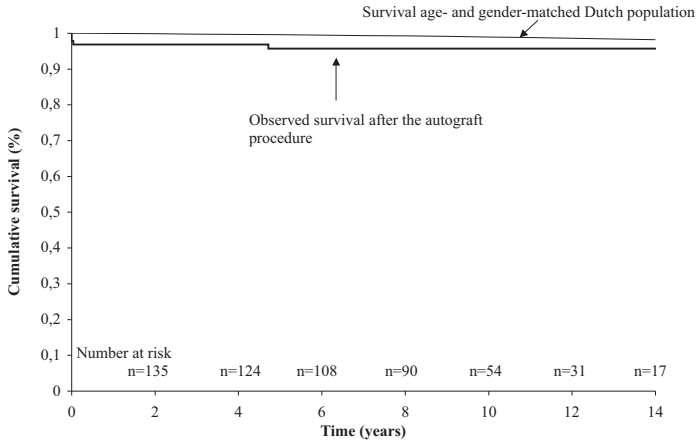

Figure 1. Observed cumulative survival after the Ross operation and survival of the age- and gender-matched general Dutch population

Table 3 Details on Ross operation-related reoperations

Patient	Sex	Age at Ross Operation	Years to reop	Indication	Prosthesis implanted	Result
			Isolated pulmonary autograft reoperation			
1	M	16	1.8	RF, AR	MP	Alive
2	M	28	4.5	RD, AR	MP	Died*
3	M	20	5.7	RD, AR	MP	Alive
4	F	27	6.7	RD, AR	MP	Alive
5	M	28	6.7	RD, AR	ALL	Alive
6	F	8	7.0	RD, AR	ALL	Alive
7	M	34	7.3	RD, AR	MP	Alive
8	M	16	7.6	RD, AR	MP	Alive
9	M	33	7.6	RD, AR	MP	Alive
10	M	39	8.6	RD, AR	MP	Alive
11	M	25	9.1	RD, AR	MP	Alive
12	M	26	10.1	RD, AR	MP	Alive
13	F	21	11.2	RD, AR	MP	Alive
14	F	26	11.7	RD, AR	MP	Alive
15	F	22	11.9	RD, AR	MP	Alive
16	M	22	12.9	RD, AR	MP	Alive
			Pulmonary autograft + pulmonary allograft reoperation			
17	M	26	3.1	Reiter, RD, AR	MP, pALL	Alive
18	M	15	7.7	RD, AR, PR, PS	ALL, pALL	Alive
19	F	29	8.3	RD, AR, PR	MP, pALL	Alive
20	F	41	9.3	RD, AR, PR	MP, pALL	Alive
21	M	16	9.5	RD, AR, PS	MP, pALL	Alive
22	M	18	13.1	RD, AR, PR	ALL, pALL	Alive
			Isolated pulmonary allograft reoperation			
1	M	12	9.4	PS, endocarditis	pALL	Alive
2	M	4	12.8	PS, PR	pALL	Alive

M = male, F= female, RF= Rheumatic fever, AR=aortic regurgitation, RD= root dilatation, Reiter= Reiter's disease, PR= pulmonary regurgitation, PS=pulmonary stenosis, MP= mechanical prosthesis implanted as a conduit, ALL =allograft, pALL= pulmonary allograft
*This patient died 2.5 months after the reoperation

Reoperation

Twenty-four patients underwent a reoperation related to the Ross operation. Of these 24 patients, 16 patients required isolated pulmonary autograft replacement, 6 patients required simultaneous replacement of both the pulmonary autograft and allograft and 2 patients required isolated pulmonary allograft replacement.

Progressive dilatation of the neo-aortic root was the main cause for autograft reoperation. Table 3 shows details of each operation.

Causes for allograft replacement were mainly structural failure, calcification or senile degeneration of the valve. One patient had a recurrent episode of rheumatic fever involving the autograft, thus requiring a reoperation. Two patients underwent a reoperation without valve replacement. One patient underwent enlargement of the pulmonary outflow tract due to supravalvular pulmonary stenosis and the other patient required reoperation for constrictive pericarditis. One patient underwent balloonvalvuloplasty of the RVOT to relieve supravalvular pulmonary stenosis.

Freedom from reoperation for autograft failure at 5 years was 97.7%±1.3% and at 13 years 69.2%±6.6% (Figure 2). Freedom from autograft reoperation was significantly better for patients younger than 16 years compared to patients aged 16 years and older at the time of operation (at 13 years 92.1%±5.4% versus 56.7%±9.6% (Log-rank test p=0.02)).

Freedom from allograft reoperation for structural failure at 5 years was 99.2%±0.8% and at 13 years 87.1%±5.5% (Figure 3). Freedom from allograft reoperation for structural failure did not differ for patients younger than 16 years compared to patients aged 16 years and older at the time of operation (80.0%±1.1% versus 92.5%±3.8% at 13 years (Log-rank test p=0.73)).

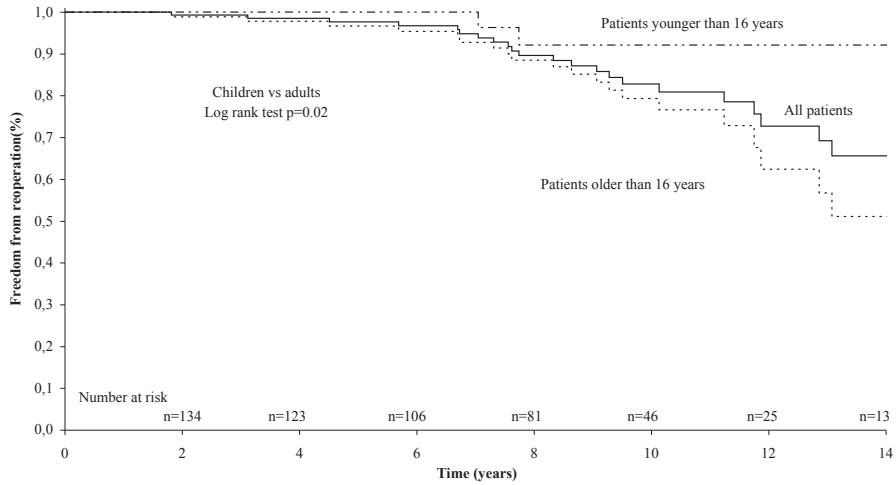

Figure 2. Overall freedom from autograft reoperation and freedom from autograft reoperation for adult patients (16 years and older) versus children

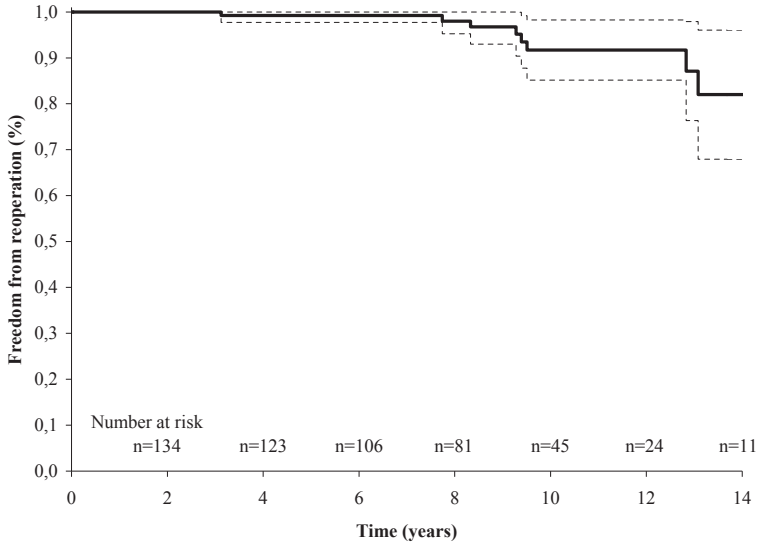

Figure 3. Freedom from pulmonary allograft reoperation for all 146 patients
The dotted lines indicates upper limit and the lower limit of the 95% confidence interval

Univariable predictors of autograft reoperation were previous aortic valve replacement (HR 2.8; 1.1-7.1 p=0.03) and adult patient age (HR 5.0; 1.2-21.1 p=0.03). After multivariable analysis adult patient age remained the only significant predictor of autograft reoperation (HR 4.6; 1.01-21.1 p=0.05) (Table 4).

Other valve-related events

During follow-up two patients developed endocarditis (0.16%/patient year), complicated by a stroke in one patient. In one patient allograft endocarditis occurred and was treated with antibiotics. One patient developed pulmonary emboli (0.08%/patient year). Bleeding events, valve thrombosis or non-structural failure were not observed.

Functional status at follow up

At last follow up, 95% of the patients were in New York Heart Association (NYHA) class I or II. Eleven percent of the patients had moderate to severe aortic regurgitation, 3% moderate to severe pulmonary regurgitation and 8% of the patients had moderate to severe pulmonary stenosis.

Discussion

Our study shows that the autograft procedure initially fulfils the prospect with regard to excellent long term survival and avoidance of anticoagulation therapy. Especially children, patients who want to live an active lifestyle and women who want to

Table 4. Risk factors for autograft reoperation

Risk factors	Univariable analysis	Multivariable analysis
	HR 95% C.I. P-value	**HR 95% C.I. P-value**
Previous AVR	2.8 (1.1-7.1) p=0.03	1.2 (0.4-4.2) p=0.74
Adult patient age	5.0 (1.2-21.1) p=0.03	4.6 (1.01-21.1) p=0.05
Bicuspid valve	0.52 (0.23-1.2) p=0.13	0.6 (0.2-1.7) p=0.36
Sex	0.80 (0.32-1.96) p=0.62	0.7 (0.3-1.8) p=0.45
Surgical technique	0.20 (0.0-24.8) p=0.53	0.0 (0.0-0.0) p=0.98
Haemodynamic diagnosis		
AS	1.0	-
AR	1.5 (0.5-4.2) p=0.5	1.03 (0.3-3.2) p=0.96
AR+AS	0.9 (0.3-2.7) p=0.9	0.7 (0.2-2.4) p=0.56

HR = hazard ratio, with 95% confidence intervals (C.I.)

become pregnant benefit the most from this operation. However, with time we also observed an increase in reoperations related to the Ross operation, confirming the scepticism about the superior durability of this procedure.

In our prospective cohort study the survival of patients who undergo a Ross operation is excellent compared with survival of patients receiving other valve substitutes, and is even comparable with the general age-and gender-matched population. The question remains if this can be ascribed solely to the autograft procedure. Patient selection bias is not unlikely since our Ross patients are mainly patients who undergo elective surgery, present with no or mild symptoms of dyspnoea, usually have isolated aortic valve disease and a normal preoperative cardiac rhythm.[17] However, in the prospective randomised trial by Yacoub and colleagues, the pulmonary autograft was compared with the allograft, and a survival advantage on the long-term was observed in favour of the pulmonary autograft.[18]

Nevertheless, we observed a worrisome increase in autograft reoperations in the second decade after the Ross operation. The main cause for reoperation after the Ross operation is dilatation of the neo-aortic root. Due to this dilatation coaptation of the cusps is lost and aortic regurgitation occurs. Reporting a small but persistent increase in root dimensions and neo-aortic root regurgitation over time, a previous study by our institution anticipated that more reoperations would be necessary in upcoming years.[19] These findings are also confirmed by other studies.[8,10]

Although the exact causes of autograft root dilatation still have to be determined, several factors may play a role. One of those factors is the root replacement technique.

Performing the autograft root replacement technique requires surgical expertise and among surgeons application of this technique varies.[9] The autograft can be inserted at annular or subannular level and with or without scalloping the muscle rim to a minimum below the valve cusps. Also, continuous or interrupted sutures can be used for the proximal suture line. Finally, the length of the autograft root can vary. Some surgeons keep it as short as possible while others leave the complete length of the pulmonary artery distal to the sino-tubular junction of the pulmonary artery. (http://www.ctsnet.org/doc/2380)

In our institution, all reoperations were in patients who underwent the root replacement technique.

When the autograft is inserted as an inclusion cylinder, the native aorta is supporting the pulmonary autograft and may thus prevent it from dilatation. However, the number of autografts implanted as an inclusion cylinder in our institution is small and follow-up duration limited so any speculations should be interpreted with caution.

Sievers and colleagues[20] report the results of a single center, single surgeon's experience with another implantation technique, the subcoronary implantation technique. They show good functional results with only 2.6% of the patients requiring a reoperation thus far. However, their follow-up period does not extend beyond 10 years, and longer-term follow-up may prove differently. Also the subcoronary implantation technique is technically much more challenging.

Interestingly, in the reports on the Ross operation that showed a high incidence of reoperation, more than one surgeon performed the initial operation.[8,10,12] In studies where only one surgeon performed the Ross operation, incidence of reoperation was lower.[9,20] This suggests that larger experience is correlated with improved durability.

Another factor that is supposed to play a role in autograft dilatation is bicuspid valve disease.[21] It is known that a bicuspid aortic valve is associated with aortic wall abnormalities.[22] Since the pulmonary valve has the same embryonic origin as the aortic valve, these abnormalities could also be present in the pulmonary artery. Microscopic evaluation of pulmonary autografts reveals media abnormalities, intimal proliferation and adventitial fibrosis suggestive of chronic exposure to high pressure.[6,23,24] However, in a recent autograft explant study no association

was observed between bicuspid valve disease and histological changes in explanted pulmonary autografts.[25]

In the present study adult patient age tended to be associated with higher autograft reoperation rates (8% at 13 years for patients under the age of 16 years compared to 44% for adults). Other reports confirm the observation that fewer reoperations are seen in children.[26-28] However, Luciani *et al.* found an opposite effect of patient age on autograft dilatation, but not on reoperation.[10] A possible explanation is that the pulmonary autograft has the capacity to increase in diameter in the paediatric patient.[27] Whether it grows or simply dilates in line with somatic growth, in children is still a matter of debate.

Finally, patients who had previously undergone AVR (6 subcoronary homografts, 3 biological prostheses, 3 mechanical prostheses) may also be at greater risk for pulmonary autograft reoperation in the future. In this regard, it might be relevant that after complete removal of the valve substitute, the remaining fibrotic annular area is removed in part as well, without leaving a fixed plane for insertion of the pulmonary autograft.

Despite the high autograft reoperation rate in our study population, the pulmonary allograft is well preserved; only 8 patients required reoperation, which is comparable to other studies.[5,8] The main reason for allograft reoperation in the present study was degeneration with calcification of the allograft. Vogt *et al.*[28] determined in their study viability of cryopreserved allografts and found both total destruction of cellular elements in endothelial cells of allografts and immunological rejection in allografts used in the RVOT. Since the allograft is a non-viable valve substitute it is predisposed to calcify, and eventually at risk for reintervention and therefore affects the durability of the Ross operation on the longer term. Still, the ideal conduit for the RVOT in adults as well as in children has to be found. In the near future there might be an interesting role for tissue engineering for this valve substitute. Considering the limitations of the existing valve substitutes this new concept of creating a viable valve out of human cells shows encouraging results.[29]

Another recent development, percutaneous valve implantation, may be applied to the degenerated pulmonary allograft. Since stenosis is the main indication for undergoing percutaneous valve replacement and since the homograft in the RVOT is subject tot calcification, this could be an alternative to surgery.[30]

During follow-up, endocarditis and thromboembolic complications were uncommon in our study patients; bleeding events and valve thrombosis did not occur. This

underlines that, in this regard, the Ross operation indeed allows patients to live their life to the fullest.

Clinical implications

In our center the Ross operation is now an operation performed only in infants and children. In adults it has been abandoned because of the high reoperation rate and because of the great complexity and difficulties that may be encountered at the eventual reoperation.

Other alternatives for the Ross operation are the mechanical prosthesis, bioprosthesis and homograft with their advantages and disadvantages. Mechanical prostheses are designed to last a lifetime but require lifelong anticoagulation therapy due to their increased thrombogenicity. Even though anticoagulation therapy is relatively safe, it does increase the risk of bleeding complications. For smaller children no artificial valves of adequate size are available and the Ross operation remains the solution of choice. Furthermore, in children or patients who want to life an active lifestyle it is preferable to avoid the use of anticoagulation therapy. And also for women in child bearing age the mechanical prosthesis has several disadvantages, including not only a higher mortality risk during pregnancy mainly due to valve thrombosis, but also an higher risk of embryopathy with oral anticoagulants.[31]

After the Ross operation patients require no anticoagulation therapy, similar to the bioprosthesis and homograft. However, tissue valves have a limited durability and therefore the patient almost certain requires a reoperation later in life. Because of the large number of patients who return to center for reoperation in the second decade after the initial procedure, we need to ensure close follow-up of the patients and be prepared for more reoperations in the near future.

Conclusions

While the Ross operation is associated with excellent patient survival in our institution, there is a considerable increase of autograft failure requiring reoperation. Careful follow-up is necessary in the second decade after the operation and greater insight into the mechanism of the pulmonary autograft dilatation is needed.

Finally, uniform well-defined and detailed technical guidelines for autograft root replacement need to be established if the Ross operation is to be maintained as a surgical option for aortic valve replacement with optimal benefits and enhanced durability for the patients.

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Chapter 10

Case Report: Dissection Of A Dilated Autograft Root

Dissection of a dilated autograft root. Klieverik LMA, Takkenberg JJM, Elbers BC, Oei FB, van Herwerden LA, Bogers AJJC. *J Thorac Cardiovasc Surg. 2007 Mar;133(3):817-8*

Although the Ross procedure is still the favourable operation for aortic and root replacement in children and young adults, in recent years the number of reoperations for autograft root dilatation after the Ross procedure has increased. (1-4)
In our ongoing prospective clinical and echocardiographic follow-up study of 146 consecutive patients undergoing a Ross procedure with the root replacement technique since 1988, to date 29 patients have undergone pulmonary autograft reoperation. In most cases valve cusps are intact but due to progressive autograft root dilatation coaptation of the cusps is lost and aortic valve regurgitation occurs. We report a patient who presented with severe aortic regurgitation due to asymmetrical autograft dilatation caused by a dissection in the non-coronary sinus of Valsalva.

Clinical summary

A 50-year-old female patient with a bicuspid native aortic valve, symptomatic moderate aortic regurgitation and dilated left ventricle with good systolic function, who had undergone a modified Ross procedure using the root replacement technique, returned 9 years after this procedure for reoperation. The patient had complaints of fatigue and dyspnoea on exertion. Echocardiographic examination 4 months prior to reoperation showed severe aortic and pulmonary regurgitation, a dilated left ventricle with end-diastolic diameter of 62 mm and end-systolic diameter of 48 mm. Furthermore, the ascending neo-aorta was severely dilated with a diameter of 54 mm.
At reoperation the neo-aortic root showed asymmetric dilatation with bulging of the non-coronary sinus of Valsalva. After opening the neo-aortic root, in the non-coronary sinus of the autograft root a large transverse intimal tear that extended into the media was seen, causing the asymmetric dilatation (see Figure 1). This tear was limited to the autograft wall and had no connection with the distal suture line. The autograft valve leaflets appeared normal. The pulmonary autograft was replaced with a mechanical valve conduit size 25 mm (St. Jude Medical Inc.) and the pulmonary allograft with a cryopreserved pulmonary allograft. The procedure and postoperative course were uneventful.
Microscopic examination revealed a viable pulmonary autograft valve and neo-aortic wall. The valve leaflets showed intimal hyperplasia on the ventricular side and intimal and adventitial fibrosis of the neo-aortic wall was present. In addition, throughout the media cystic medial necrosis with fragmentation, loss of elastic fibres and deposition of mucopolysaccharides were found. The tear of the neo-aortic wall extended beyond the intima into the media. The defect was already covered with

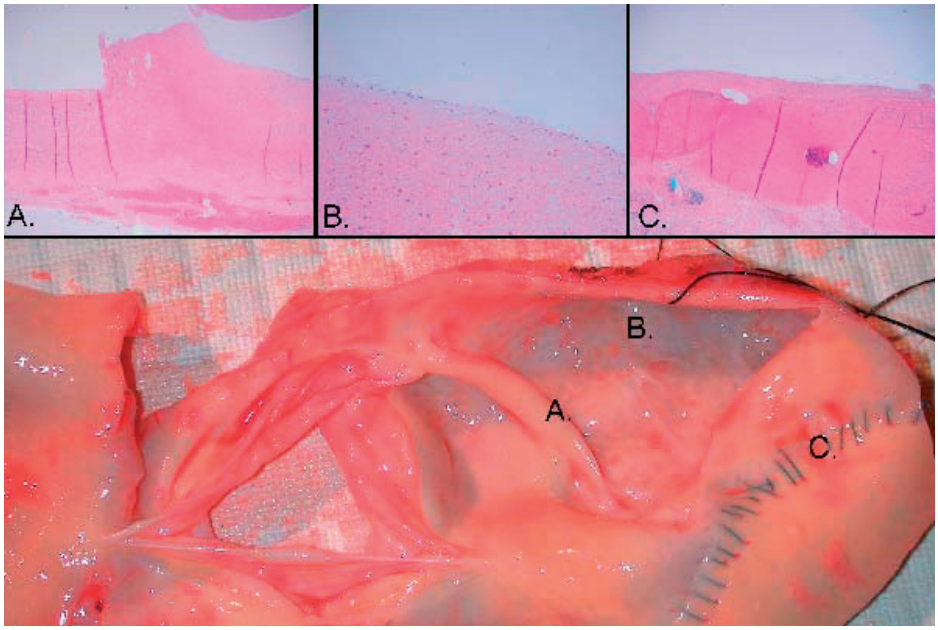

Figure 1. Explanted autograft root with a transverse dissection of the non-coronary sinus.

mucopolysaccharides, but without neo-endothelization suggesting that this tear was at least a few months old, but existed no longer than one year.

Discussion

In most of the 29 reoperative autograft cases in our institution progressive dilatation of the neo-aortic root resulting in aortic regurgitation necessitated reoperation. Histological findings in the explanted autografts comprised cystic medial necrosis with fragmentation, loss of elastic fibres and deposition of mucopolysaccharides. (1) The current case is different from the other reoperative autograft cases in our experience and raises concern for the following reasons.

The asymmetrical root dilatation was a result of an intimal tear of the non-coronary sinus extended into the media causing a limited dissection that potentially could lead to a free wall rupture. The autograft dissection presented 9 years after the initial Ross procedure. Luciani and colleagues previously reported an autograft dissection 8.5 years after the initial Ross procedure.(5) This dissection also occurred in the non-coronary sinus suggesting possible vulnerability of this specific location to rupture. Their intima rupture was in longitudinal direction and did not interfere with any of the suture lines (personal communication). Aortic dissection is usually characterized by longitudinal cleavage of the aortic media by a dissecting column of

blood, which was neither present in Dr Luciani's nor our own explanted autograft root.

A new observation emerging from our report is that apparently with progressive dilatation of the neo-aortic wall it becomes increasingly weak and may be prone to rupture late after the initial Ross procedure.

Furthermore, the dissection in the neo-aortic wall existed for months without any clinical signs. Due to the limited size of the intimal tear and denervation of the neo-aortic root, the patient does not complain of pain and this potentially lethal complication is hard to recognize without careful echocardiographic monitoring.

In conclusion, this report illustrates that the pulmonary autograft not only can show dissection but may also rupture causing a potentially life threatening complication. High awareness of potential neo-aortic root dissection is required in all autograft root patients and particularly those patients whose autograft root gradually dilates over the years.

Therefore, continuing and frequent systematic echocardiographic surveillance of this patient group is highly recommended also in the second decade after the operation.

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Chapter 11

Characteristics And Outcome Of Reoperative Aortic Root Replacement

Characteristics and Outcome of Reoperative Aortic Root Replacement. Bekkers JA, Klieverik LMA, Bol Raap G, Takkenberg JJM, Bogers AJJC. *Submitted*

Abstract

Background

Reoperative aortic root replacement(RARR) is complex and a high risk operation. We studied outcome of patients who underwent RARR after previous surgery on aortic valve, aortic root or ascending aorta.

Methods

Between 1981 and 2006, 141 consecutive patients underwent 156 RARRs at our institution. Patient and peri-operative characteristics, short and long-term outcome were analyzed.

Results

Mean age was 37 years(0.3-76 years). RARR was performed on 56 prosthetic valves(PV), 23 allografts(ALLO), 28 pulmonary autografts(AUTO) and 49 native valves(NV).

RARR indications were: structural failure 46%(n=72), neo-aortic root dilatation 18%(n=28), aneurysm/dissection 13%(n=21), endocarditis 15%(n=24), non-structural failure 6%(n=10) and valve thrombosis 1%(n=1). Thirty-six percent(n=56) received an allograft, 34%(n=54) an aortic valve conduit(Bentall) and 30%(n=46) a pulmonary autograft.

Hospital mortality was 9%(n=14): 14%(n=8) PV patients, 13%(n=3) ALLO patients, 6%(n=3) NV patients, and 0% AUTO patients died. Potential hospital mortality predictors were longer perfusion and cross clamp time, older patient age, female gender, unplanned CABG, concomitant mitral valve replacement and emergency surgery.

During follow-up(mean 6.5years, range 0-18years) 13 patients died(LOR 1.3%/patient year); 8 PV patients, 1 ALLO patient, 3 NV patients and 1 AUTO patient.

Overall 10-year survival was 78%±4%; for PV patients 65%±8%, for ALLO patients 82%±8%, for NV patients 87%±5% and for AUTO patients 96%±4%.

Conclusions

RARR can be safely performed. Especially, pulmonary autograft reoperation has low hospital mortality and morbidity rates with excellent survival. In this respect, these results may contribute to decision making in valve substitute selection in primary aortic valve replacement, especially in adolescents and young adults.

Keywords: reoperation, aortic root, heart valve (allograft), heart valve (autograft), statistics, survival analysis

Introduction

Primary aortic root replacement (ARR) is a reliable and relatively safe operation with a low mortality rate, especially in the elective setting and regardless of the composite graft used.[1-3] Recent developments in aortic valve and root surgery, including valve sparing procedures on the aortic root, pulmonary autograft implantation, aortic allograft implantation and aortic valve preservation in acute aortic dissection, will lead to an increasing incidence of secondary ARR after these procedures. Reoperative ARR is a complex and high risk operation. In particular reopening of the chest with possible adherence of the aorta to the sternum and the need for mobilization and reimplantation of the coronary arteries may contribute to the high risk character of the operation and therefore to a higher expected mortality risk in these patients.[4-6] In our centre we have performed a high volume of pulmonary autograft procedures and aortic allograft implantations over the past 2 decades. The use of these valve types has been questioned and recent reports have shown an increasing incidence of reoperations when using allograft and pulmonary autograft as valve substitutes in aortic valve or root replacement.[7-11] Furthermore, these reoperations are complex due to extensive calcification of the allograft wall and at annular level and due to dilatation of the autograft, which might negatively influence reoperative and long-term outcome.[12-14]

In this perspective we analyzed our experience in reoperative aortic root replacement after surgery on the aortic valve, the ascending aorta or both.

Patients and Methods

Patients

Between 1981 and 2006 141 patients underwent 156 aortic root replacements as a reoperation. All patients underwent RARR after aortic valvulotomy, aortic valve replacement, aortic root replacement or surgery on the ascending aorta. All patients who receive an autograft or allograft in aortic position in our center are enrolled in our ongoing prospective follow-up study.[14-17] Approval from the Institutional Review Board was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent. Patients who underwent previous isolated coronary artery bypass grafting or other cardiac procedures that were not aortic valve-related were not included. In fifty-six patients a prosthetic valve (PV) was replaced (36 mechanical prostheses and 20 bioprostheses), in 23 patients an allograft (ALLO), in 28 patients a pulmonary autograft (AUTO) and in 49 patients the native valve (NV). In the latter group 36 patients had previously undergone aortic valve

Table 1. Patient characteristics per valve substitute in situ before RARR

	All valves (n=156)	Prosthetic valve (n=56)	Native valve (n=49)	Allograft (n=23)	Autograft (n=28)
Mean age (yrs, (range))[a]	37 (0.3-76)	51 (7-76)	22 (0.3-61)	38(16-65)	34 (15-50)
Male gender[a]	69% (n=107)	73% (n=41)	53% (n=26)	87% (n=20)	71% (n=20)
Systolic LVF					
Good[a]	80% (n=125)	71% (n=40)	90% (n=44)	78% (n=19)	82% (n=23)
Impaired	14% (n=22)	18% (n=10)	10% (n=5)	9% (n=2)	18% (n=5)
Moderate/bad	6% (n=9)	11% (n=6)	-	13% (n=3)	-
Cardiac rhythm					
Sinus rhythm	90% (n=141)	86% (n=48)	96% (n=47)	82% (n=19)	96% (n=27)
Atrial fibrillation	4% (n=6)	5% (n=3)	-	9% (n=2)	4% (n=1)
Other	6% (n=9)	9% (n=5)	4% (n=2)	9% (n=2)	-
Creatinin (µmol/L)	79 (22-305)	95 (32-305)	61 (22-142)	79 (58-125)	79 (61-110)
NYHA					
I	37% (n=57)	32% (n=18)	41% (n=20)	26% (n=6)	46% (n=13)
II/III	31% (n=49)	43% (n=24)	53% (n=26)	65% (n=14)	54% (n=15)
IV/V[a]	32% (n=19)	25% (n=14)	6% (n=3)	9% (n=2)	-
Hemodynamic diagnosis					
AR[a]	53% (n=83)	53% (n=30)	20% (n=10)	61% (n=14)	100% (n=28)
AS[a]	20% (n=31)	13% (n=7)	47% (n=23)	4% (n=1)	-
AR+AS	18% (n=28)	13% (n=7)	31% (n=15)	26% (n=6)	--
None[a]	10% (n=15)	21% (n=12)	2% (n=1)	9% (n=2)	
Time interval (years,(range))	8 (0-33)	6 (0-20)	9 (0-33)	7 (0-14)	10 (4-16)
Indication RARR[a]					
SVD	47% (n=72)	18% (n=10)	84% (n=41)	92% (n=21)	-
NSVD	6% (n=10)	16% (n=9)	-	4% (n=1)	-
Endocarditis	15% (n=24)	41% (n=23)	2% (n=1)	-	-
Active	*12% (n=18)*	*n=18*	-	-	-
Aneurysm/dissection	13% (n=21)	23% (n=13)	14% (n=7)	4% (n=1)	100% (n=28)
RD and/or AR	18% (n=28)	-	-	-	-
Valve thrombosis	1% (n=1)	2% (n=1)	-	-	
Preop ventilation support	5% (n=8)	5% (n=3)	8% (n=4)	4% (n=1)	-
Type surgery[a]					
Emergent	5% (n=7)	9% (n=5)	2% (n=1)	4% (n=1)	-
Urgent	30% (n=47)	57% (n=32)	10% (n=5)	26% (n=6)	14% (n=4)
Elective	65% (n=102)	34% (n=19)	88% (n=43)	70% (n=16)	86% (n=24)

[a] Significant differences between the groups with $p<0.05$

AR= aortic regurgitation, AS= aortic stenosis, LVF = left ventricular function, NSVD= non-structural valve degeneration, NYHA = New York Heart Association, Other cardiac rhythm = pacemaker rhythm and heart block, RD = autograft root dilatation, SVD= structural valve degeneration, Time interval = mean time interval between last aortic valve-related or ascending aorta-related operation and root re-replacement

repair or a valvulotomy, 7 patients had had surgery of the ascending aorta for acute aortic dissection and 6 patients had had surgery of a discrete subaortic stenosis. Preoperative patient characteristics are displayed in Table 1. For patients who had an allograft or pulmonary autograft inserted at primary operation or reoperation, information was collected from the ongoing prospective cohort study.[15] For all other patients, information on patient characteristics, perioperative details and follow-up was collected retrospectively from hospital records, correspondence with the treating physicians and through the civil registry.

Surgical procedures

All operations were performed through a median sternotomy and on cardiopulmonary bypass with moderate hypothermia. We used central canulation in the ascending aorta and right atrium or caval veins. To anticipate on possible perforation of the heart or aorta when reopening the chest, we instituted cardiopulmonary bypass with canulation of the femoral vessels and deep cooling of 9 patients before performing the sternotomy. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Total circulatory arrest with deep hypothermia was needed in 30 patients with ascending aorta or arch pathology.

In patients with a native aortic valve or valve prosthesis in situ, root replacement followed the removal of the valve or the prosthesis. In patients with an allograft in situ it was necessary to remove all calcified allograft material before root replacement. The original coronary buttons were dissected from the allograft aortic wall. In patients with a pulmonary autograft in situ, the neo-aortic root was in most cases dilated without any signs of root or valve calcification. After opening the autograft root, the autograft valve leaflets were excised and the coronary buttons mobilized. Excess autograft wall tissue was removed, leaving parts of the autograft at annular level in situ.

Mortality and Follow up

Mortality and other valve-related events were registered according to the guidelines for reporting morbidity and valve-related events.[18] The database was frozen on January 1st, 2007. Follow-up was 93.7% complete.[19] Three patients were lost to follow-up due to emigration.

Statistical analysis

For data analysis SPSS 12.0.1 for Windows was used (SPPS, Chicago, Illinois). Descriptive statistical analysis was done for preoperative and perioperative data. Continuous variables are displayed as mean ± 1 SD and compared using the unpaired T-test or Kruskal Wallis-test. Discrete variables are displayed as proportions and

compared using the Chi-square Test. Univariable logistic regression was used to determine factors of different valve substitute groups and to determine potential risk factors for hospital mortality. The following factors were analyzed: age at operation (continuous variable), sex, time period of operation (before and after 1998), New York Heart Association Class (defined as I, II, III IV, and cardiogenic shock as NYHA V), preoperative creatinin level (micromoles/L), preoperative ventilation support, abnormal cardiac rhythm preoperative (other rhythm preoperative than sinus rhythm), left ventricular function (defined as good when ejection fraction was >50%, impaired when ejection fraction was 40-50% and moderate/bad when ejection fraction was <40%), emergent surgery (<24hrs after diagnosis), concomitant procedures, indication for reoperation, active endocarditis (operated on before completing a standard course of antibiotics), cardiopulmonary bypass time (in minutes) and cross clamp time (in minutes). The variable valve prosthesis type used at reoperation was additionally analysed to determine its possible influence on hospital mortality.

Cumulative survival, freedom from reoperation and freedom from valve-related events were analyzed with the Kaplan Meier method. The Log-Rank test was used to compare the Kaplan-Meier curves and Tarone-Ware test was used where appropriate to correct for significant differences in follow-up time between the different groups. The Cox regression proportional hazards model was used for univariable analysis for time-related events. The following factors were analyzed: age at operation, sex, time period of operation, NYHA class, preoperative creatinin level, preoperative ventilation support, abnormal cardiac rhythm, preoperative left ventricular function, active endocarditis, emergent surgery, concomitant procedures, valve prosthesis type used at reoperation, cardiopulmonary bypass time and cross clamp time. A p-value ≤ 0.05 was considered statistically significant. All testing was two-sided.

Results

Perioperative details are displayed in Table 2. In 46 patients a pulmonary autograft was inserted, in 56 patients an allograft root replacement, and in 54 patients an aortic valved conduit (Bentall procedure).

Determinants of different valve substitute groups

Patients who received an allograft were more likely to be older (OR 1.04, 95% CI 1.02-1.06; p<0.001), had a prosthetic valve in situ (OR 8.3, 95% CI 3.9-17.5; p<0.001), endocarditis as the indication for reoperation (OR 13.3, 95% CI 4.3-41.7; p<0.001), were in NYHA class IV or V (OR 6.3, 95% CI 2.1-18.7; p=0.001), had an

Table 2. Perioperative data per valve substitute in situ before RARR

	All valves (n=156)	Prosthetic valve (n=56)	Native valve (n=49)	Allograft (n=23)	Autograft (n=28)
CPB time[a] (min, (range))	236 (79-685)	246 (79-660)	217 (116-685)	278 (118-542)	214 (115-389)
Cross clamp[a] (min, range))	151 (61-331)	158 (61-302)	139 (70-240)	175 (79-331)	137 (85-271)
Circulatory arrest[a] (min,((range))	n=30 27 (2-99)	n=9 20 (10-34)	n=5 55 (16-99)	n=7 22 (7-48)	n=9 22 (2-59)
Valve type inserted[a]					
Aortic valved conduit (Bentall)	35% (n=54)	20% (n=11)	12% (n=6)	52% (n=12)	89% (n=25)
Allograft root	35% (n=56)	67% (n=38)	22% (n=11)	22% (n=5)	11% (n=3)
Pulmonary autograft	30% (n=46)	13% (n=7)	66% (n=32)	26% (n=6)	-
Concomitant procedures					
Planned CABG	3% (n=4)	4% (n=2)	-	9% (n=2)	-
Unplanned CABG	2% (n=3)	2% (n=1)	3% (n=2)	-	-
MVR	3% (n=4)	7% (n=4)	-	-	-
MVP	4% (n=6)	4% (n=2)	-	9% (n=2)	7% (n=2)
PVR[a]	3% (n=5)	2% (n=1)[b]	-	-	14% (n=4)
Extended root	26% (n=17)	16% (n=9)	12% (n=6)	17% (n=4)	25% (n=7)
Other	14% (n=22)	7% (n=4)	20% (n=10)	4% (n=1)	25% (n=7)
Complications					
Rethoracotomy	17% (n=26)	23% (n=13)	10% (n=5)	26% (n=6)	7% (n=2)
Stroke	2% (n=3)	4% (n=2)	-	-	3% (n=1)
Myocardial infarction	1% (n=1)	-	2% (n=1)	-	-
Permanent pacemaker	1% (n=2)	2% (n=1)	2% (n=1)	-	-
Hospital death	9.0% (n=14)	14% (n=8)	6% (n=3)	13% (n=3)	0%

[a] Significant differences between the groups with $p<0.05$, [b] Other than the autograft procedure
CABG = coronary artery bypass grafting, MVP= mitral valve repair, MVR= Mitral valve replacement, Other= including surgery for discrete subaortic stenosis, closure patent ductus arteriosus and tailoring ascending aorta

impaired left ventricular function (OR 3.8, 95% CI 1.5-9.8; p=0.005), underwent more urgent surgery (OR 3.3, 95% CI 1.6-6.6; p=0.001) and had an increased preoperative creatinin level (OR 1.02, 95% CI 1.01-1.03; p=0.008).

Patients who received a Bentall procedure were also more likely to be older (OR 1.02, 95% CI 1.003-1.04; p=0.02), had a previously inserted pulmonary autograft (OR 28.4, 95% CI 8.0-101.0 p<0.001) and had an aortic aneurysm as the indication for reoperation (OR 5.6, 95% CI 2.0-15.6; p=0.001). Finally, patients who received a pulmonary autograft were more likely to be younger (OR 1.09, 95% CI 1.06-1.12; p<0.001), had a normal preoperative creatinin level (OR 1.04, 95% CI 1.02-1.06; p<0.001), a good left ventricular function (OR 3.4, 95% CI 1.1-10.4; p=0.03) and underwent more elective surgery (OR 4.1, 95% CI 1.7-10.1; p=0.002).

Early morbidity and mortality

A total of 14 patients died in hospital (9.0%). Details on hospital deaths are shown in Table 3.

Patient 3 died on the first day after RARR due to a perioperative myocardial infarction caused by a kink in the reimplanted right coronary artery.

Patient 5 died on the 5th day after RARR due to multi organ failure. One day previously to RARR the patient received a biological prosthesis. The patient required reoperation for bleeding and a perioperative complication necessitated RARR.

Patient 8 died on the 22nd day after RARR. Indication for RARR was an aortic dissection 60 days after aortic valve replacement with a bioprosthesis.

Patient 10 died on the 5th day after RARR. On the same day as the RARR a subcoronary allograft was implanted but required replacement due to technical failure.

Patient 12 was a 6 month old child with congenital mitral valve and aortic valve abnormalities, underwent previously aortic and mitral valve repair and surgery of a discrete subaortic stenosis, and died during RARR of heart failure.

Patient 13 died during RARR of heart failure after CABG as a procedural complication.

Potential predictors of hospital mortality were longer perfusion time (OR 1.01, 95% CI 1.01-1.02; p<0.001), longer cross clamp time (OR 1.02, 95% CI 1.01-1.04; p<0.001), older patient age (OR 1.07, 95% CI 1.03-1.10; p=0.001), female gender (OR 3.3, 95% CI 1.1-10.1; p=0.04), abnormal cardiac rhythm preoperative (OR 7.3, 95% CI 2.1-26.1; p=0.02), NYHA class IV or V (OR 10.8, 95% CI 3.3-36.1; p<0.001), concomitant mitral valve replacement (OR 11.7, 95% CI 1.5-90.3; p=0.02), preoperative ventilation support (OR 14.7, 95% CI 3.1-68.5; p=0.006), emergency surgery (OR 18.5, 95% CI 3.6-94.5; p<0.001) and unplanned CABG (OR 23.3, 95% CI 1.9-278.3; p=0.01). A good left ventricular function was associated with a lower hospital mortality (OR 0.2, 95% CI 0-07-0.63; p=0.006). The type of valve prosthesis type used at RARR had no effect on hospital mortality.

Follow-up and survival

Mean follow-up was 6.2 years, range 0-18.3 years with total follow-up of 973 patient years.

For PV patients mean follow-up was 6.2 years, range 0-16.3 years with total follow-up of 347 patient years. For NV patients mean follow-up was 9.3 years, range 0-18.3 years with total follow-up of 455 patient years. For ALLO patients mean follow-up was 4.8 years, range 0-14.4 years with total follow-up of 110 patient

Table 3. Details on hospital deaths

Nr	In situ valve	Age RARR	Time since previous operation	Indication RARR	Implanted	Cause of death	Days postop
1	Prosthetic	65	0.9 years	Endocarditis	Allograft	Heart failure	Peroperative
2	Prosthetic	69	19.8 years	Endocarditis	Allograft	Myocardial infarction	Peroperative
3	Prosthetic	74	17 days	Endocarditis	Allograft	Myocardial infarction	1
4	Prosthetic	53	8.1 years	NSVD	Allograft	Heart failure	4
5	Prosthetic	71	1 day	NSVD	Allograft	Multi organ failure	5
6	Prosthetic	66	9.7 years	NSVD	Allograft	Heart failure	23
7	Prosthetic	63	5.8 years	Aneurysm ascending aorta	Allograft	Heart failure	34
8	Prosthetic	61	60 days	Dissection ascending aorta	Bentall	Heart failure	22
9	Allograft	49	14.4 years	SVD	Bentall	Heart failure	Peroperative
10	Allograft	63	0 days	SVD	Allograft	Heart failure	5
11	Allograft	65	14.0 years	SVD	Bentall	Heart failure	16
12	Native valve	0.3	31 days	SVD	Pulmonary autograft	Heart failure	Peroperative
13	Native valve	40	9.2 years	SVD	Pulmonary autograft	Heart failure	Peroperative
14	Native valve	24	13.7 years	SVD	Pulmonary autograft	Mediastinitis + sepsis	13

NSVD= non structural failure, SVD= structural failure

years. For AUTO patients mean follow-up was 2.1 years, range 0.1-8.8 years with total follow-up of 58 patient years.

During follow-up 13 patients (LOR 1.3%/patient year) died; 8 PV patients, 3 NV patients, one ALLO patient and one AUTO patient died. Table 4 shows details on late deaths.

Overall 10-year survival after RARR was 78.3%±4.0%. For PV patients 10-year survival was 65.4%±7.6%, for NV patients 86.6%±5.2%, for ALLO patients 82.4%±8.0% and for AUTO patients 10-year survival was 96.4%±3.6% (p=0.06). See also Figure 1.

Potential predictors for late mortality were longer perfusion time (HR 1.01, 95% CI 1.003-1.01; p=0.001), older patient age (HR 1.04, 95% CI 1.004-1.07; p=0.03), preoperative increased creatinin level (HR 1.01, 95% CI 1.001-1.02; p=0.03), active endocarditis (HR 4.1, 95% CI 1.2-13.7; p=0.02), abnormal cardiac rhythm

Table 4. Details on late deaths

Nr	In situ valve	Indication RARR	Implanted	Cause of death	Years postop
1	Prosthetic	Endocarditis	Allograft	Endocarditis	1.5
2	Prosthetic	SVD	Allograft	SUUD	2.3
3	Prosthetic	NSVD	Allograft	Heart Failure	3.8
4	Prosthetic	Endocarditis	Allograft	Cancer	3.8
5	Prosthetic	Endocarditis	Allograft	Heart Failure	6.2
6	Prosthetic	Endocarditis	Allograft	COPD	8.2
7	Prosthetic	Aneurysm ascending aorta	Allograft	Heart Failure	10.4
8	Prosthetic	Aneurysm ascending aorta	Bentall	Heart failure	0.2
9	Allograft	SVD	Allograft	Heart Failure	0.3
10	Pulmonary autograft	SVD	Bentall	Myocardial infarction	0.1
11	Native	Aortic dissection	Allograft	Myocardial infarction	0.3
12	Native	Aneurysm ascending aorta	Allograft	Heart Failure	4.3
13	Native	SVD	Allograft	Traumatic intracerebral bleeding	8.4

RARR= reoperative aortic root replacement, NSVD= non-structural valve degeneration, SUUD = sudden unexplained unexpected death, SVD= structural valve degeneration

preoperative (HR 4.4, 95% CI 1.2-16.2; p=0.03), the use of an allograft root at RARR (HR 10.0, 95% CI 2.2-45.5; p=0.003) and concomitant mitral valve repair (HR 23.6, 95% CI 5.6-99.5; p<0.001). RARR on a prosthetic valve showed a trend to be a risk factor for late mortality (HR 2.8, 95% CI 0.9-8.6; p=0.07).

Valve-related events

One PV patient, who received an allograft root at RARR, underwent an aortic valve re-reoperation for structural failure. The allograft was replaced 9.7 years after RARR by a stentless bioprosthesis and the patient survived the procedure. One patient who received an allograft root at RARR had a non-fatal stroke after 14.1 years. Four patients had a TIA during follow up; one patient who underwent a Bentall procedure at RARR had a TIA after 0.1 years and three patients who received an allograft at RARR had a TIA respectively after 0.3, 3.6, and 4.5 years, of which one patient had two TIAs in the first year after RARR at 0.3 and 0.5 years, respectively. Linearized occurrence rates for thrombo-embolic complications were 1.2%/patient year for RARR with an allograft and 0.65%/patient year for RARR with a Bentall procedure. One patient who received an autograft at RARR had a late episode of recurrent endocarditis after 8.8 years (LOR 0.20%/patient year) and

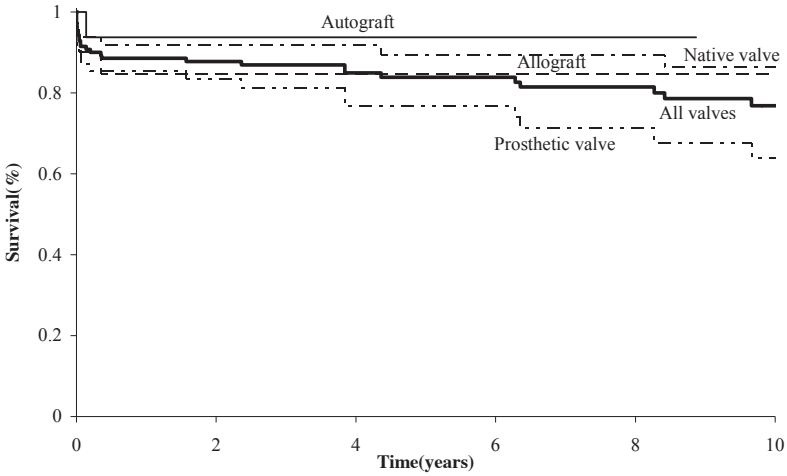

Figure 1 Patient survival after reoperative aortic root replacement per valve substitute in situ

one allograft recipient at RARR had an episode of recurrent endocarditis after 1.5 years (LOR 0.30%/patient year). Both patients were treated medically and survived. No bleeding events, valve thrombosis, or non-structural failure were observed.

Comment

Reoperative aortic root replacement remains a high risk and demanding procedure, however, our study shows that it can be performed with satisfying results, regarding operative mortality and long term survival.

Hospital mortality

Overall hospital mortality after reoperative aortic root replacement is comparable to other series that report on hospital mortality after this type of surgery.[4,6,20] Hospital mortality for RARR after a previously inserted prosthetic valve was 14% in our study. Although this seems high compared with most of the other valve substitutes, in the majority of these patients endocarditis was the indication for reoperation. Most of these patients were severely symptomatic, had an impaired left ventricular function and often underwent emergent or urgent surgery, which were all potential predictors of hospital mortality. This is also described by David and colleagues.[20] Furthermore, surgery for prosthetic valve endocarditis is known to be associated with a higher urgency of surgery and a high hospital mortality rate,[21,22] which can explain the high hospital mortality risk in these patients in our study.

Reoperative aortic root replacement after a previous allograft valve or root replacement in our study resulted in 13% hospital mortality. A possible explanation

for this might be that RARR after a previous allograft implantation is a technically difficult and demanding procedure. It is complicated to make a proper proximal anastomosis due to the fact that the allograft not only calcifies in the part of the root but also at the annular level. Furthermore, the coronary buttons need to be dissected from the calcified allograft making it difficult to maintain a large enough button that can be properly reinserted without distortion or kinking. In some patients unforeseen bypass grafting is necessary. These factors contribute in our study to a significantly longer CPB time and aortic cross clamp time compared with the other groups, which are potentially associated with higher hospital mortality in our study.

Patients who had their native valve in situ and required RARR had a hospital mortality rate of 6%. All patients that died underwent a pulmonary autograft procedure. A pulmonary autograft procedure carries more risk than a conventional root replacement, especially as a reoperation, but after successful operation survival of these patients is comparable to the age-matched general population.[11]Patients reoperated on their native valve are the youngest of all study groups with low co-morbidity and required in most cases an elective reoperation with almost no concomitant procedures.

The pulmonary autograft procedure is the optimal solution in pediatric patients requiring aortic valve replacement.[23,24].Many studies favor the pulmonary autograft procedure also in young adult patients [14,25,26], but enthusiasm for this operation has been tempered in recent reports due to the high incidence of reoperations.[8,11,27]However, in this study reoperation after the pulmonary autograft procedure shows a much better outcome with 0% hospital mortality so far, suggesting that reoperation after this procedure can safely be performed. This is comparable to the findings of Brown and colleagues.[28] Main indication for reoperation was an aneurismal dilatation of the aortic root causing aortic valve regurgitation. Although an aneurismal aortic root is still difficult to reoperate on, it takes lesser effort to explant a dilated autograft root than a calcified allograft root. The dilated aortic root allows a clear view at the insufficient autograft and its dilated annulus, on which an anastomosis is easier to perform. Furthermore, the dilated pulmonary autograft wall shows no signs of calcification.[12] Although a reoperation after the pulmonary autograft procedure also requires reinsertion of the coronary arteries, the coronary buttons can be maintained to a larger size in absence of calcification which necessitates resizing. However, reinsertion of the coronaries after a pulmonary autograft is also not without the risk of kinking of the coronary arteries sometimes necessitating coronary bypass grafting.

Three patients required an unplanned CABG due to distortion of the coronaries as a procedural complication; two autograft patients and one allograft patient, of which one autograft patient and one allograft patient died. In our study the need for an unplanned CABG is potential associated with a higher hospital mortality, which is also reported in other series.[4]

Long-term survival

The overall 10-year survival in our study is 78% at 10 years and is satisfactory and even better compared with other reports.[4,6,20]Comparing the four study groups, it shows that reoperation with a pulmonary autograft has the best long-term survival. Reoperation with an allograft root after previous surgery on the aortic valve or ascending aorta was one of the potential predictors of late mortality in our study and is also shown in Figure 2. Most of the allograft recipients were older patients with prosthetic valve endocarditis, which implies that not the inserted allograft but mostly patient and operative characteristics contributed to the increased late mortality we observed in allograft recipients.

Limitations

The partially retrospective nature of study may have lead to an underestimation of the valve-related events during follow-up which might have influenced our results. Furthermore, the four study groups differ in baseline characteristics which make comparisons between the groups difficult.

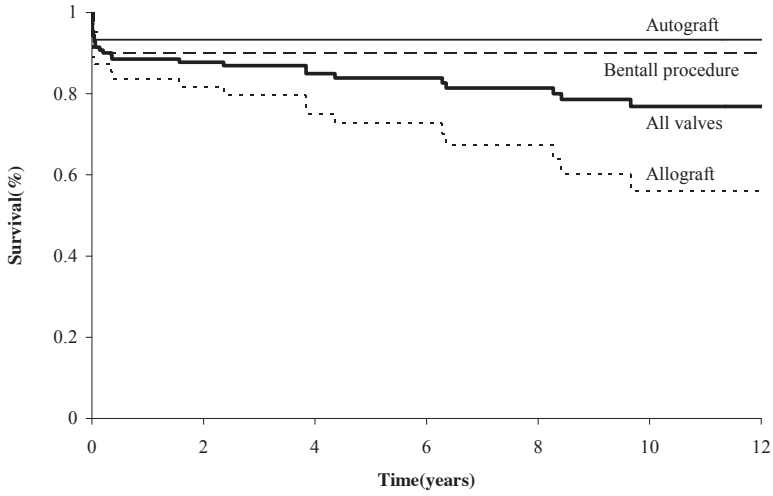

Figure 2 Patient survival after reoperative aortic root replacement per valve substitute inserted at reoperation

Conclusions

Our study indicates that reoperation after previous surgery on the aortic valve, ascending aorta or both, can be safely performed. Although several patient factors play role, reoperation after a pulmonary autograft procedure has low hospital mortality and morbidity rates with long-term survival that is better compared with patients in which a reoperation is necessary after native valve repair or valvulotomy, a previous inserted allograft or prosthetic valve. In this respect, these results may contribute in the decision making in selecting the proper valve substitute in primary aortic valve replacement, especially in adolescents and young adults.

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Chapter 12

General Discussion

The aim of this thesis was to gain insight into the determinants of prognosis after aortic valve replacement in young adult patients with the different available valve substitutes and to study whether there is a preferred valve substitute for this particular age group. From the studies in this thesis it has become clear that prognosis of young adults who require aortic valve replacement is determined by multiple interrelated factors that are at least in part also affecting prosthetic valve selection. These observations will be discussed below by:

1. Providing an overview of valve substitute-related factors that influence prognosis and discuss the magnitude of their impact on patient prognosis found in the studies in this thesis
2. Evaluating patient-related factors associated with prognosis and prosthetic valve selection that were found in the studies in this thesis
3. Commenting on other factors that may be important for prosthetic valve selection

Furthermore, it will be discussed how these new insights obtained in the studies in this thesis may help clinicians to optimize prosthetic valve selection in young adult patients. Finally, recommendations with regard to future research will be presented.

Valve Substitute-Related Factors

When selecting a prosthetic aortic valve type for young adult patients who have a relatively long life expectancy, the increased hazard of thrombo-embolism and bleeding associated with the use of mechanical prostheses is weighed against the increased hazard of structural failure when using tissue valves.

Mechanical prostheses, durable and easy to implant

Mechanical prostheses are designed to last a life time, and the risk of a reoperation, although not absent, is very low.

A major disadvantage of these valve substitutes is the required anticoagulation treatment with a high risk of thrombo-embolic complications and bleeding events.[1] Especially in younger patients, who lead an active lifestyle or young females who may want to become pregnant later in life, these valve substitutes may not always be the valve of choice, due to their increased thrombogenicity, increased bleeding hazard and maternal and fetal morbidity and mortality associated with anticoagulant use. [2, 3]

In Chapters 2, 4 and 11 mechanical prostheses were studied. In Chapter 2 it was shown that patients who receive a mechanical prosthesis have an impaired survival compared with allograft and autograft recipients. However, the characteristics of patients who receive mechanical prostheses differ from patients who undergo aortic valve replacement with an allograft or an autograft, and may explain at least in part this observed difference in survival (see also section on patient related factors below). Bleeding and thrombo-embolic events proved to be quite common in mechanical prosthesis patients, one of the key issues when it comes to selecting the proper valve substitute. Ruel and colleagues studied the quality of life after aortic valve replacement with mechanical prostheses and biological prostheses.[4] Aortic biological prostheses appear to be associated with better physical capacity, social functioning, and prosthesis satisfaction.[4] Although long-term anticoagulation can cause some degree of discomfort from blood tests and may disrupt daily life, it does not have an important effect on quality of life.[4, 5] Another characteristic of the mechanical prosthesis, the sound of valve leaflet closure, may influence the quality of life of patients. The majority of mechanical prosthesis patients have no complaints of valve noise and may adapt to the valve sounds over the years.[6] However, being a female patient and younger patient age were significant risk factors for greater disturbance by valve noise.[6]

Recurrence of endocarditis, early and late mortality after aortic valve replacement for active native endocarditis is comparable between allografts and mechanical prostheses as shown in Chapter 4. Furthermore reoperation rates in mechanical prosthesis patients are considerably lower compared to allograft patients who underwent aortic valve replacement for active native endocarditis. Although reoperations are less frequent in patients that receive a mechanical prosthesis, 10 years survival after reoperation is significantly worse compared with the autograft or the allograft. This was described in Chapter 11.

Despite main advantage, the life-long durability of the mechanical prosthesis with a low reoperation rate, the use of anticoagulation, valve sound and worse outcome after reoperation compared with other valve substitutes, may have a greater impact on outcome after valve replacement with these valve substitutes and moreover on the quality of life in young adult patients.

Human tissue valves and their characteristics

Allografts

Allografts and autografts do not require anticoagulation, an important advantage for young and active adult patients.

However, allografts valves have the major disadvantage that because of the non-viable nature these valve substitutes are subject to calcification resulting in a limited durability.[7] Allografts induce an immunologic response by activating T-cells.[8] This activation leads to chronic rejection and inflammation, which results in the destruction of tissue. The calcification process begins at the free walls of the allograft, where immunologic cells have the best access by ingrowing vessels from the surrounding scar tissue. Eventually, the calcification process extents to the cusps.[7]

This almost inevitably will result in a reoperation later during life, in particular in young patients with a relatively long life expectancy. Other disadvantages include limited availability of allografts and the specific surgical expertise that is required to implant human tissue valves, especially when the subcoronary implantation technique is employed.

Chapter 3 showed that the limited durability of the allografts is inversely related to patient age. Younger patient age is associated with increased reoperation rates for structural valve deterioration, an observation confirmed by several other reports[9-11] Furthermore, the effect of patient age on valve durability proved to be comparable to pericardial and stented biological prostheses, suggesting a common pathway of degeneration.[11]

Comparing allograft implantation techniques it showed that freedom from any valve-related reoperation was better using the root replacement technique than the subcoronary implantation technique. This is in accordance with the observations in a recent systematic review of the effect of allograft implantation technique on reoperation rate.[12] However, when only reoperation for degenerative structural valve deterioration is studied, reoperation rates are comparable for the allograft root replacement technique and the subcoronary implantation technique. Yet, the complexity of the reoperation between both implantation techniques differs.

Chapter 11 points out the complexity of reoperation after a previous allograft implantation. It is technically demanding to make a proper proximal anastomosis after previous allograft implantation due to the fact that the allograft not only calcifies in the part of the root but also at the annular level. Furthermore, the coronary buttons need to be dissected from the calcified allograft posing a challenge to maintain a large enough button that can be properly reinserted without distortion or kinking.

Reoperation after insertion of an allograft with the subcoronary implantation technique the coronary still remains complex, but technically less demanding, since the coronary arteries are not mobilized during initial implantation and therefore do not require remobilization and reinsertion at reoperation. Possible complications associated with this reinsertion of the coronary arteries are avoided and because the aortic root is untouched, only a mechanical prosthesis has to be reimplanted.

In endocarditis, the allograft is the preferred valve substitute of choice, due to the assumption of its excellent resistance to infection, the natural biocompatibility to absorb antibiotics and preservation of the natural anatomy of the aortic valve and the adjacent structures with excision of all infected tissue.[13] Chapter 4 questions this indication and demonstrates that radical excision of infection tissue combined with implantation of a mechanical prosthesis is also a suitable option. The use of allografts may be refined to only those patients with active endocarditis with root abscesses, where it can be used to reconstruct the distorted anatomy.

Insertion of an allograft at reoperation was a significant predictor of late mortality. Although this might be related to the allograft, it is more obvious this is due to the patient characteristics of the allograft recipients, such as older patient age, endocarditis as cause for reoperation and worse preoperative condition. On the other hand, Yacoub and colleagues observed the opposite. Survival after a reoperation after a previous allograft with a new allograft is comparable to the first operation and the mode of failure is not accelerated. [14]

It is obvious, that the enthusiasm in the early 1990s selecting the allograft for a wide range of indications has been tempered, and narrowed down to patients with active endocarditis, in particular with extensive destruction of cardiac tissue. The attention has shifted to other valve alternatives of the allografts in more recent years. Stentless aortic biological prostheses provide a good alternative for the allograft regarding survival and other valve-related events, and in endocarditis these valve substitutes provide comparable results. Furthermore, these valve substitutes have the advantages to have an unlimited availability. [15, 16] Moreover, recently it was shown that stentless aortic biological prostheses show a trend towards lower calcification rates compared with allografts. [17]

Autografts

The autograft procedure is the only operation that provides, in the longer term, a living valve substitute capable of reproducing the function of the normal aortic valve.[18, 19] The pulmonary autograft diameter increases parallel to somatic growth in children.[20] However, a worrisome increase in autograft reoperations is observed

in the second decade after the Ross operation.[21-24] The main cause for reoperation after the Ross operation is dilatation of the neo-aortic root. Due to this dilatation coaptation of the cusps is lost and aortic regurgitation occurs. A recent report on explanted autografts showed that compared to normal pulmonary and aortic valves, the explanted autograft valve also has an intact laminar architecture and cellularity, but apposition of fibrous tissue on the ventricular surface have let to an increase in overall valve thickness, as observed in long existing valvular insufficiency. The autograft wall typically shows severe aneurysm formation with intimal hyperplasia, and medial degeneration characterized by elastin loss and fragmentation, hypertrophy of smooth muscle cells and adventitial fibrosis containing functional vasa vasorum.[25]

Given the increasing autograft failure rates in the second decade after the procedure careful follow-up of autograft patients is required. Although the frequency of follow-up has to be further determined, an annual visit to the cardiologist with a structural echocardiography is highly recommended, since the failure rate of the autograft is observed to be accelerating in the second decade of operation and there is a potential chance of dissection of the autograft, as described in Chapter 10.

Reoperations for a failing autograft have a high risk and demanding character due to the possible attachment of the aneurysmatic ascending aorta to the sternum, and the fact that the pulmonary allograft may be compressed by and attached to the dilated autograft root. Also, the coronary buttons may pose problems when they are dissected from the autograft and reimplanted in a new root. Despite the complexity of these reoperations, satisfactory results are achieved, and these results are even better when compared to other valve substitutes. The outcome after reoperation on the pulmonary autograft can contribute to the debate of selecting the optimal valve substitute in young adults. In Chapter 11 it was described that none of these reoperative patients have died yet, an observation in concordance with other reports.[22, 26] One can argue if this is an advantage or a disadvantage to the contribution of the debate, since the experience with reoperations on autografts is still very limited. The fact that yet no reoperative mortality for these patients was observed despite the complexity of the operation suggests that this reoperation can safely be performed, but is no guarantee for future patients returning for a reoperation after the pulmonary autograft procedure.

The variability in the durability results of the autograft procedure may also in part be explained by the surgical technique employed, and by individual variation of the application of the root replacement technique. The subcoronary implantation

technique, as originally employed by Donald Ross[18] was abandoned by most centers for multiple reasons including its technical complexity and the attractive option of the root replacement technique that preserves the autograft valve geometry.

Most patients nowadays receive an autograft using the freestanding root replacement technique with reimplantation of the coronary arteries. This surgical technique can be applied in a variety of ways. The autograft can be inserted on the annulus or below the annulus and scalloping of the muscle rim can be done to a minimum below the valve cusps. Also, either continuous or interrupted sutures can be used for the proximal suture line. It is also possible to use a strip of pericardium to support the proximal suture line. Finally, the length of the autograft root can be varied. Some surgeons keep the neoaortic root as short as possible above the sinotubular junction while others preserve its complete length distally.

In a number of centers where the pulmonary autograft procedure is still performed, results are adequate and the procedure is performed by only one surgeon.[27,28] Surgical expertise thus seems an important success factor. Although there seems to be a learning curve in the beginning of employment of this operation, a larger experience seems to enhance durability. Systematic application of the root replacement technique into the fine details may also represent an important determinant of durability.

It may therefore be advisable for this operation to be concentrated in a restricted number of centers in which large experience can be obtained thus improving the results maintaining this particular operation with benefits for particular selected patient populations.

In Chapter 9 it described that durability of the autograft procedure not only depends on the pulmonary autograft but also on the valve substitute in the right ventricular outflow tract (usually an allograft). With time, both the autograft and the valve substitute in the right ventricular outflow tract show a limited durability and reoperation of the autograft and reintervention of the right ventricular outflow tract for structural valve deterioration are the most common valve-related complications both for adults and paediatric patients. Still, the ideal conduit for the right ventricular outflow tract in adults as well as in children has to be found and there might be an interesting role for tissue engineering for this valve substitute in the near future. Considering the limitations of the existing valve substitutes this new concept of creating a viable valve out of human cells shows encouraging results in the experimental setting.[29] Another recent development, percutaneous valve implantation, may be applied to the degenerated pulmonary allograft. Since stenosis is the main indication for undergoing percutaneous valve replacement and since the

allograft in the right ventricular outflow tract is subject tot calcification, this could be an alternative to surgery.[30]

Magnitude of impact on patient prognosis of mechanical prostheses and human tissue valves

The different valve substitutes have their own characteristics and the magnitude of impact on patient prognosis varies per valve substitute.

Aortic valve replacement can be done safely with a mechanical prosthesis and in selected cases of aortic valve endocarditis this valve substitute is also a good option. The prognosis after aortic valve replacement is mainly determined by the occurrence rate of the complications that are associated with anticoagulation use. Furthermore, the use of anticoagulation brings an extra burden of monitoring INR levels, affecting day to day activities of patients. Bleeding events, increased thrombogenicity and the increased risk of maternal and foetal adverse outcome in pregnancy, are reasons for using other alternative valve substitutes in these particular patients populations, thus improving patient prognosis and outcome.

Yet, the mechanical prostheses are still frequently used, suggesting that the durability of the valve outweighs the occurrence of side-effects of anticoagulation use, thus having a limited effect on patient prognosis.

Human tissue valves do not require anticoagulation, an important advantage for young adult patients with an active lifestyle, and have low valve-related event rates. However, these valves have a limited durability, which has an important effect of prognosis. The complexity of the operation and the requirement of specific surgical expertise influence this durability. Furthermore, surgical variation in application of implantation techniques also has an influence on durability. For the autograft, durability depends not only on the pulmonary autograft but also on the valve substitute implanted in the right ventricular outflow tract.

Due to the limited durability, a reoperation is inevitable later in life. These reoperations are not without risks and young adult patients who received a human tissue valve, face these risks a second time, thus influencing patient prognosis.

Despite that characteristics of the valve substitutes have an impact on patient prognosis; other factors also influence prognosis after aortic valve replacement. These factors are patient-related factors.

Patient-Related Factors

In the studies in this thesis, the characteristics of patients who received a mechanical prosthesis, an allograft or an autograft were clearly different. It can be concluded from Chapter 2 that patient factors play an important role in the type of valve substitute in that is implanted young adult patients. In this chapter various preoperative patient-related factors were analyzed and determined if these factors were associated with implantation of a particular valve substitute. It appeared that patients who received a mechanical aortic valve prosthesis were older, had more often an impaired left ventricular function and needed more often concomitant mitral valve surgery. Patients who received an allograft at operation, presented more often with acute symptoms, were in higher preoperative NYHA classes, had more often aortic root pathology, active endocarditis or Marfan's disease. Finally, patients that received a pulmonary autograft, were the youngest of the three valve substitute groups, had mainly isolated aortic valve disease, and had more often a balloonvalvulotomy in preoperative history, indicating congenital heart disease. Apparently, there is refined strategy in valve substitute selection for young adult patients beyond the general guidelines. [31, 32] Over the years valve substitute selection according the guidelines available and also determined by experience and preference of the clinic the patient is referred to.

Mechanical valves are in general implanted in patients younger than 65 years, with a long life ahead and no contraindications for anticoagulation treatment.

The allograft was expected to be the valve substitute of choice in young adult patients, but due to disappointing results and the limited durability many centers have stopped using this valve substitute for aortic valve replacement or are only using it for specific indications. Nowadays the major indication for implanting an allograft is aortic valve endocarditis with complex aortic root pathology, although there are centers that believe in the function and capability of this valve and its major advantage of avoidance of anticoagulation treatment.

The pulmonary autograft procedure is the only operation in which the patient's own living valve substitute is used and was widely applied due to the encouraging results on patient survival and few valve-related events reported. Pulmonary autograft recipients were mainly young adult patients, with isolated aortic valve disease and little co-morbidity. However, in recent years, most centers abandoned the use of the pulmonary autograft procedure in (young) adults due to its complexity and the high frequency of reoperation rates that have become apparent, with the potential accompanying operative mortality and morbidity risks. The operation still remains

a good treatment option in children with congenital aortic valve disease, in whom balloonvalvulotomy and aortic valve repair are not sufficient enough to maintain a (near) normal life.

In the sections below, patient outcome after aortic valve replacement for different specific patient groups is discussed.

Endocarditis

According to the ACC/AHA guidelines for management of patients with heart valve disease, surgical treatment of active native aortic valve endocarditis should preferably consist of valve repair because of the risk of infection of prosthetic materials.[31] When repair is not an option, valve replacement is necessary. Thus far, there are no specific recommendations for the use of a particular valve prosthesis for the surgical treatment of active native aortic valve endocarditis besides the general criteria for aortic valve selection.

In patients with active aortic valve endocarditis the allograft is an adequate option. Particularly when there is extensive destruction of the surrounding tissue, the allograft can be modelled in such a way that defects are covered and natural anatomy of the heart is preserved.[13, 33] The mechanical prosthesis is, however, also frequently used and the risk of reinfection being reported to be very low.[34] Not surprisingly, in one of the studies in this thesis a trend was observed towards allograft implantation in patients with active native endocarditis with root abscesses. On the other hand a mechanical prosthesis was more often used in those patients, in whom the active endocarditis was not only limited to the aortic valve leaflets but also affected the mitral valve, necessitating implantation of a mitral valve prosthesis and warranting lifelong anticoagulation medication for that reason.

Although patient age is an important factor for valve selection according the ACC/AHA guidelines[31], it did not play a role for patients with active native aortic valve endocarditis as is described in Chapter 4. Underlying co-morbidities related to the severity of the infection, such as renal failure, may therefore play an important role and these should be taken into consideration when selecting a valve substitute.

Factors studied that were potentially associated with early mortality were preoperative increased creatinin, NYHA class IV, emergent surgery, longer perfusion time and endocarditis caused by S. *aureus*. These variables were also reported by other authors to influence early mortality in active native valve endocarditis.[34-37] Early mortality was comparable between the allograft and mechanical prosthesis.

Still, early mortality remains high, and indicates that in this serious condition early surgery is necessary.
In active native valve endocarditis, allografts did not met the expectations regarding improved early and long-term outcome and the resistance to recurrent endocarditis. Besides, durability was found to be limited. The mechanical prosthesis showed comparable results regarding survival, recurrence of endocarditis was lower, although not significant and reoperation rate was lower. Other valve-related events such as bleeding or thrombo-embolic events were rare. One would expect higher rates of bleeding for mechanical prosthesis that are associated with the required anticoagulation treatment.
In conclusion, in active native aortic valve endocarditis no specific recommendations for valve substitute selection can be made. The general recommendation for use of an allograft in endocarditis may be refined to restricting the use an allograft to those patients in whom the endocarditis causes extensive tissue destruction and implantation of a mechanical prosthesis is not sufficient enough to reconstruct all infected tissue.

Congenital aortic valve disease

Prosthetic valve selection for young adult patients with a congenital aortic valve stenosis who require aortic valve replacement remains a delicate and complicated topic of discussion. The guidelines state that "although the Ross operation, allograft, heterograft, and valve repair each appear to offer patients with congenital aortic valve disease an attractive alternative to a mechanical valve for those with a relative contraindication to warfarin for anticoagulation (e.g., athletes or women desiring pregnancy), in the absence of long-term results, it is not believed that the indications for surgery with the Ross operation, heterograft, or allograft differ from those for mechanical valve replacement at this time".[31]
It was analyzed in Chapter 5 that late survival for patients with an autograft is comparable to that of the general age-matched Dutch population and for allograft patients slightly worse. This can partly explained by the fact that autograft patients are significantly younger and in better preoperative condition than the allograft patients. Besides, allograft patients more often underwent aortic valve replacement for endocarditis on the aortic valve or valve prosthesis, another factor that may have an effect on long-term prognosis since active aortic valve endocarditis is a life threatening disease associated with considerable morbidity and mortality.

Although the survival seems slightly better with the autograft compared to the allograft, this is not significant. However, it is still better when compared to survival of other young adult congenital patients with other valve substitutes.[1]
No conclusive recommendation can be given regarding valve selection in this particular patient population. In this population with few co-morbidities and a relatively long life-expectancy both valve substitutes are an adequate treatment option. However, reoperations for structural failure remain of major concern. In this thesis an age-dependency of allograft durability was observed; younger patients with an allograft had an increased structural failure rate. Since most of the patients with congenital aortic valve disease present in childhood or at a young adult age, in this particular subset the autograft may be preferable.

Pregnancy
Young girls and women of childbearing age who have undergone AVR with an allograft or an autograft are a patient population that requires special attention, due to their potential desire to have children. During pregnancy significant haemodynamic changes occur with an important demand on cardiac function with an increase in cardiac output, heart rate and blood volume. Furthermore, systemic vascular resistance decreases, resulting in a lower blood pressure, despite the increase in cardiac output. These cardiac changes may have an influence on progression of deterioration of the pulmonary autograft and allograft although hormonal changes may also play a role.
Women with mechanical prostheses are at increased risk of developing thrombo-embolic events during pregnancy, regardless of the type of anticoagulation used. During pregnancy, these patients also have a higher risk on foetal morbidity and mortality. The implantation of human tissue valves allows a considerable proportion of young female patients who contemplate pregnancy to have children without the risks associated with anticoagulant use. Pregnancy was not a factor associated with increased reoperation rates for valve failure, but given the small sample size and the fact that only clinical outcome was reported, further echocardiographic longitudinal studies may provide more insights into the potential effect of pregnancy on valve durability. Both the allograft and autograft both provide an adequate valve substitute at the cost of a reoperation later in life in young female patients who want to become pregnant within the next decade. The allograft and autograft are therefore preferred above mechanical prostheses.

Reoperative patients

Recent developments in aortic valve and root surgery have established the aortic root replacement as a safe and commonly performed procedure. However, due to this increase, the limited durability of tissue valves and the relatively long life expectancy of young adult patients, more reoperations can be expected in the future. Reoperation after aortic valve or aortic root replacement is an operation with an increased risk, and high mortality and morbidity rates are expected. [38, 39] However, we observed that it can be performed with satisfying early and long-term results and patient related-factors played an important role. Although hospital mortality for reoperative aortic root replacement after a previously inserted mechanical prosthesis seemed high compared with most of the other valve substitutes, most of these patients were severely symptomatic, had an impaired left ventricular function and often underwent emergent or urgent surgery. Furthermore, in the majority of these patients endocarditis was the indication for reoperation and surgery for prosthetic valve endocarditis is known to be associated with a higher urgency of surgery and a high hospital mortality rate.[40, 41]

It appeared that the use of an allograft at reoperation is associated with worse long-term outcome, but most of the allografts implanted were in patients with a mechanical prosthesis in situ. These allograft recipients were older patients, had prosthetic valve endocarditis, and were in worse preoperative condition which implies that not only the inserted allograft but also patient-related factors contributed to the increased late mortality we observed in allograft recipients.

That patient-related factors play a role is also emphasized in outcome after reoperation on the pulmonary autograft procedure. This reoperation is associated with low hospital mortality and morbidity rates with good long-term survival. These patients were relatively young, with good preoperative condition, a good left ventricular function and few symptoms related to aortic regurgitation.

In conclusion, reoperation after previous implanted aortic valve or aortic root can safely be performed and it is obvious that patient-related factors play an important role in outcome. Especially in the young adult patient, who has a long life-expectancy, with few co-morbidities, desire to avoid anticoagulation use, and a possible child wish for females, the pulmonary autograft may provide an adequate treatment option despite need for a reoperation later in life and the and complexity of the operation.

Other Relevant Factors

Other factors that are not related to valve substitutes or patients can influence valve selection.

Patient preference also has to be taken into account when selecting a valve substitute. Patients may not want to use anticoagulation due to the fact that they live an active life, or they prefer a different valve substitute than is recommended. Furthermore, valve selection particularly in young adult patients is influenced by the treating physician as well, bringing in a personal set of experience and expertise.

Moreover, health care resources can also play a role in valve substitute selection. Not all countries have a proper support of professional support regarding INR monitoring and this has an effect on which valve substitute is implanted. In these countries, biological valve substitutes are the preferred valve substitute due to the absent need of anticoagulation treatment.[42]

Clinical Relevance

To what extent can the results of this thesis be useful in clinical practice, i.e. how can they help cardiac surgeons or cardiologists who council young adult patients requiring aortic valve replacement in tailoring treatment selection? Using the knowledge obtained through the studies in this thesis, clinicians will gain improved awareness of the fact that patient profile is a far more powerful factor that determines outcome after aortic valve replacement than the prosthetic valve that will be implanted. Therefore, better timing of surgery in an early stage of aortic valve disease, may for example have a greater impact on patient survival compared with selecting a particular valve substitute. On the other hand, improved knowledge of the burden of prosthetic valve disease associated with the different valve substitutes –as outlined throughout this thesis- may assist the clinician in optimizing valve selection is such a way that an optimal quality of life for the patient can be achieved.

Final Conclusions

In summary, from the studies in this thesis a number of important insights emerged:

1. Patient prognosis is mainly determined by patient characteristics and only to a lesser extent by the valve type implanted
2. Several patient factors that are associated with prosthetic valve selection, also play a major role in patient survival
3. Human tissue valves have a comparable durability in young adult patients although the mode of failure differs considerably. Given the age-dependency of allograft structural valve deterioration in contrast to the autograft, in children and young adults the autograft procedure may be a more preferable solution
4. In endocarditis patients with a long life expectancy and with no extensive destruction of cardiac structures aortic valve replacement with a mechanical valve may be a preferable solution
5. Young female patients who want to have children, benefit from human tissue valves as a good valve substitute, at the cost of a reoperation later in life
6. Reoperative patients have a low mortality rate and especially reoperation after a previous autograft procedure shows good patient outcome

Recommendations

In the decision making process of selecting the most suitable valve substitute for primary aortic valve placement in adolescents and young adults, patient-related factors should play a central role. Clinical decision support tools based on the findings in this thesis should be developed, given the complexity of the decision making process and the multiple inter-related factors involved. This will require a durable collaborative effort of multiple centers in order to gather enough data to build and maintain a valid tool that will remain useful for the decennia to come.

Furthermore, it can be considered to either pursue a randomized controlled trial or a propensity-matched study of large high quality cohorts of young adult patients with either an autograft or mechanical prosthesis, to determine whether the survival advantage observed in autograft patients can be assigned to the superior haemodynamics of this viable human tissue valve or whether this is due to patient selection. Another interesting part to investigate is the quality of life of the patients after implantation of a pulmonary autograft or mechanical prosthesis and whether would be large differences on various aspects of life, e.g. daily activities, social life or work. This may contribute to the decision making process of selecting the optimal valve substitute in young adults.

Also, further study of the decision making process of surgeons and cardiologists with regard to prosthetic valve selection in young adult patients may result in identification of other factors that may be important determinants of outcome and may allow weighing of the value of the different factors that were already identified in this thesis.

Finally, since patient factors play such a central role in survival after aortic valve replacement irrespective of the valve substitute used, further study of the timing of aortic valve replacement and in particular study of the effect of surgery earlier in the natural history of aortic valve disease is warranted. Although aortic valve replacement will give a patient prosthetic valve disease for the remainder of life, this may very well outweigh the potential damage to the myocardium and resulting increased risk of cardiac death in patients who are operated at a later stage of their aortic valve disease.

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Summary

Chapter 1 comprises the introduction of this thesis. It describes the haemodynamic diagnosis of aortic valve disease, the different valve substitutes available and the valve substitutes commonly used in young adult patients with their advantages and disadvantages. A balanced and objective selection between the valve substitutes available and the corresponding advantages and disadvantages has to be made in selecting the proper valve substitute. Prognosis after aortic valve replacement depends on multiple factors that are associated with the patient and the type of valve substitute used. The aim of this thesis was to gain insight in these factors predicting outcome after aortic valve replacement with different valve substitutes and evaluate if there is a preferred valve substitute in this particular age group. This was accomplished by studying different cohorts of young adult patients that underwent aortic valve replacement.

Chapter 2 compares the two types of valve substitutes available since optimal prosthesis choice in young adults requiring aortic valve replacement remains controversial. An evaluation has been made whether patient profile or the type of valve substitute predicts outcome after aortic valve replacement. It appeared that patient factors play an important role in selecting a valve substitute and that these patient factors determine outcome after aortic valve replacement. Furthermore, this chapter briefly introduces the discussion on which valve substitute can be considered in young adult patients weighing the advantages and disadvantages.

Chapter 3 describes the clinical experience of aortic valve replacement with allografts at Erasmus Medical Center in Rotterdam and it questions whether the allograft is the preferred valve substitute in young adult patients. All 336 patients were prospectively followed over time. With the use of the microsimulation model freedom from reoperation for structural failure for allograft was compared to biological prostheses. It showed that structural failure rate of the allograft is similar to that of a biological prosthesis and that this failure rate is age-dependent. Furthermore, in our institution the allograft is preferred in patients with active aortic root endocarditis and in patients with a contraindication for anticoagulation use.

Chapter 4 gives insights in the influence of the choice of valve substitute on outcome after active native aortic valve endocarditis. It describes the combined experience of two centers of 138 patients with this disease that underwent aortic valve replacement with 106 allografts and 32 mechanical prostheses. Both mechanical prostheses and

allografts show comparable outcome and reoperation remains the major problem after aortic valve replacement with an allograft. Mechanical prostheses can be a proper valve substitute in active native endocarditis, in combination with extensive excision of infected tissue, in a specific patient population without presence of aortic root abscesses.

Chapter 5 compares the outcome after aortic valve replacement with autografts and allografts in young adult patient with congenital aortic valve disease. The reason to compare these tissue valve substitutes is to asses whether there is a preference for one of these valve substitutes in these particular patients. The main conclusion of this study was that outcome after surgery with autografts or allografts is satisfactory and comparable. Furthermore, for both valve substitutes reoperation remains a major concern.

Chapter 6 is a study of the specific patient population of 98 young adult female patients in the child bearing age that underwent aortic valve replacement with an autograft or an allograft. It was hypothesized that durability of the autograft or the allograft is influenced by the altered haemodynamic state that exists during pregnancy. All female patients were prospectively followed over time and to gather information on pregnancy after operation all patients were requested to fill in a structured questionnaire. This resulted in 23 patients reporting 37 pregnancies. During follow-up 18 patients required a reoperation, with no effect of pregnancy on the durability of the valve substitute. Furthermore, patient survival is good and for the autograft even comparable to the age-matched population, thus tissue valves are a good option in young adult female patients who want to become pregnant and require aortic valve replacement.

Chapter 7 evaluates a two center experience of 264 patients that underwent the Ross procedure. This study discusses different aspects of prognosis and outcome after aortic valve replacement with the Ross procedure. Due to the low incidence of valve-related complications and a good survival after this operation that is comparable to age-matched individuals, patients can live their life without physical impairment although there is an increasing reoperation risk.

Chapter 8 consists of a systematic review of reported outcome after the Ross procedure, and discusses patient-related factors, surgical-technical considerations

and histological aspects of the Ross procedure. This was done in order to improve insight into potential determinants of success for this special operation since varying results are reported in the literature. After reviewing the considerable experience with the Ross procedure worldwide, it can be concluded that it provides children and young adults in the first decade after the operation with results that are superior to any other valve substitute. On the downside, it also has several limitations that become apparent in the second decade after the procedure. Whether these limitations may at least in part be addressed by the surgical details and postoperative measures discussed in this paper remains to be determined.

Chapter 9 gives an overview of the pulmonary autograft procedure in our own institution. It raises the question whether the Ross procedure is still a good treatment option of aortic valve disease since in recent years more and more reoperations due to autograft failure are observed. Moreover, insights are given in possible factors playing a role in autograft failure. In our cohort the Ross procedure has the alleged excellent patient survival and particular patient populations benefit from this operation. Careful follow-up of these patients after operation is warranted to gain more insight in the mode of autograft failure.

Chapter 10 describes a case report of an asymmetrical dilated autograft root. Described is the observation that the aortic wall may become increasingly weak after gradually increase of autograft dilatation. This can lead to a limited dissection that is prone to a free wall rupture causing a potential lethal complication.

Chapter 11 describes the outcome of aortic root replacement after previous operation on the aortic valve, ascending aorta or both and that this can be safely performed. Four groups of patients were compared; patients that required replacement of the native valve, prosthetic valve, of an allograft or an autograft. Factors were determined of the different valve substitute groups, of hospital mortality and of time-related events such as late mortality. Although patient-related factors are influencing the decision which valve is inserted at primary operation, reoperation after pulmonary autograft procedure shows the best early and long-term outcome. This result may contribute in the decision making in selecting a proper valve substitute in young adult patients.

Chapter 12 includes the general discussion of this thesis in which the aims of the thesis are described and insights that emerged from the studies in this thesis are discussed. It is also discussed in what way the results can be used in practice, in helping clinicians to optimize prosthetic valve selection in young adult patients. Also, perspectives and recommendations with regard to future research are presented.

Samenvatting

Hoofdstuk 1 is de introductie van het proefschrift. Het beschrijft de haemodynamische diagnose van aortaklep ziekte, de verschillende klepprothesen die beschikbaar zijn met hun voordelen en nadelen en welke van deze klepprothesen vaak in jongvolwassen patienten worden gebruikt.
Een gebalanceerde en objectieve afweging tussen de beschikbare klepprothesen met bijbehorende voordelen en nadelen zou moeten worden gemaakt wanneer getracht wordt de meest geschikte klepprothese te kiezen. De prognose na aortaklepvervanging hangt af van verscheiden factoren die van de patient of van de te implanteren klepprothese afhankelijk zijn. Het doel van het proefschrift was om inzicht te verkrijgen in deze factoren die een voorspellende waarde hebben op uitkomst na aortaklepvervanging met de beschikbare klepprothesen in jongvolwassen patienten en evalueren of er een voorkeur te bepalen is voor een bepaalde prothese voor patienten in dezeleeftijdscategorie. Om dit inzicht te verkrijgen zijn verschillende cohorten van jongvolwassen patienten die een aortaklepvervanging ondergingen bestudeerd.

Hoofdstuk 2 vergelijkt de verscheidene soorten klepprothesen die beschikbaar zijn. De optimale klepkeuze in jongvolwassen patienten blijft controversieel. Daarnaast is bekeken of patient-gerelateerde factoren of het type klepprothese dat geimplanteerd wordt bij aortaklepvervanging de uitkomst na de aortaklepoperatie voorspelt. Het blijkt uit deze studie dat patient-gerelateerde factoren een belangrijke rol spelen in het kiezen van de klepprothese en dat deze factoren ook van invloed zijn op de uitkomst na aortaklepvervanging. Daarnaast wordt kort ingegaan op de discussie welke klepprothese als beste keuze zou kunnen worden beschouwd in jongvolwassen patienten met afweging van de verschillende voordelen en nadelen.

Hoofdstuk 3 beschrijft de klinische ervaring van aortaklepvervanging met een allograft in het Erasmus Medisch Centrum Rotterdam. Daarbij wordt de vraag gesteld of de allograft de klep van voorkeur is in jongvolwassen patienten. Alle 336 patienten in deze studie zijn prospectief gevolgd over tijd. Met gebruikmaking van het microsimulatiemodel is vrijheid van reoperatie vanwege structureel falen vergeleken tussen de allograft en de biologische klepprothese. Uit de resultaten komt naar voren dat de mate van structureel falen van de allograft gelijk is aan die van de biologische klep en dat deze mate van falen leeftijdsafhankelijk blijkt. Bovendien blijkt dat de allograft in ons centrum voornamelijk gebruikt wordt in patienten die

een actieve aortaklep endocarditis hebben en in patienten bij wie het gebruik van antistolling gecontraindiceerd is.

Hoofdstuk 4 geeft inzicht in de invloed van klepkeuze op de uitkomst van aortaklepvervanging bij patienten met een actieve natieve aortaklependocarditis. Het beschrijft de gecombineerde ervaring van twee centra met 138 patienten met deze aortaklepziekte, die aortaklepvervanging ondergingen waarbij 106 allografts en 32 mechanische klepprothesen werden geimplanteerd. Het blijkt uit de resultaten dat zowel de allograft als de mechanische klep dezelfde uitkomst na operatie hebben. Reoperatie blijft echter het grootste probleem na implantatie van een allograft. Mechanische klepprothesen kunnen een goede optie zijn in actieve natieve aortaklep endocarditis, echter wel in combinatie met uitgebreide excisie van geinfecteerd weefsel en in een specifieke patientenpopulatie waarbij geen abscessen van de aortawortel aanwezig zijn.

Hoofdstuk 5 vergelijkt de uitkomst na aortaklepvervanging met autografts en allografts in jongvolwassen patienten met een congenitale aortaklepafwijking. De reden om deze kleptypes te vergelijken was om te beoordelen of er een voorkeur bestaat voor een van beide kleptypes in deze patientenpopulatie. De belangrijkste conclusie van de studie is dat uitkomst na operatie met een allograft of autograft uitstekend is en er werden geen duidelijke verschillen waargenomen tussen beide kleppen. Daarbij blijkt dat voor beide kleptypen het toenemende aantal reoperaties een belangrijke zorg blijft.

Hoofdstuk 6 is een studie van 98 jongvolwassen vrouwelijke patienten in de vruchtbare leeftijd die aortaklepvervanging hebben ondergaan met een autograft of een allograft en na deze operatie mogelijk zwanger zijn geworden. Het wordt namelijk aangenomen dat de duurzaamheid van deze kleppen beinvloedt kan worden door de veranderingen in de hemodynamiek die optreden tijdens de zwangerschap. Alle vrouwelijke patienten in deze studie zijn prospectief gevolgd over tijd en vragenlijsten werden afgenomen om informatie over eventuele zwangerschappen te verkrijgen. Uiteindelijk zijn er 37 zwangerschappen in 23 patienten geobjectiveerd. Gedurende follow-up ondergingen 18 patienten een reoperatie. Zwangerschap blijkt geen effect te hebben op de duurzaamheid van de klep. Daarnaast blijken de patienten een goede overleving over tijd te hebbben en voor de autograft is deze overleving zelfs vergelijkbaar met leeftijdsgenoten die geen aortaklepvervanging hebben ondergaan.

Het kan dus geconcludeerd worden dat weefselkleppen een goede optie zijn wanneer er een klepkeuze moet worden gemaakt in jongvolwassen vrouwelijke patienten die een aortaklepvervanging moeten ondergaan en na deze operatie zwanger willen worden.

Hoofdstuk 7 bespreekt de ervaring van twee centra met 264 patienten die de Ross procedure ondergingen. Deze studie richt zich op verschillende aspecten van de prognose en uitkomst na aortaklepvervanging met de Ross procedure. Dankzij de lage incidentie van klep-gerelateerde complicaties en de goede overleving na deze ingreep die vergelijkbaar is met leeftijdsgenoten, kunnen patienten na deze operatie een normaal leven leiden zonder fysieke beperkingen, hoewel een reoperatie op lange termijn onvermijdelijk lijkt.

Hoofdstuk 8 beschrijft een systematische review van studies over de Ross procedure en bespreekt patient-gerelateerde factoren, chirurgisch technische overwegingen en histologische aspecten van deze ingreep. Deze review is verricht om beter inzicht te krijgen in de varierende resultaten die bereikt worden na de Ross procedure. Na het reviewen van de wereldwijd uitgebreide ervaring met de Ross procedure, kunnen we concluderen dat het voor kinderen en jongvolwassenen een ingreep betreft met superieure resultaten vergeleken met andere kleptypen. Maar de keerzijde is dat er verscheidene beperkingen ontstaan in het tweede decennium na deze ingreep. Of deze beperkingen deels zijn toe te schrijven aan chirurgische technieken of het postoperatieve beleid, zoals besproken in dit artikel, zal verder moeten worden onderzocht.

Hoofdstuk 9 geeft een overzicht van de Ross procedure in ons eigen centrum. De vraag die wordt gesteld is of de Ross operatie nog steeds een goede behandelingsoptie is aangezien er in recente jaren steeds meer studies verschijnen die rapporteren over reoperaties vanwege het falen van de autograft. Daarnaast worden inzichten gegeven in mogelijke factoren die een rol spelen in het falen van de autograft. In onze patientenpopulatie blijkt dat de Ross procedure de verwachte superieure patientenoverleving heeft en dat bepaalde patientenpopulaties profijt hebben van deze operatie. Echter, deze patienten moeten nauwkeurig gevolg worden over tijd om meer inzicht te krijgen in de manier waarop de klep faalt.

Hoofdstuk 10 bestaat uit een case report van een asymmetrisch verwijde autograft wortel. Er wordt beschreven dat de aortawand kan verzwakken wanneer de autograft geleidelijk toeneemt in diameter. Dit kan leiden tot een beperkte dissectie wat kan resulteren in een vrije wandruptuur met een fatale afloop tot gevolg.

Hoofdstuk 11 beschrijft de uitkomst van aortawortelvervanging na een eerdere aortaklepoperatie, aortachirurgie of een aortaklepoperatie met aorta ascendensvervanging. Er werden vier patientengroepen bekeken; patienten waarvan de natieve klep vervangen moest worden, waarvan een eerder geimplanteerde mechanische danwel een allograft of een autograft aan vervanging toe was. Er is gekeken naar welke factoren mogelijk van invloed kunnen zijn van voor de indeling in deze vier groepen en welke factoren van invloed kunnen zijn op ziekenhuissterfte en late sterfte. Uit deze studie blijkt dat een reoperatie van de aortawortel veilig kan worden uitgevoerd. Hoewel patienten-gerelateerde factoren een rol blijken te spelen in de keuze welke klep geimplanteerd wordt gedurende de primaire operatie, geeft reoperatie na een eerdere Ross procedure de beste resultaten op de vroege en late termijn. De resultaten van deze studie zouden kunnen bijdragen in het besliskundige proces om de beste klep te kiezen voor de jongvolwassen patient.

Hoofdstuk 12 bevat de discussie van dit proefschrift waarin het doel van het proefschrift is beschreven en inzichten die voortvloeien uit dit proefschrift worden behandeld. Daarnaast behandelt dit hoofdstuk ook hoe de resultaten van dit proefschrift toegepast zouden kunnen worden in de klinische setting, om klinici te helpen de klepkeuze in jongvolwassen patienten te optimaliseren. Tenslotte worden perspectieven en aanbevelingen gedaan ten aanzien van toekomstig onderzoek en wordt afgesloten met een algemene conclusie.

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Op naar het volgende avontuur!

Curriculum Vitae

Loes Klieverik was born September 18, 1979, in Hengelo, The Netherlands. After graduating from Twickel College in Hengelo, she studied Psychology at the State University Groningen. After one year she got the opportunity to study Medicine at the Erasmus University Rotterdam and moved to Rotterdam. In August 2002 she obtained her pre-medical degree. During her internships she worked for three months at Harefield Hospital, Harefield, United Kingdom, doing research with Prof. Sir Magdi H. Yacoub. In February 2005 she obtained her Medical Degree at the Erasmus University Rotterdam and in February 2005 she also started with her PhD project at the Department of Cardio-Thoracic Surgery of the Erasmus University Medical Center Rotterdam.
In September 2007 she has started as a resident at the Department of Cardio-Thoracic Surgery.

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