Decades of Surgery on the Thoracic Aorta

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Decennia operaties van de thoracale aorta

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Ter nagedachtenis aan mijn vader

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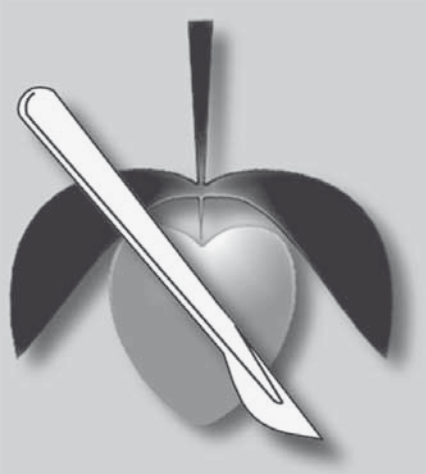
General introduction and aim of the thesis



INTRODUCTION

Thoracic aortic disease is an infrequently encountered condition of which the true prevalence and incidence is hard to establish. New thoracic aortic aneurysms are estimated to be present in 5-16/100.000 inhabitants in the USA and Sweden and seem to increase in prevalence.[1-3] Probably this increase is largely due to improved diagnostics and ascertainment.[4] In the USA aortic aneurysms were 19th in rank in the 2007 mortality statistics and constituted 0.5% of all deaths.[5,6]

In the Netherlands 1302 people were registered as having died due to aneurysms and dissections of the aorta in 2010. This is approximately 2 deaths per day and represents 1% of all mortality.[6]

In this introduction we will discuss the normal anatomy of the aorta, aortic pathology, surgical therapy of aortic diseases and the aims and outline of the thesis.

THE AORTA

The aorta is the large artery providing blood supply to the body. The aorta originates in the heart, ascends from the aortic root to the top of the chest (ascending aorta), curves dorsally to the posterior part of the chest (aortic arch), and runs downward through the diaphragm (descending aorta). The abdominal aorta runs further down until the bifurcation in the iliac arteries.[7] (Figure 1)

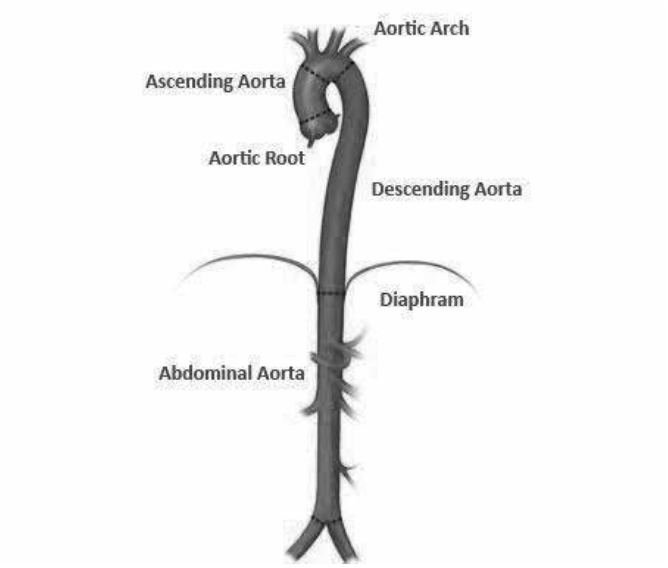


Figure 1. Schematic overview of the aorta.

The ascending aorta is located intra-pericardially and has a close relation to the heart. At the origin of the aorta the aortic valve is located at the junction of the left ventricular outflow tract and the aorta. At its origin the aorta has a slightly larger diameter and consists of three sinuses of Valsalva. This part of the aorta is also referred to as the bulbus aortae or aortic root. The coronary arteries are the first side branches of the aorta, arising from the sinuses of Valsalva directly above the attachments of the aortic valve leaflets. The junction of the aortic root to the tubular part of the ascending aorta is called the sinu-tubular junction.

The aortic arch normally gives rise to the three large arteries supplying the upper body: the brachiocephalic trunk, the left common carotid artery and the left subclavian artery.

In the descending aorta the pairwise intercostal arteries originate and constitute a major contribution to the blood supply of the spinal cord.

The abdominal aorta gives rise to the visceral arteries: the coeliac trunk, superior mesenteric artery, the renal arteries and the inferior mesenteric artery.

The aortic wall is composed of three layers: the intima, the media and the adventitia. The aorta is an elastic artery, primarily functioning as a conduit for a large volume of blood flow to the rest of the body. Elastic arteries typically have a well-developed medial layer consisting of smooth muscle cells and elastic fibers.

AORTIC DISEASE

Aortic aneurysms and aortic dissections represent the most common aortic diseases requiring surgery. Other less common conditions that require surgery are traumatic aortic injuries, inflammatory diseases, penetrating ulcers, intra-mural hematoma and neoplasms of the aorta.

Aortic aneurysm

An aortic aneurysm is a dilatation of the aorta, causing an increase of the aortic diameter compared with the normal diameter for a patient's body size.[8] This dilatation may also occur in the aortic root. A distinction can be made between a true and a false aneurysm. In a true aneurysm the composition of the aortic wall is intact: the intimal layer, media and adventitia can all be recognized. The aorta is dilated in all directions and forms a *fusiform* aneurysm. The aorta may also become enlarged longitudinally: aortic elongation. In a false aneurysm or pseudo-aneurysm the integrity of the aortic wall is lost. Usually the intima and part of the medial layer are disrupted, leading to an asymmetrical dilatation of the aorta: a *saccular* aneurysm.

Symptoms related to the presence of an aortic aneurysm may be chronic pain in the chest, neck or back, shortness of breath, related to compression of major airways, dyspha-

gia, related to compression of the esophagus or reveal itself through remote symptoms, e.g. hoarseness, caused by recurrent laryngeal nerve compression. An aortic aneurysm, however, can be present in patients for a long time period without specific complaints or symptoms. The first symptom is often a fatal aortic rupture, an acute aortic dissection or contained rupture.

The majority of thoracic aneurysms are degenerative in origin.[9,10] Pathological examination of the aortic wall shows a loss of smooth muscle cells and fragmentation of elastic fibers. In part these alterations can be considered as a normal phenomenon in aging.[11] Other factors that are associated to aneurysmal degeneration of the thoracic aorta are hypertension, tobacco use and hyperlipidemia.[12] Inherited conditions are increasingly considered to be associated with aneurysmal disease of the aorta. It is estimated that at least 20% of aneurysms result from inherited diseases.[13] Marfan syndrome, an autosomal dominant genetic disease, caused by a mutation in the gene encoding type 1 fibrillin on chromosome 15 is the most common inherited connective tissue disease causing aortic aneurysms with an incidence of at least 1/10.000.[14] In recent years many other syndromic and non-syndromic causes of aortic aneurysms have been described.[15,16] In syndromic aortic aneurysms the aortic dilatation is one of several phenotypic abnormalities found in a patient. On the other hand, in non-syndromic aortic aneurysms the aortic dilatation is not related to other phenotypical abnormalities.

For aortic aneurysms it has been proven, that the risk of rupture or dissection is strongly related to the aortic diameter.[17,18] Therefore elective replacement of asymptomatic aortic aneurysms, based on size criteria is widely recommended.[2,19,20] Especially for aggressive forms of familial aortic syndromes early resection of only mildly dilated aortas is advocated.

Aortic dissection

Aortic dissection is an acute condition, presenting with pain and shock. In acute dissection an intimal tear leads to separation of the aortic wall into two layers. Usually the plane of separation is found in the medial layer of the aortic wall. From the primary intimal tear the separation propagates distally and sometimes proximally, often involving the aortic root. The dissection process causes the aorta to form two lumina separated by the intimal flap: the lumen delineated by the original circumferential intimal layer (true lumen) and the false lumen, located within the media or adventitia of the aorta. Along the course of the dissection more intimal tears may exist: re-entry tears. Aortic dissections are originally classified according to DeBakey.[21] In DeBakey type 1 dissection the aortic wall of the ascending aorta, the aortic arch and the descending aorta, and frequently the abdominal aorta are involved. Type 2 dissection is limited to the intra-pericardial ascending aorta and in type 3 dissection the descending aorta and frequently the abdominal aorta are involved. The more recent Stanford classification groups de DeBakey type 1 and 2 together to Stanford type A and classifies DeBakey type 3 dissection as Stanford type B.[22] The latter classification separates

the highly lethal proximal dissection, with involvement of the intra-pericardial ascending aorta, from the less malignant distal aortic dissection. In both classifications the location of the primary intimal tear does not play a role in the dissection typing. From a surgical standpoint the Stanford classification is most practical, indicating the life-threatening type A dissection, with an indication for acute surgery from the more benign type B dissection, treated preferably medically initially. The DeBakey classification, however, provides more information about the extent of the disease. This extra information is useful in further treatment of operated patients and may be related to the long-term prognosis after an acute dissection. In acute dissection symptoms are usually related to the acute process of intimal rupture and progressive separation of the aortic wall layers. Acute pain, often migrating following the course of the aortic wall separation is the most frequently reported and most prominent symptom. Hypotension and shock are frequently caused by pericardial tamponade. In patients with a frank aortic rupture, either intra-pericardially, in the pleural space or abdominal cavity, fatal shock will occur within minutes, usually leaving too little time for adequate medical and surgical treatment. In other patients a slowly progressive accumulation of blood in the pericardium will lead to a progressive pericardial tamponade with a fatal outcome, unless the tamponade is relieved by means of pericardial puncture or emergency operation. The incidence of acute aortic dissections is estimated to be 30-43 per million of population per year.[23,24] The mortality of an acute ascending aortic dissection is estimated to be 1-2% per hour [25,26] in the first 48 hours, leading to about 90% mortality if left untreated. Other complaints in the dissection process are related to abrupt closure of branching vessels of the aorta. The intimal flap may narrow or finally occlude arteries, giving rise to symptoms, not always easily recognized to be caused by an acute dissection. Depending on the vessels involved patients may present with cardiac ischemia (coronary artery), cerebral dysfunction (carotid artery or vertebral artery), paraplegia (intercostal artery), abdominal complaints (visceral artery), renal failure (renal artery) or limb ischemia (subclavian or iliac artery).

Intra-mural hematoma and penetrating ulcer

An intra-mural hematoma is considered to be an acute aortic syndrome related to aortic dissection. In an intra-mural hematoma the aortic wall is thickened over a longer segment, without the clear presence of two lumina. It is suggested, that such an intra-mural hematoma is caused by a local bleeding in the aortic wall caused by rupture of intra-aortic small blood vessels, the vasa vasorum.[27] Several reports describe the development of a classic aortic dissection, after a primary presentation as an intra-mural hematoma.[28] An intra-mural hematoma is usually considered to be a surgical emergency, others advocate a more conservative approach.[29]

A penetrating ulcer may also present as an acute aortic syndrome. A disruption of the intimal layer leads to a, sometimes quickly progressive, eccentric aneurysm formation within the aortic wall or surrounding tissues.[30]

Traumatic aortic rupture

Traumatic aortic rupture is related to a sudden impact on the body. The trauma leading to an aortic rupture is often referred to as a deceleration trauma. This may be the sudden impact of a car collision from the side or a frontal impact to another vehicle or static object. Other accidents frequently associated with an aortic rupture are a fall from a height.[31] Although ruptures of the aorta or other large vessels are found in various segments, the classical anatomical location of a traumatic aortic rupture is the proximal descending aorta. It is hypothesized, that this location is prone to twisting or kinking of the aorta, leading to the disruption of the aortic wall. Patients with a frank rupture will usually die at the spot of the accident, due to rapid exsanguination into the pleural space or mediastinum. It is estimated that a traumatic rupture is causing acute death in 80% of the cases.[32] In patients arriving alive in the hospital, the severity of the aortic rupture may vary from a small rupture of only the intimal part of the aortic wall to a circular disruption of the aorta, with a large hematoma only contained by the adventitia or mediastinal structures. Frequently these patients are multi-trauma patients with a variety of other possible severe injuries.

Aortitis

Aortitis is an inflammation of the aortic wall. The etiology may be infective (syphilitic aortitis or caused by bacteria or fungi) or non-infective due to vasculitis (e.g. Takayasu's arteritis or giant-cell arteritis). Especially bacterial aortitis may lead to rapidly progressive aneurysm formation due to aortic wall destruction. Non-infective forms of aortitis may lead to arterial wall thickening or obstruction of major side branches of the aorta.

SURGERY OF THE AORTA

Surgery of the thoracic aorta became first possible in the 1950's, with the first replacements of the descending aorta using an allograft[33] or a Dacron graft.[34] In 1956 and 1957 successful replacement of the ascending aorta and aortic arch using cardiopulmonary bypass followed.[35,36] Replacement of the thoraco-abdominal aorta was first reported in 1965.[37] In 1968 the first complete replacement of the aortic root by means of a composite valve graft was described.[38] Alternative techniques for aortic root replacement are the use of aortic allografts or the pulmonary autograft (Ross operation).[39,40] In addition, these operations were increasingly performed for isolated aortic valve pathology, thus treating aortic valve disease by means of a complete root replacement.

Since this pioneering phase of aortic surgery a rapid evolution in anesthesiology, cardio-pulmonary bypass techniques and surgery has enabled surgeons to treat many patients with a variety of aortic diseases. Modern techniques include the use of impregnated vascular grafts, both tubular and with pre-fabricated side branches. Composite grafts are available for combined replacement of the aortic valve and the ascending aorta. Alternative techniques to replace the aortic root and ascending aorta with preservation of the patient's aortic valve became available.[41,42] Operations on the aortic arch can be safely performed using deep hypothermic circulatory arrest or cerebral perfusion techniques for brain protection.[43,44] For descending aortic and thoraco-abdominal aortic replacement specific cardio-pulmonary bypass techniques and additional measures can be used to reduce operative risks and prevent post-operative paraplegia.[45,46] The most recent technical innovation has been the placement of endovascular stent-grafts inside the aortic lumen to treat aortic aneurysms.[47]

The frequency of thoracic aortic operations is increasing rapidly. In Sweden the annual incidence of thoracic aortic operations has increased 7-fold in men and 15-fold in women between 1987 and 2002.[3] In 2002 the number of thoracic operations was 56 per million in men and 30 per million in women. According to data from the *Begeleidingscommissie Hartinterventies Nederland* and the Netherlands Association for Thoracic Surgery, in the Netherlands the number of thoracic aortic operations rose from about 500 in 2000 to 1023 in 2010.[48,49] (Figure 2) The annual number of thoracic operations in the Netherlands can thus be estimated to be 60 per million inhabitants.

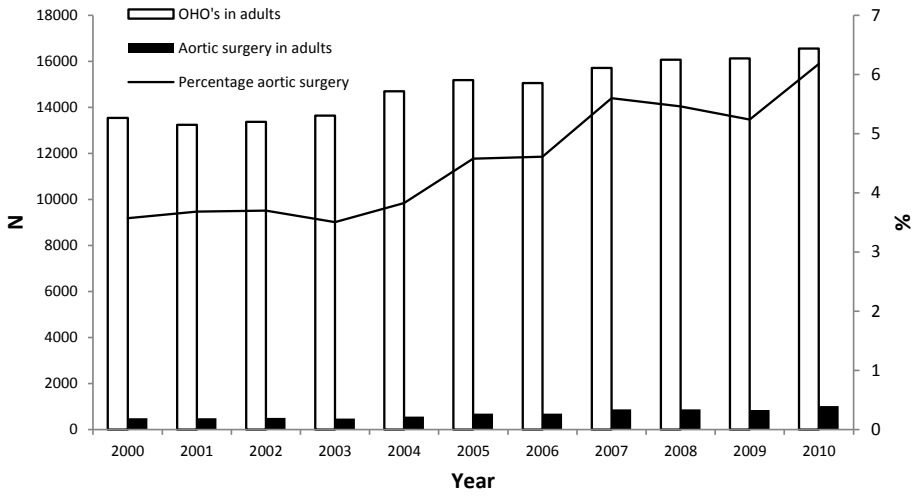


Figure 2. Overview of the total number of heart operations, number of aortic operations and the percentage of aortic operations in the Netherlands.

AIM OF THE THESIS

This thesis studies various aspects of thoracic aortic surgery including early and late results, with special attention to reoperations on the aortic root, and includes the total experience of thoracic aortic surgery in the Erasmus University Medical Center.

All patients operated upon for thoracic aortic diseases since 1972 until present are entered in a dedicated thoracic aortic surgery database. In this database we collect clinical data on all patients, with the exception of those operated upon for aortic coarctation, acute endocarditis with involvement of the aortic root or aortic pathology as a part of complex congenital cardiac malformations. All patients who undergo allograft or autograft implantation are entered in dedicated allograft and autograft databases, and are followed prospectively. Information on the pre-operative condition of the patients, operative details and post-operative complications are extracted from hospital records. Follow-up information is collected from our dedicated aortic surgery outpatient clinic, referring cardiologists and other sources. Information on the vital status of the patients is collected from the civil registry and supplemented by information from hospital records or general practitioners.

Chapter 1 is the general introduction of the thesis.

In the chapters 2-5 the long-term result of previous aortic root replacement by means of an aortic allograft or pulmonary autograft implantation (the Ross-operation) are studied, focusing on the following research questions:

- What is the long-term survival of these -often young- patients?
- Which factors determine the long-term survival?
- What is the incidence of allograft and autograft failure and which potential determinants can be identified?

Chapters 6-9 focus on the reoperations after previous aortic allograft or autograft implantation and analyze:

- The long term survival after first allograft or autograft implantation.
- The technical details of the reoperations and the techniques that can be used for subsequent aortic valve replacement and replacement of the aorta.
- Early and late results of the reoperations.

Chapters 10 and 11 further analyze patients with acute dissections for the early results of surgery and risk factors associated with early mortality. Regarding long-term results, research will focus on:

- The long term survival of patients after surgery for acute aortic dissection.

- Clinical factors in type of dissection and type of operation in relation to differences in long-term outcome.
- The incidence of reoperations on the aortic valve or the aorta after surgery for acute dissection.
- Clinical factors associated with the need for reoperation.

In chapter 12 we will report on surgical experience with patients with a recently discovered aggressive inherited syndrome, caused by a SMAD3 mutation.

And finally, chapter 13 provides an overview of the total patient group operated upon for thoracic aortic diseases in 4 decades, with a particular focus on:

- The trends in diagnoses and patient profiles in this 40 year time period.
- Early results, especially early mortality and post-operative complications over time.
- Technical developments in the conduct of the operations and their influence on early and late results.
- The long-term survival of patients operated upon for various types of aortic pathology in relation to the survival in the general population.
- Trends in long-term survival over 4 decades.

In the discussion the results of the studies are summarized and put into perspective. Trends and developments in thoracic aortic surgery are further analyzed and future directions in thoracic aortic surgery and prospects for further studies are provided.

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Chapter 2

Evolution of allograft aortic valve replacement over 13 years: results of 275 procedures

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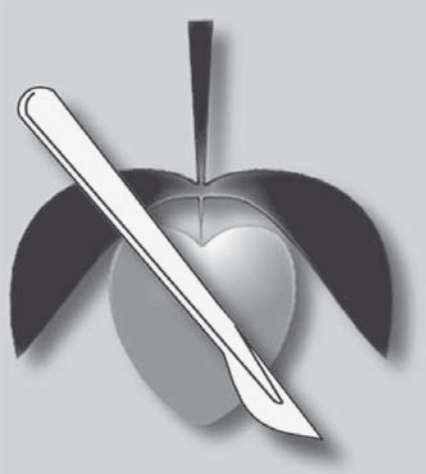

ABSTRACT

Objective: We describe our center's experience with the use of allografts for aortic valve or root replacement, illustrating the impact on outcome of the changes made in surgical and preservation techniques.

Methods: Between 4/1987 and 1/2001 275 allografts were used in 267 consecutive patients to replace the aortic valve or root. All patients were prospectively followed over time. Mean patient age was 46 years (SD 16; range 0.06-83), male/female ratio was 201/74. Prior cardiac operations took place in 73 patients; 49 patients presented with active endocarditis. Pre-op NYHA-class was ≥ III in 51%. Initially, the subcoronary technique was used (SC; N=95) while in recent years root replacement (ARR; N=180) became the technique of choice. Seven fresh (2 pulmonary and 5 aortic) and 268 cryopreserved (4 pulmonary and 264 aortic; 35 glycerol and 233 DMSO) allografts were implanted. Concomitant procedures took place in 133 (48%).

Results: Operative mortality was 5.5% (N=15) and during follow-up (99% complete) 29 more patients died. Overall cumulative survival was 73% (95% CI 65-81%) at 9 years postop and significantly better for SC compared to ARR patients (p=0.005). Freedom from allograft-related reoperation (N=34) was 77% (95% CI 69-85) at 9 years, and worse in the SC compared to ARR group due to increased early technical failure (p=0.03). Freedom from reoperation for structural failure (SVD; N=22) was 81% (95%CI 73-89) at 9 years and did not differ between SC and ARR (p=0.51). Independent predictors of degenerative SVD were younger patient age (HR 0.93 with age as continuous variable; 95% CI 0.90-0.97), older donor age (HR 1.06 with age as a continuous variable; 95% CI 1.00-1.11), larger allograft diameter (HR1.38; 95% CI 1.11-1.71) and the use of pulmonary allografts (HR 10.72; 95% CI 3.88-29.63). Calculated median time to reoperation for structural valve deterioration ranged from 23 years in a 65-year-old patient to 12 years in a 25-year-old.

Conclusions: Aortic valve replacement with allografts yields adequate midterm results. Although important changes have been made over the years to improve durability, allografts still have a limited life span especially in young patients.

Key words: allograft, aortic valve replacement, surgical technique, preservation technique

INTRODUCTION

The use of allografts for replacement of the aortic valve was initiated by Ross in 1962[1] and over the past decades the allograft has become a well-known aortic valve substitute. During this time period several changes in surgical techniques have been attempted to improve durability, and different preservation techniques have been employed to increase shelf half-life time and improve durability.

Ross initially employed the subcoronary implantation technique with good results. However, in the hands of less experienced surgeons early technical failure requiring reoperation was observed.[2,3] Nowadays, most centers use cryopreserved aortic allografts and employ the root replacement implantation technique with reimplantation of the coronary arteries.[4-6] A major advantage of this technique is the preservation of the aortic root geometry, minimizing initial regurgitation.[7] On the other hand, it requires radical root resection with the risk of complications associated with the reimplantation of the coronary arteries. In addition, on the long term the root may calcify and cause loss of aortic root compliance and an increased risk of leaflet damage caused by contact with the calcified root. Finally, replacement of allograft roots may be more complicated compared to subcoronary implanted allografts.

Also with regard to preservation and sterilization techniques changes have taken place over the years. Most centers now use cryopreserved valves, with the advantage of a long shelf half-life time. Whether the durability of cryopreserved valves is better compared to fresh 4ºC antibiotic stored allograft valves remains unclear.[4] The role of immunologic processes in allograft valve failure is still under debate, and although both cryopreserved and fresh allografts elicit a donor-reactive immune response there is (yet) no clear clinical evidence of associated increased allograft valve failure.[8,9]

We present our center's experience with the use of allografts for aortic valve or root replacement, illustrating the impact on outcome of the changes made in surgical and preservation techniques.

MATERIALS AND METHODS

Patients

From April 1987 until January 2001 275 allografts were used in 267 consecutive patients to replace the aortic valve or root. Eight patients had 2 aortic valve replacements with an allograft. In Table 1 the patient characteristics at the time of operation are displayed for all 275 operations, and separately for the subcoronary implantation group (SC group; N=95) and the root replacement group (ARR group; N=180).

Table 1. Pre-operative patient characteristics.

	All patients (N=275)	SC group (N=95)	ARR group (N=180)
Patient age (yrs) Mean (SD; range)	46.1 (16; 0.06-83.7)	45.9 (15; 14.2-83.7)	46.1 (17; 0.06-75.7)
Gender (M/F ratio)	201/74	67/28	134/46
NYHA class			
I	23% (N=62)	13% (N=12)	28% (N=50) *
II	26% (N=72)	27% (N=26)	26% (N=46)
III	32% (N=88)	48% (N=46)	23% (N=42)
IV-V	19% (N=53)	12% (N=11)	23% (N=42)
Heart rhythm			
Sinus	93% (N=256)	91% (N=86)	94% (N=170)
Atrial fibrillation	2.5% (N=7)	3% (N=3)	2% (N=4)
Other	4.5% (N=12)	6% (N=6)	3% (N=6)
Etiology			
Endocarditis	29% (N=81)	33% (N=31)	28% (N=50) *
Active endocarditis	*N=49*	*N=13*	*N=36*
Congenital	29% (N=80)	32% (N=30)	28% (N=50)
Aneurysm	8% (N=23)	--	12% (N=23)
Dissection	7% (N=18)	--	10% (N=18)
Rheumatic/degenerative	16% (N=44)	26% (N=25)	11% (N=19)
Other	11% (N=29)	9% (N=9)	11% (N=20)
Ischemic heart disease	9.5% (N=26)	12% (N=11)	9% (N=16)
Hypertension	15% (N=41)	15% (N=14)	15% (N=27)
Diabetes	3.3% (N=9)	4% (N=4)	3% (N=5)
Previous CVA	5% (N=14)	8% (N=8)	3% (N=6)
Prior cardiac operation	27% (N=73)	20% (N=19)	30% (N=54)
Mean creatinin (µmol/L)	104 (SD 88)	113 (SD 107)	98 (SD 75)
Left ventricular function			
Good	73% (N=201)	79% (N=75)	70% (N=126)
Impaired	19% (N=52)	17% (N=16)	20% (N=36)
Moderate-bad	7% (N=18)	4% (N=4)	8% (N=14)
Missing	1% (N=4)	--	2% (N=4)

SC= subcoronary implantation, ARR= root replacement.
* $p<0.05$ Pearson Chi-square test SC versus ARR group.
SD= standard deviation.

Allograft characteristics

Of the 275 allografts, 95 were implanted using the subcoronary implantation technique and 180 using the aortic root replacement technique. Initially the subcoronary technique was used, while in recent years the root replacement technique has become the technique

Table 2. Allograft properties.

	All patients (N=275)	SC group (N=95)	ARR group (N=180)
Type allograft			
Aortic	269	90	179 *
Pulmonary	6	5	1
Preservation			
Fresh	7	6	1 *
Cryopreserved	268	89	179
DMSO	*233*	*58*	*175 **
Glycerol	*35*	*31*	*4*
Diameter (mm; N=273)			
Mean (SD)	22.8 (2.2)	23.4 (2.3)	22.6 (2.1)#
<25 mm	220	64	156 *
≥ 25 mm	53	29	24
Type donor			
Non-heart-beating	71	13	58
Heart-beating	135	47	88
Domino heart	61	29	32
Donor age; Mean (SD; range)	39.7 (12; 9-63)	36.0 (13; 12-61)	41.6 (12; 9-63)
Quality code (N=263)			
1-2	114	59	55 *
3-5	149	29	120

SC= subcoronary implantation, ARR= root replacement, SD= standard deviation.
* Pearson Chi-square test or Fisher Exact test.
#ANOVA ($p<0.05$ SC versus ARR group).

of choice. In Table 2 the allograft characteristics are displayed. Most of the allografts were provided by the Rotterdam Heart Valve Bank (N=234), as allocated by Bio Implant Services, Leiden, The Netherlands. The remaining allografts were shipped from the Deutsches Herzzentrum, Berlin, Germany (N=17), the National Heart Hospital, London, United Kingdom (N=9), the Hospital Clinic I, Barcelona, Spain (N=8), the Karolinska Homograft Bank, Stockholm, Sweden (N=4), the Homograftbank AKH, Linz, Austria (N=1), the Oxford Heart Valve Bank, Oxford, United Kingdom (N=1), and the Heart Center North Rhein Westphalia, Bad Oeynhausen, Germany (N=1). No attempt was made to achieve ABO blood type or HLA type matching.

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 32 patients with ascending aorta or

arch pathology. Subcoronary implantation was initially done with scalloping of the sinus of Valsalva (N=32), while later on the non-coronary sinus was preserved (N=53).[10] Root replacement was performed as a freestanding root with reimplantation of the coronary arteries.[11] Surgical techniques were applied as described previously.[10,11] At the end of the operation routine echocardiography was done to assess allograft function.

Follow-up

All patients were prospectively followed over time either through the outpatient clinic and/or by means of an annual telephone survey. Standardized echocardiographic follow-up was done as described previously.[3] Mean duration of follow-up was 4.8 years (SD 3.6 years), ranging from 0 days- 13.8 years. Total follow-up was 1315 patient years, and 99% complete. Morbidity and mortality during follow-up were defined according to the 1996 guidelines for reporting morbidity and mortality after cardiac valvular operations.[12]

Statistical methods

Data are expressed as mean ± 1SD. Means were compared by the unpaired T-test. The χ^2-test or Fisher's Exact test was used to compare categorical variables. All tests were 2-sided, with an α-level of 0.05. Logistic regression was used to study potential determinants of early mortality (death during hospitalization or within 1 month after operation). Multiple logistic regression was used to study independent determinants for early mortality. The final model was obtained using the stepwise backward method with criteria for entry $P<0.05$ and removal $P>0.10$.

Cumulative survival and freedom from reoperation were analyzed using the Kaplan-Meier method. The survival of a patient started at the time of aortic valve operation and ended at death (event) or at 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 differences between Kaplan-Meier curves were evaluated using the log-rank test.

Multivariate analysis of time-related events (death, reoperation, and reoperation for structural valve deterioration) was done using the Cox proportional hazard regression model. Backward stepwise selection of potential predictors (criteria for entering variables: log-rank χ^2-test $P<0.05$) was employed. Covariables were examined by complete case analysis.

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.[13-15] 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.[16,17]

RESULTS

Early morbidity and mortality

Peri-operative data of all 275 patients and of the subcoronary implantation (N=95) and root replacement groups (N=180) are displayed in Table 3. In the root replacement group there were more urgent operations (within 24 hours after diagnosis), perfusion time was longer, and there were more patients who underwent concomitant procedures compared to the subcoronary implantation group. In addition, in the root replacement group circulatory arrest was employed in 32 patients (mean age 45 years; SD 17, range 5-75 years) for aortic arch surgery, in comparison to no patients in the subcoronary implantation group. 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 ostium stenosis. Another patient had annular calcifications extending up to the right coronary artery ostium that was very thin-layered and ruptured after reimplantation. A third patient had an acute endocarditis of an aortic bioprosthesis with abscesses, and the edematous right coronary

Table 3. Peri-operative data.

	All patients (N=275)	SC group (N=95)	ARR group (N=180)
Urgent operation (<24h)	11% (N=30)	2% (N=2)	16% (N=28) *
Valve pathology			
Stenosis	26% (N=70)	26% (N=25)	25% (N=45)
Regurgitation	61% (N=168)	58% (N=55)	63% (N=113)
Combined	13% (N=37)	16% (N=15)	12% (N=22)
Perfusion time (min); Mean (SD; range)	196 (74; 79-589)	175 (40; 116-316)	206 (85; 79-589)#
Cross clamp time (min); Mean (SD; range)	136 (43; 0-326)	132 (30; 79-248)	138 (48; 0-326)
Circulatory arrest	N=32	N=0	N=32*
Concomitant procedures			
No	52% (N=142)	68% (N=65)	43% (N=78)*
Yes	48% (N=132)	32% (N=30)	57% (N=102)
Early mortality	5.5% (N=15)	5.3% (N=5)	5.6% (N=10)
Perioperative stroke	3% (N=8)	2% (N=2)	3% (N=6)
Reoperation bleeding	12% (N=33)	14% (N=13)	11% (N=20)
Permanent pacemaker	3% (N=8)	4% (N=4)	2% (N=4)
Procedure-related CABG	2% (N=6)	--	3% (N=6)

SC= subcoronary implantation, ARR= root replacement, SD= standard deviation.

* Pearson Chi-square test or Fisher Exact test.

#ANOVA ($p<0.05$ SC versus ARR group).

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. Important postoperative complications were permanent pacemaker insertion in 8 patients, and reoperation for persistent bleeding in 33 patients.

During the procedure 4 patients died, and 11 more patients died during the same hospitalization or within 30 days postoperative (operative mortality 5.5%). The 4 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) and left ventricular failure in 1 patient who presented with acute endocarditis with fistula to the left atrium. Causes of death in the 11 patients who died during the same hospitalization or within 30 days postoperative were registered as cardiac and not valve-related in 8 patients, 1 patient 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. Independent risk factors for early mortality were patient age>40 at operation (OR 8.8, 95% CI 1.1-70.8; p=0.04), preoperative kidney dysfunction (expressed as preoperative creatinin level (continuous variable), OR 1.0, 95% CI 1.0-1.0; p=0.007), and procedure-related CABG (OR 12.1, 95% CI 1.2-119.0; p=0.03). In addition, longer perfusion times showed an association with impaired early survival (P=0.07).

Long-term mortality

During follow-up another 29 patients died. Of these patients 21 died of non-valve-related causes. Six patients died sudden unexpected and unexplained deaths, 1 patient died due to a major bleeding, and 1 patient died of acute heart failure caused by severe aortic insufficiency while waiting for reoperation of a degenerated aortic allograft 7.9 years after the initial procedure. Overall cumulative survival including early survival was 93% at 1 year (95% CI 90-96%), 87% at 5 years (95% CI 83-92%), and 73% at 9 years postoperative (95% CI 66-81%). In Figure 1 cumulative survival for patients operated with the subcoronary implantation technique and the root replacement technique is displayed separately (Log-rank test p=0.006). Independent risk factors for overall mortality were older patient age>40 years (HR 3.6, 95% CI 1.7-7.5; p=0.001), root replacement technique (HR 2.2, 95% CI 1.1-4.7; p=0.04), preoperative heart rhythm other than sinus rhythm (HR 1.9, 95% CI 1.3-2.7; p<0.001), longer perfusion time (in minutes, HR 1.0, 95% CI 1.0-1.0, p=0.02), diabetes mellitus (HR 3.0, 95% CI 1.1-8.3; p=0.03), and preoperative ventilatory support (HR 4.1, 95% CI 1.3-12.9; p=0.02).

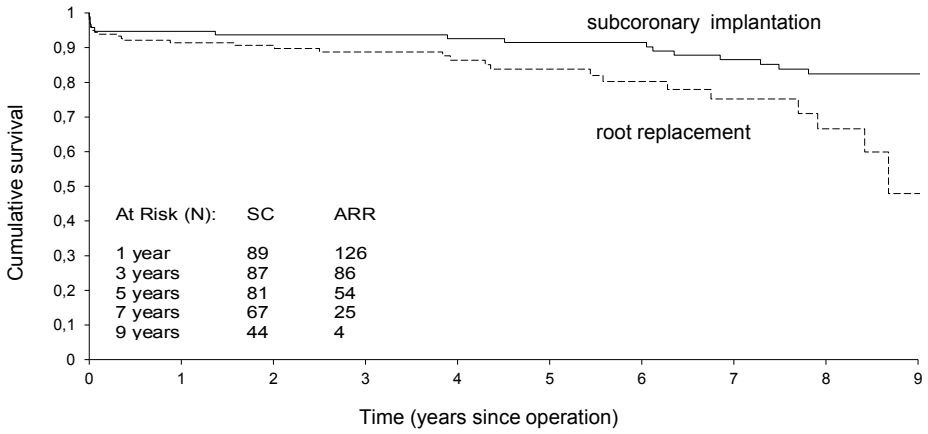

Figure 1. Cumulative survival of patients operated using the subcoronary implantation technique (solid line; SC) and the root replacement technique (interrupted line; ARR); Log-rank test p=0.005.

Reoperation

Reoperation for allograft related causes was necessary in 34 patients. Reason for reoperation was structural valve deterioration in 22 patients (early technical in 3 SC patients at 0.5, 0.8 and 1.1 years postop; degenerative in 19 patients at 0.4, 4.4, 4.9, 5.0, 5.7, 5.7, 6.0, 6.2, 6.4, 6.7, 6.8, 8.1, 8.3, 8.4, 8.5, 9.8, 10.0,and 10.9 years postoperative). Non-structural valve failure required reoperation in 11 (paravalvular leakage in 8 patients from the SC group at 0.05, 0.2, 0.5, 1.1, 1.2, 1.3, 2.0 and 3.7 years postop, 1 replacement of an allograft root for pseudo-aneurysm at 2.6 years, 1 closure of a false aneurysm in a ARR patient at 1.9 years, 1 removal vegetation from proximal suture line of an allograft root at 0.06 years postop), and persistent endocarditis in 1 patient at 0.06 years. Freedom from reoperation for allograft-related causes was 97% at 1 year (95% CI 95-99%), 90% at 5 years (95% CI 86-94%), and 77% at 9 years (95% CI 69-85%), and worse in the SC compared to ARR group due to increased early technical failure (Figure 2; Log-rank test p=0.03).

Structural valve deterioration

Structural valve deterioration requiring reoperation and replacement of the allograft occurred in 22 patients. In 3 patients in the SC group allograft replacement occurred early after operation due to technical valve failure related to the implantation technique. In 2 of these patients a prolapse of one of the cusps caused moderate to severe regurgitation that was already noticed at discharge by means of echocardiography and necessitated replacement with a bioprosthesis and a mechanical valve at 0.8 and 1.1 year postop. The prolapse of the cusps was most likely caused by imperfect positioning of the allograft

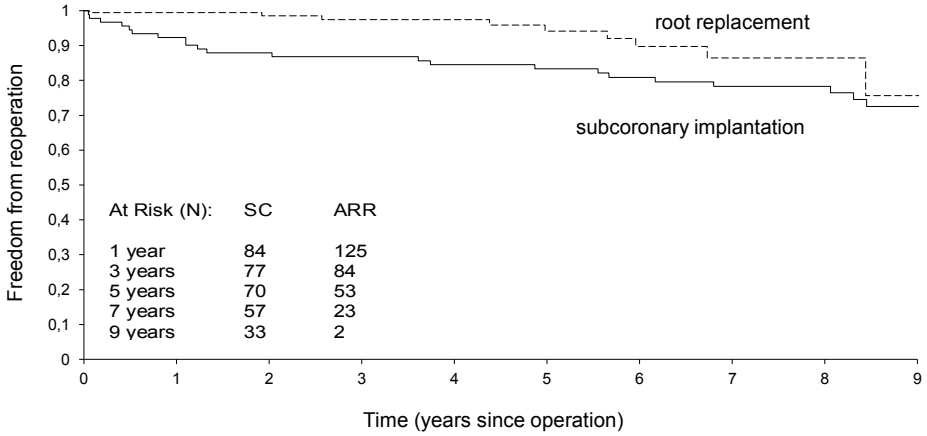

Figure 2. Cumulative freedom from allograft-related reoperation of patients operated using the subcoronary implantation technique (solid line; SC) and the root replacement technique (interrupted line; ARR); Log-rank test p=0.03.

valve in the aortic annulus. The third patient developed progressive dyspnea with severe aortic regurgitation 4 months postoperative and at reoperation (6 months postoperative) the non-coronary cusp was noted to be fused with the aortic wall and the allograft was replaced with a mechanical valve. The fusion of the cusp with the aortic wall was most likely caused by oversizing of the allograft valve.

In the other 19 patients structural valve deterioration caused by degeneration of the allograft was the reason for replacement of the allograft. This occurred in 12 patients in the SC group and in 7 patients in the ARR group. The allograft was replaced by a mechanical valve in 14 patients, an allograft in 3 patients (1 subcoronary implantation; 2 root replacement), and a modified autograft procedure was performed in 2 patients. Freedom from reoperation for structural valve deterioration caused by degeneration of the allograft (N=19) was 97% at 5 years (95% CI 93-100), 89% at 7 years (95% CI 85-95%) and 83% at 9 years postoperative (95% CI 75-91%). The results of the univariate and multivariate analyses of potential determinants of degenerative structural valve deterioration are displayed in Table 4. Independent predictors of structural valve deterioration requiring reoperation were younger patient age at the time of operation, the use of fresh allografts, larger allograft diameter, and older donor age. Mean age at the time of operation of those patients requiring reoperation for degenerative structural valve deterioration (N=19) was 33 years (SD 12; range 14-57 years). In Figure 3 the Weibull function representing the effect of patient age on freedom from structural valve deterioration is displayed. For example, for a 45-year-old patient median time to reoperation for structural allograft valve deterioration was 16.5 years.

Table 4. Risk factor analysis for degenerative structural valve deterioration requiring reoperation (N=19).

	Univariate model HR (95% CI)	P-value	Multivariate model HR (95% CI)	P-value
Patient age (yrs)	0.96 (0.93-0.98)	0.002	0.93 (0.90-0.97)	<0.001
SC vs ARR technique	1.41 (0.51-3.92)	0.51	--	--
Donor age (yrs)	1.04 (1.00-1.08)	0.05	1.06 (1.00-1.11)	0.045
Diameter allograft (mm)	1.41 (1.13-1.76)	0.003	1.38 (1.11-1.71)	0.004
Pulmonary vs aortic allograft	4.43 (2.01-9.74)	<0.001	10.72 (3.88-29.63)	<0.001
Cryopreserved vs fresh allograft	0.63 (0.14-2.88)	NS	--	--
Cryo method*	1.38 (0.71-2.69)	NS	--	--

*Cryo method = Glycerol versus DMSO preservation; NS = not significant (p>0.20).

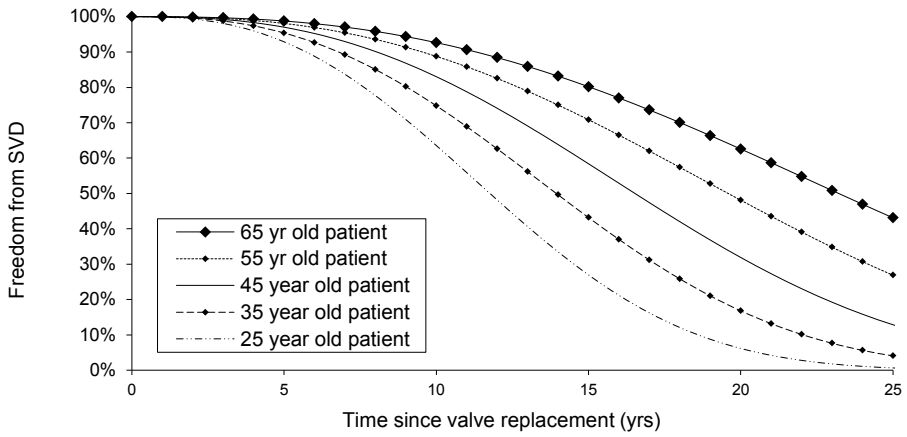

Figure 3. Weibull estimate of age-dependent freedom from structural valve deterioration (SVD) after allograft aortic valve or root replacement for patients aged 25, 35, 45, 55 and 65 years at the time of operation.

Other valve-related complications

One patient had a non-fatal ischemic stroke of the right hemisphere 2.5 years postoperative of which he recovered partially. Another patient, who had a perioperative stroke, developed a non-fatal ischemic stroke 3 years postoperative. The linearized annual occurrence rate (LOR) for stroke was 0.15%/patient year. One patient had a reversible neurological deficit (RIND), and 6 patients had one or more episodes of transient ischemic attacks. One patient who received cumarin therapy because of a mechanical valve in mitral position had a major kidney bleeding 2.2 years postoperative, of which he recovered completely (INR 4.8 at the time of the event). Another patient, who received cumarin therapy for atrial fibrillation, developed a lethal intracerebral bleeding 4.8 years postoperative (INR>8.0 at the time of

the event). The LOR for major bleeding was 0.15%/patient year. One patient developed an endocarditis with intracranial abscesses 5 years postoperative that was treated medically (LOR 0.08%/patient year). No valve thrombosis or peripheral embolism was observed.

DISCUSSION

During the past 13 years major changes have taken place in allograft aortic valve replacement in our center, not only in surgical and preservation techniques but also with regard to patient profile. Root replacement has become the preferred surgical technique, and solely cryopreserved aortic allografts are used nowadays. With the shift of surgical technique from subcoronary implantation to root replacement, the patient profile also changed. While isolated disease of the aortic valve leaflets requiring elective surgery was most common when the subcoronary implantation technique was still in use, nowadays a considerable proportion of patients presents with complex aortic root disease and/or active endocarditis often requiring urgent surgery. Also, concomitant procedures are more common and circulatory arrest is employed more often in the root replacement technique group compared to patients operated using subcoronary implantation. Surprisingly, this has not resulted in an increase in early mortality and reflects the growing surgical expertise with allograft aortic root replacement in our center. On the downside, procedure-related coronary artery bypass grafting has emerged as an important complication of the root replacement technique.

Important predictors of early mortality were patient age and impaired preoperative renal function, and confirm the findings by Lund et al.[5] Procedure-related coronary artery bypass grafting was also associated with increased early mortality (2 of the 6 patients; OR 13.1). This operative complication is restricted to root replacement and related to the reimplantation of the coronary arteries that is necessary using this technique.

Overall survival was better in patients operated with the subcoronary technique compared to the root replacement technique, reflecting the change in patient profile that took place over the years. This is contradictory to what Lund et al report[5], and also not supported by the experience from O'Brien's group.[4] It can be explained by the fact that the patient populations of these other centers consist of relatively more patients with isolated valve disease, while only a minority presents with aortic root disease and/or endocarditis.

As has been reported previously[3-5] younger patient age is the most important predictor of structural valve deterioration. This is confirmed by our findings. In addition, we used a Weibull model to calculate long-term freedom from reoperation for structural valve deterioration based on our current midterm results. It should be stressed that the estimates from the Weibull model are based on the assumption that the risk of structural valve deterioration increases with time. Therefore, the estimates beyond 13 years are still

hypothetical and will require regular validation and refinement using the growing experience with allografts worldwide. Currently, using the Weibull model the calculated median time to reoperation for structural valve deterioration varies from 23 years in a 65-year-old patient down to 12 years in a 25 year old (Figure 3). This reflects the need for improvement of the durability of the allograft, and also raises the question whether allografts are the preferred aortic valve substitute in the younger age groups. In these patients other valve substitutes should be seriously considered. In our center, children who require surgical treatment of their aortic valve disease preferably undergo valvotomy or a modified autograft procedure. We reported previously that in patients after autograft aortic root replacement calculated median time to explantation of the autograft for structural valve deterioration was 25 years[18], much better than the estimates derived from our allograft population. Also, no relation between autograft structural valve deterioration and patient age was observed. On the other hand, there is yet little information on the durability of the allograft in the right ventricular outflow tract after autograft aortic root replacement. This is a factor that may be of influence when considering the durability of the autograft procedure. In selected patients a mechanical valve is also a good alternative to the allograft. We previously showed that in younger patients with mechanical bileaflet prostheses the impact of bleeding and thrombo-embolic complications is relatively low, since the life expectancy of these patients is markedly reduced and they will not reach older age where these events become important determinants of outcome.[19]

According to our findings, older donor age is also a predictor of structural valve deterioration. Lund et al previously described that the difference between donor age and patient age is the most important determinant for tissue failure after aortic valve replacement with 'homovital' allografts.[5] We did not attempt to investigate this factor in our model, since in our opinion it combines two separate risk factors for allograft structural valve deterioration. Younger patient age is an approximation of an increased workload on the allograft and possibly an increased immune response, while older donor age represents the aging and wear out of the valve substitute. Although donor age is not (yet) a very strong risk factor for structural valve deterioration, it may be advisable to preferably use allografts from younger donors, at the least in the younger patient group.

Other well-known risk factors for structural valve failure in our series were large diameter of the allograft and the use of pulmonary allografts. With the introduction of the root replacement technique, matching of the size of the allograft to the recipient aortic annulus has become less important. Nevertheless, in the multivariate analysis larger allograft size still was an important predictor of allograft structural valve failure independent of patient age and surgical technique. Further investigation into the possible causes that could explain this observation is necessary.

Our experience with fresh wet-stored allograft valves (N=7) is limited, and we find no difference in the durability of fresh compared to cryopreserved allografts. Previous reports

tended to be in favor of cryopreserved over fresh valves with regard to durability.[20,21] However, a recent publication from O'Brien and colleagues[4] shows that in their extensive experience with over 1,000 implantations the freedom from structural valve deterioration at 20 years is similar for cryopreserved and 4°C anti-biotic stored valves.

Another issue that is often being raised is the influence of surgical technique on the durability of the allograft in aortic position. We have shown previously that the subcoronary implantation technique has a surgeon's learning curve that results in more initial aortic regurgitation and early reoperation compared to the root replacement technique.[3] The progression of aortic regurgitation over time is small in both techniques and it yet remains unclear whether and how the surgical technique will influence durability. The high incidence of early technical failure with the subcoronary implantation technique in our center, and the potential advantage of the preservation of the aortic root geometry using aortic root replacement, has led us to nowadays only use the root replacement technique. It is however a more extensive operation that requires reimplantation of the coronary arteries with the potential complication of coronary malperfusion. Therefore it is essential to pay close attention to the sizing of the coronary buttons and to carefully select the reimplantation site to avoid kinking or stretching of the reimplanted coronary artery. From our current study, we still observe the early increased reoperation rate due to technical failure in the subcoronary implantation group, and thereafter progression of structural valve deterioration is similar to that of the root replacement group. There may however be evidence in favor of the subcoronary implantation technique over the root replacement technique with regard to long-term freedom from reoperation, when carefully studying O'Brien's most recent update of the pioneer series from Australia.[4]

With regard to the other valve-related events after allograft aortic valve replacement that were observed in this prospective ongoing study, it can be stated that these occur infrequently. In this respect the allograft is far superior to mechanical and bioprosthetic valves.

In conclusion, we have shown that aortic valve replacement with allografts yields adequate midterm results. Although important changes have been made over the years to improve durability, allografts still have a limited life span especially in young patients. Effort should be made to improve the durability of this valve substitute and to optimize the use of allografts. Most importantly, given the current evidence other aortic valve substitutes should be seriously considered in younger patients.

ACKNOWLEDGEMENTS

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Chapter 3

Allografts for aortic valve or root replacement: insights from an 18-year single-center prospective follow-up study

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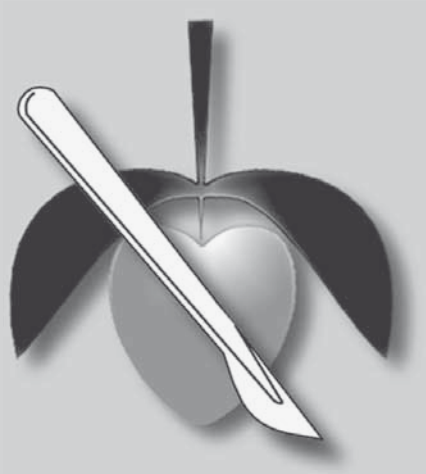

ABSTRACT

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 micro-simulation, 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 technique was used, while since

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.

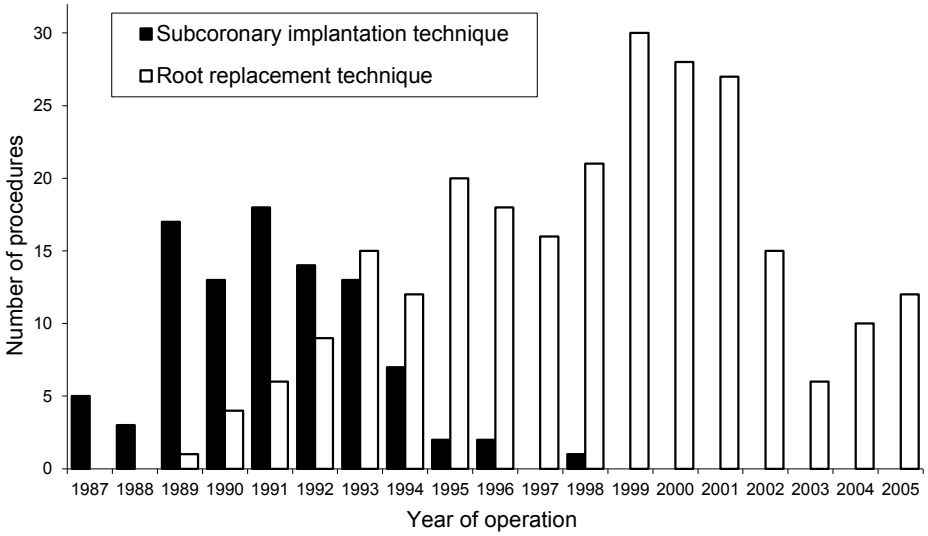

Figure 1. Number of allografts implanted with the subcoronary implantation technique and the root replacement technique by year of operation

1998 the root replacement technique has become the technique of choice (Figure 1). 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. Cat-

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.

egorical data are presented as proportions, and comparison 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 Tyrone-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 bioprosthesis.[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

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.

coronary artery buttons were very big, probably causing malperfusion of both the right and left coronary artery.

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 (Tyrone-Ware test p=0.03). Independent predictors of late mortality were older patient age (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

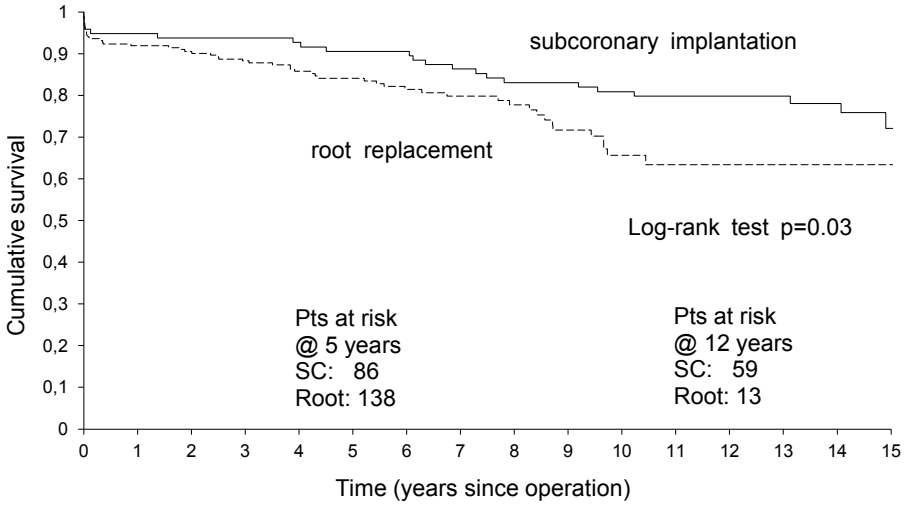

Figure 2. Cumulative survival after subcoronary implantation versus root replacement.

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 (Tyrone-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 (Tyrone-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.

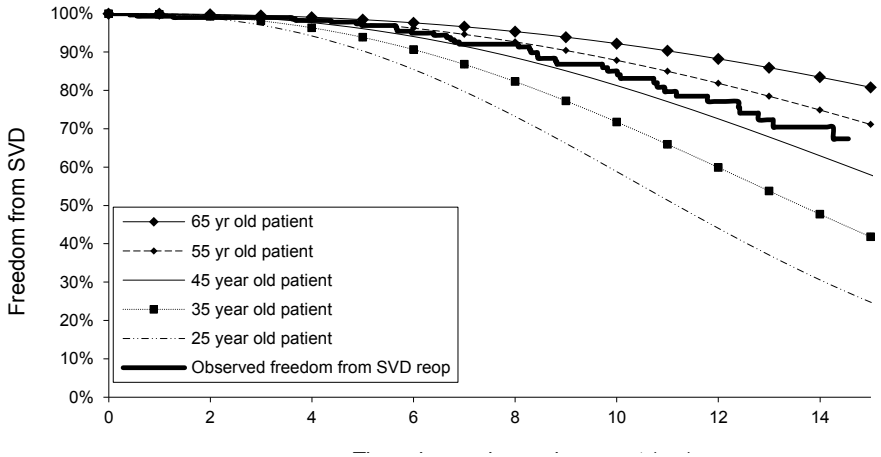

Figure 3. Observed freedom from reoperation for structural valve deterioration (SVD). Superimposed on this curve is the age-dependent Weibull estimate of age-specific freedom from reoperation for structural valve deterioration for patients aged 25 through 65 years at the time of operation.

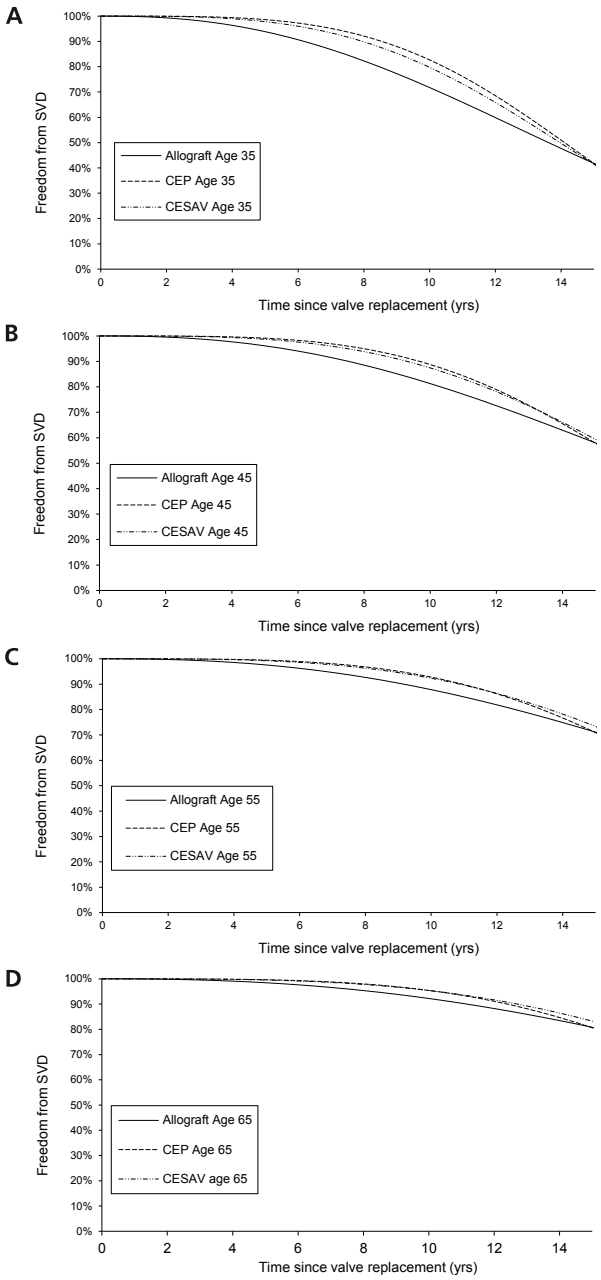

Figure 4a-d. Weibull estimate of age-specific freedom from reoperation for structural valve deterioration of allografts versus CE pericardial versus CE-SAV stented bioprostheses for patients aged 35 (Figure 4a), 45 (Figure 4b), 55 (Figure 4c) and 65 years (Figure 4d) at the time of operation.

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 than 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 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 through 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

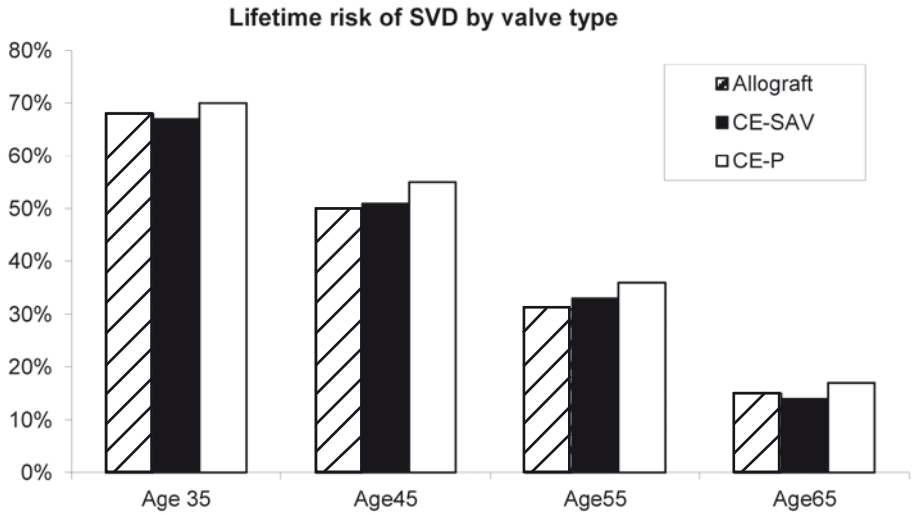

Figure 5. Age-specific microsimulation-based estimates of actual patient lifetime risk of structural valve deterioration requiring reoperation for allografts versus CE pericardial versus CE-SAV stented bioprostheses.

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 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

Autograft or allograft aortic valve replacement in young adult patients with congenital aortic valve disease

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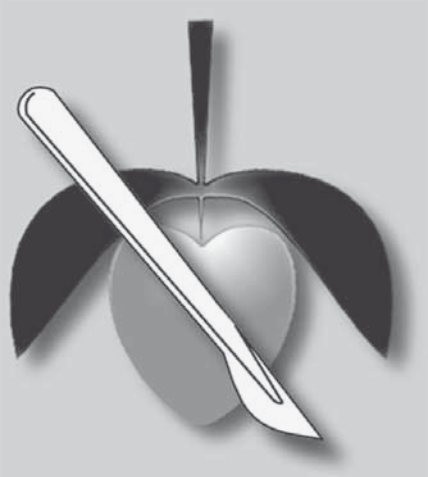

ABSTRACT

Aims: We analysed the 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, participating in our ongoing prospective follow-up study, underwent 63 autograft and 106 allograft aortic valve replacements (AVRs). Mean age was 35 years (SD 10.8), 71% were males. Aetiology was 71% bicuspid valve, 14% other congenital, and 15% BV endocarditis. Twenty-two percent underwent previous cardiac surgery; 11% had an ascending aorta aneurysm. Two patients died in hospital. During follow-up six more patients died and 45 patients required valve-related re-operations. Thirteen-year survival was 97% for autograft and 93% for allograft recipients, 13 year freedom from valve-related re-operation was 63% for autograft and 69% for allograft patients.

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

Key words: Aortic valve replacement, congenital aortic valve disease, young adults, prosthetic valve selection, autograft, allograft

INTRODUCTION

Prosthetic valve selection for patients who require aortic valve replacement (AVR) 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 a 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 AVR in the late 80s, assuming that their durability would be better compared with 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 make present reliable observations on valve performance and patient outcome well into the second decade after operation.

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

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 receive an autograft or allograft in aortic position in our centre are followed prospectively at yearly intervals. Completeness of follow-up is currently 98%.[2–4] Institutional Review Board approval was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent.

We performed in this prospective cohort of 499 patients a retrospective analysis of those patients with congenital aortic valve disease, no previous AVR, 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 enrolment was based on the presence of congenital aortic valve disease, either determined on pre-operative echocardiography or based on the abnormalities seen at operation.

The total number of excluded patients was 330, of these patients, 70 patients were younger than 16 years of age and 106 patients were older than 55 years. These patients were excluded 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 aetiology than congenital aortic valve disease. Other aetiologies were rheumatic disease (*n* = 21), endocarditis (*n* = 44), senile degeneration of a tricuspid valve (*n* = 20), aneurysm (*n* = 15), dissection (*n* = 13), and re-operation (*n* = 41). This selection resulted in 169 patients: 63 autograft patients and 106 allograft patients. Pre-operative 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 re-implantation of the coronary arteries in 61 autograft patients and 66 allograft patients. In two 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 (LVOT) 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 is paid to place the autograft inside the annulus. During the autograft procedure, reconstruction of the right ventricular outflow tract (RVOT) was done using an allograft. Details on these allografts are displayed in Table 2. 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 receive 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 post-operative, 1 year post-operative, 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 re-operation or death.

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.

The study database was frozen for analysis on 1 April 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.

Table 2. Allograft characteristics

	Autograft (RVOT conduit), n=63	Allograft, n=106
Type allograft		
Pulmonary	100% (n=63)	2% (n=2)
Aortic	-	98% (n=104)
Size allograft (mm)		
Mean (SD; range)	25 (2; 19-30)	23 (2; 20-28)
≤ 24 mm	63% (n=40)	80% (n=85)
>24 mm	37% (n=23)	20% (n=21)
Type donor (4 missing)		
Heart beating	44% (n=28)	51% (n=54)
Non heart beating	54% (n=34)	31% (n=33)
Domino	2% (n=1)	14% (n=15)
Donor age; Mean (SD; range)	43 (11;10-59)	40 (12; 15-62)
Donor sex (7 missing)	42 male/ 21 female	65 male/ 34 female
Preservation method		
Cryopreserved	100% (n=63)	96% (n=102)
Fresh	-	4% (n=4)

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 χ^2 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 two categories.

Univariable logistic regression was used to assess differences in patient and procedural characteristics between autograft and allograft procedures. Univariable logistic regression was used to determine factors associated with the different valve substitute groups. The following factors were analysed: age at operation (continuous variable expressed in years), sex, previous surgery on the LVOT, New York Heart Association Class (defined as I, II, III and IV), pre-operative creatinin level (micromoles/L), pre-operative ventilation support, abnormal cardiac rhythm pre-operative (other pre-operative 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 pre-operative haemodynamic diagnosis.

Cumulative survival and freedom from re-operation or re-intervention were analysed 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 analysed as potential risk factors for re-operation for structural failure:

Patient age, gender, previous cardiac surgery, endocarditis as the aetiology 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 statistically significant. All testing was performed two-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 re-operation 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; $P = 0.005$), more commonly underwent elective surgery (OR 2.6, 95% CI 1.01–6.6; $P = 0.05$), and had a good pre-operative 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 pre-operative 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 among allograft recipients.

Two allograft patients received a pulmonary allograft in the aortic position (Table *2*). One of the patients required a re-operation within 2 weeks after initial implantation of the pulmonary allograft and received a new aortic allograft. Six years after this allograft implantation this patient required another re-operation and received a mechanical prosthesis. This patient is alive today. The other pulmonary allograft patients required a re-operation 6 years after allograft implantation. Unfortunately, this patient died 3 years after the re-operation due to an intracerebral bleeding.

Early morbidity and mortality

Peri-operative 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 in what follows). The other autograft patient died on the 13th post-operative 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

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.

employed in four allograft root replacement patients because additional replacement of the ascending aorta with a vascular prosthesis was required, and in one autograft patient because the ascending aorta perforated during sternotomy.

Follow-up and survival

During follow-up six 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.

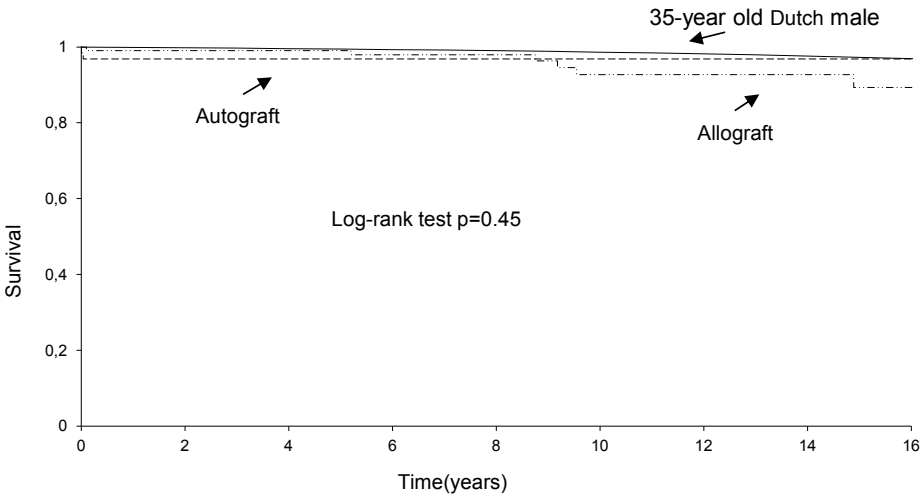

Figure 1. Survival after allograft or autograft operation compared with 35-year old males in the general Dutch population

Re-operation

During follow-up there were 45 valve-related re-operations: 37 for structural valve deterioration, seven for non-structural valve deterioration, one for recurrent endocarditis.

Sixteen autograft recipients (LOR 2.5%/patient year) and 21allograft recipients (LOR 1.9%/patient year) required re-operation 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 four of the 10 autograft re-operations 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 seven re-operations for non-structural valve failure or technical valve failure occurred all in allografts that were implanted using the subcoronary technique (LOR 0.64%/patient year).

The re-operation for recurrent endocarditis was in a patient with a subcoronary allograft (LOR 0.09%/patient year). See Table 4 for details on re-operations.

There was no re-operative mortality. One autograft patient who received a mechanical valve conduit had a major stroke in the immediate post-operative period.

Overall freedom from aortic valve re-operation was 94.5 ± 1.8% at 5 years and 61.4 ± 5.5% at 13 years. For autograft patients freedom from aortic valve re-operation was 100% at 5 years and 63.4 ± 9.6% at 13 years, for allograft patients 91.2 ± 2.8% at 5 years and 59.8 ± 6.8% at 13 years (P = 0.48). See also Figure *2*.

Table 4. Details on reoperations

	Autograft (n=16)	Allograft (n=29)	p-value
Total patient years	650	1093	0.99
Cause for aortic valve reoperation			
Structural failure	n=16	n=21	0.02
Non-structural valve deterioration	-	n=7	0.03
Endocarditis	-	n=1	0.45
Valve substitute inserted at reoperation			
Mechanical prosthesis	-	n=15	<0.001
Bentall procedure	n=13	n=6	<0.001
Autograft	-	n=4	0.12
Allograft	n=2	n=3*	0.83
Stentless bioprosthesis	n=1	n=1	0.66
Mean CPB time (n=29, minutes; range)	237 (129-389)	182 (79-321)	0.07
Mean clamp time ((n=29,minutes; range)	151 (96-271)	120 (59-196)	0.10

* subcoronary allografts

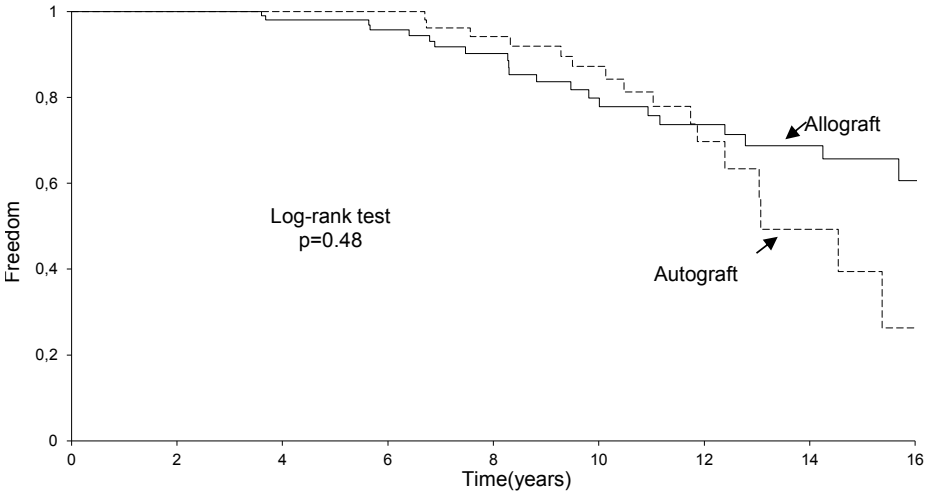

Figure 2. Freedom from reoperation for any cause

Freedom from aortic valve re-operation 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 re-operation for structural failure in both the allograft and autograft group. Figure 3 shows the observed freedom from re-operation from structural valve deterioration

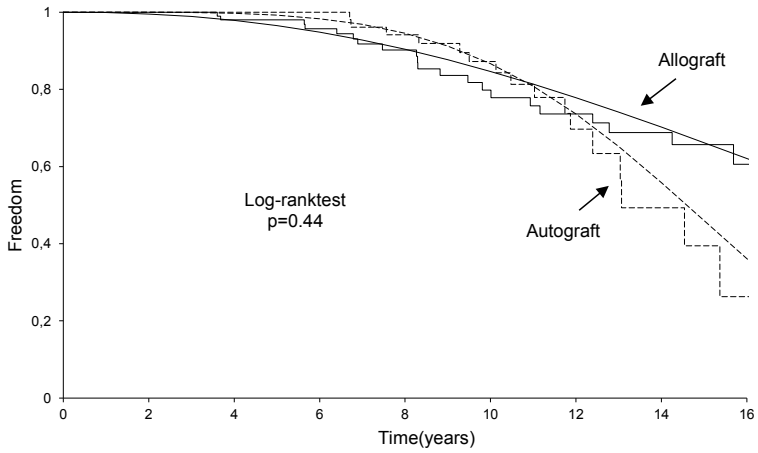

Figure 3. Freedom from reoperation for structural failure. The smooth curves (solid for allografts; interrupted for autografts) represent Weibull estimates of reoperation for structural failure)

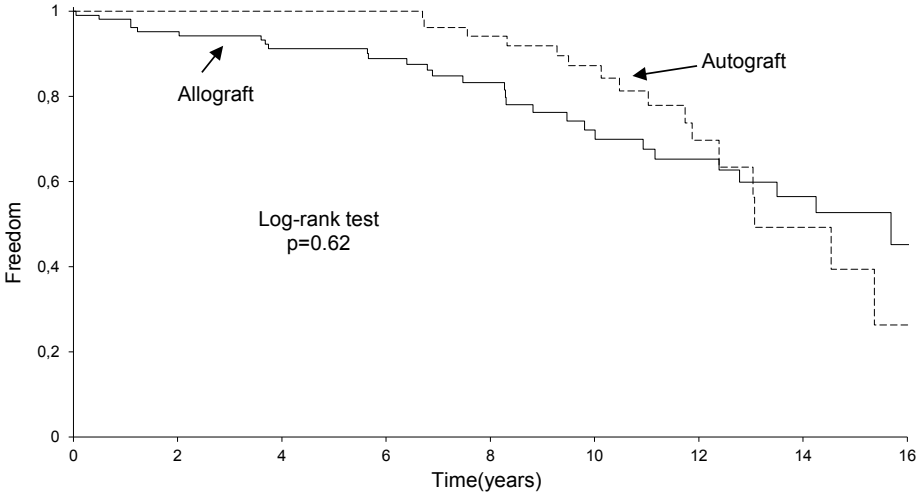

Figure 4. Freedom from any valve-related even

and the corresponding Weibull functions representing the increasing hazard with time of structural valve deterioration for both allografts and autografts.

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

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

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 re-operation 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 re-operation later in life.

Early morbidity and mortality

AVR 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 with that of the general age-matched Dutch population. Allograft patients more often underwent AVR for endocarditis on the aortic valve or valve prosthesis, a factor that may have affected long-term survival. However, only one of the six late deaths was in a patient with endocarditis aetiology, 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 *et al*.,[11] although survival differences between the two valve substitutes were not significant. When comparing patient survival after AVR 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.

Re-operation

Although freedom from re-operation for any cause was comparable for both the allograft and autograft, causes for re-operation differed considerably between the valve types. Indications for re-operation 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 re-operation 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 LVOT 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 re-operation 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 *et al*.[24] observed in a recent autograft explant study that there was no association between bicuspid valve disease and histological changes in explanted pulmonary autografts.

The necessity for re-operation 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 with 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 *et al*.[30] 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. 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]

Although the CPB times for re-operation on a pulmonary autograft are observed to be longer, yet not significant, re-operation on a calcified allograft 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 re-operations are low in our study population.Concha *et al*.[32] 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,

thrombo-embolic complications related to coumarin, and prosthetic valve endocarditis in mechanical prosthesis group. 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 re-operations for structural valve deterioration in the second decade after operation.

Conflict of interest: none declared.

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Chapter 5

The Ross operation: a Trojan horse?

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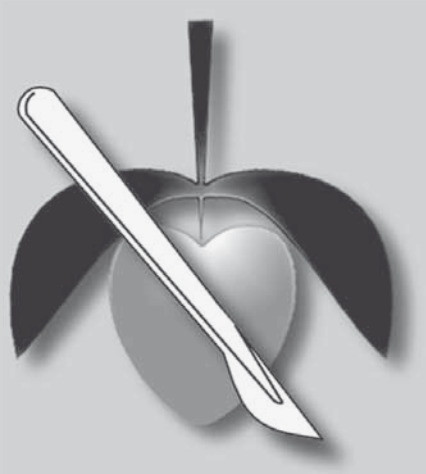

ABSTRACT

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 four more patients died. Thirteen-year survival was 94 ± 2%. Over time, 22 patients required autograft reoperation for progressive neo-aortic root dilatation. In addition, eight 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 ± 5%. Risk factors for autograft reoperation were previous AVR and adult patient age.

Conclusion: 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 (LV) outflow tract with encouraging results.[2] It became a worldwide-accepted procedure for aortic valve replacement (AVR) 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 years most of the centres shifted towards the root replacement technique—the most commonly used implantation technique nowadays. Conservation of the autograft root appeared to be more versatile and associated with a decreased incidence of early and late failure when compared with the other techniques.[3,4]

Several studies reported satisfactory mid-term 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 when 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 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 AVR: six subcoronary homografts, three biological prostheses, and three 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.

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)

CABG= coronary artery bypass grafting, LVOT= left ventricular outflow tract, CPB= cardiopulmonary bypass.
*Includes patients requiring tailoring of the ascending aorta or subvalvular membrane resection.

Operation

Perioperative data are shown in Table 2. All surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. In three 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 by 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 two 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.

Follow-up

All patients were followed-up prospectively, contacted annually and interviewed over 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 to 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 the time of reoperation or death. Patient survival started at the time of Ross operation and ended at the time of death or at last follow-up. Survival of the autograft or pulmonary allograft started at the 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 1 October 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 SD and were compared using the unpaired *t*-test. Discrete data are presented as proportions and were compared using the χ^2 test or Fisher's exact test. Cumulative survival and freedom from reoperation or reintervention were analysed using the Kaplan–Meier method. Survival is displayed as proportion ± SE. 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 AVR, patient age, bicuspid valve disease, the surgical technique used (root replacement vs. inclusion cylinder technique), and haemodynamic diagnosis (regurgitation vs. stenosis vs. 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 ≤ 0.05 was considered statistically significant. All testing was performed two-sided. For all data analysis, SPSS 12.0.1 Windows (SPSS, Chicago, IL, USA) was used.

RESULTS

Hospital mortality and late survival

Hospital mortality was 2.7% (four 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 LV hypertrophy died due to mediastinitis and sepsis 13 days after surgery.

During follow-up four more patients died. There were one valve-related and three 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 $P = 0.35$).

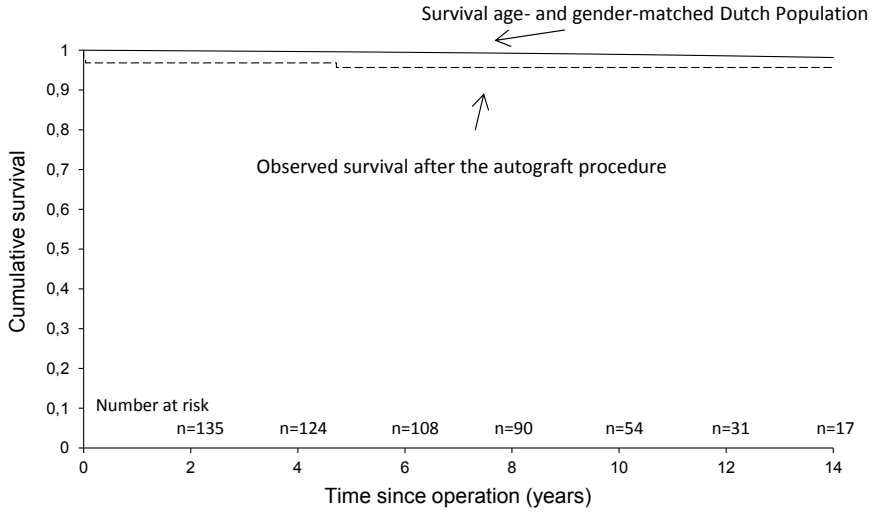

Figure 1. Observed cumulative survival after the Ross operation and survival of the age- and gender-matched general Dutch population

Reoperation

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

Table 3 Details on Ross operation-related reoperations

Patient	Sex	Age at Ross operation	Years to reoperation	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

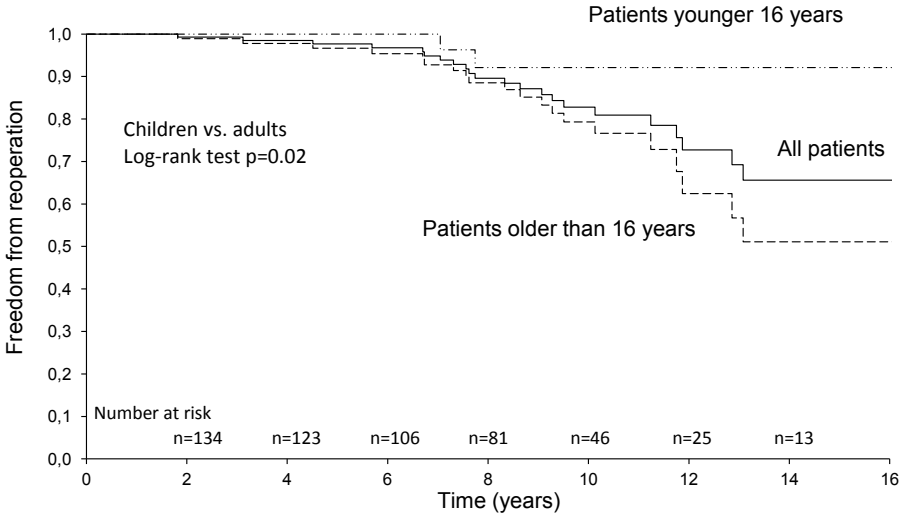

Figure 2 Overall freedom from autograft reoperation and freedom from autograft reoperation for adult patients (16 years and older) versus children

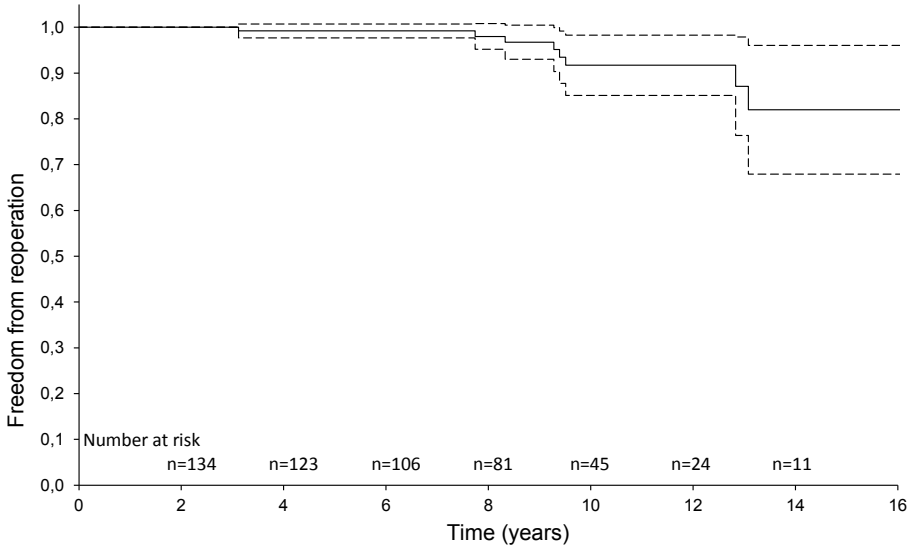

Figure 3 Freedom from pulmonary allograft reoperation for all 146 patients. The dotted lines indicate upper limit and lower limit of the 95% confidence interval.

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 balloon valvuloplasty of the RVOT to relieve supravalvular pulmonary stenosis.

Table 4. Risk factors for autograft reoperation HR = hazard ratio, with 95% confidence intervals (C.I.)

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

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 was 87.1 ± 5.5% (Figure 3). Freedom from allograft reoperation for structural failure did not differ for patients younger than 16 years when compared with patients aged 16 years and older at the time of operation [80.0 ± 1.1 vs. 92.5 ± 3.8% at 13 years (log-rank test $P = 0.73$)].

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

During the last follow-up, 95% of the patients were in New York Heart Association (NYHA) class I or II. Eleven per cent of the patients had moderate to severe aortic regurgitation, 3% with 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 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 when 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 those 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 randomized trial by Yacoub and co-workers,[18] the pulmonary autograft was compared with the allograft, and a survival advantage on the long-term was observed in favour of the pulmonary autograft.

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 the 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 the application of this technique varies among surgeons.[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, whereas 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 *et al*.[20] report the results of a single centre, 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 when compared with 44% for adults). Other reports confirm the observation that fewer reoperations are seen in children.[26–28] However, Luciani *et al*.[10] found an opposite effect of patient age on autograft dilatation, but not on reoperation. 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 (six subcoronary homografts, three biological prostheses, three 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 eight patients required reoperation, which is comparable with 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 the 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 to calcification, this could be an alternative to surgery.[30]

During follow-up, endocarditis and thrombo-embolic 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 centre, 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 a 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 certainly requires a reoperation later in life. Because of the large number of patients who return to our centre 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

Although 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 AVR with optimal benefits and enhanced durability for the patients.

Conflict of interest: none declared.

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Chapter 6

Aortic root replacement after aortic valve or ascending aortic surgery

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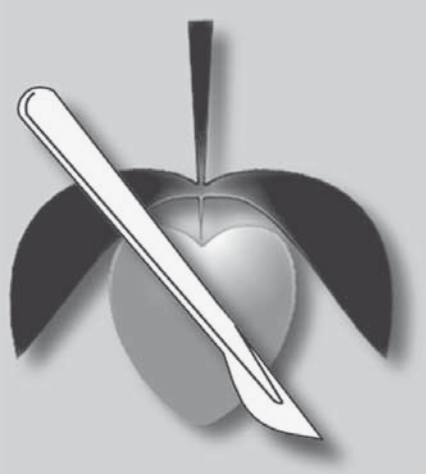

ABSTRACT

Background: Reoperative aortic root replacement (RARR) is a complex and 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, 23 allografts, 28 pulmonary autografts and 49 native valves.

RARR indications were: structural failure 47%(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) prosthetic valve patients, 13%(n=3) allograft patients, 6%(n=3) native valve patients, and 0% autograft 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 0-18 years) 13 patients died(LOR 1.3%/patient year); 8 prosthetic valves patients, 1 allograft patient, 3 native valve patients and 1 autograft patient.

Overall 10-year survival was 78%±4%; for prosthetic valve patients 65%±8%, for allograft patients 82%±8%, for native valve patients 87%±5% and for autograft 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 type of 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, and the aging population 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.[4-7] In our center a high volume of pulmonary autograft procedures and aortic allograft implantations was performed over the past 2 decades. The use of these operations is a matter of debate and recent reports have shown an increasing incidence of reoperations when using allografts and pulmonary autografts as valve substitutes in aortic valve or root replacement.[8-12] 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.[13-15]

The purpose of this study was to analyze our experience in reoperative aortic root replacement after previous surgery on the aortic valve, the ascending aorta or both. Main focus is the type of valve in situ at the moment of reoperation and the influence on outcome after reoperation. This may be helpful in the choice for a valve substitute at primary operation.

MATERIALS AND METHODS

Patients

Between October 1981 and December 2006 141 patients underwent 156 reoperative aortic root replacements. 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.[15-18]

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, of which 28 patients had a bicuspid valve, had previously undergone aortic valve repair or a valvulotomy. None of the repairs were either a David reconstruction or a Yacoub reconstruction. Furthermore,

7 patients (1 bicuspid valve) underwent surgery of the ascending aorta for acute aortic dissection and 6 patients (4 bicuspid valves) underwent surgery for a discrete subaortic stenosis. Approval from the Institutional Review Board was obtained for this study; the Institutional Review Board waived informed consent. For patients who received an allograft or pulmonary autograft at primary operation or reoperation, information was collected from the ongoing prospective cohort study.[17] 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 in 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

All patients who receive an autograft or allograft at Erasmus MC are followed prospectively by annual telephone interviews and through visits to their cardiologist. For patients who underwent surgery for a dissection of the ascending aorta or those who had replacement of a prosthetic aortic valve, information on patient characteristics, perioperative details and follow-up was collected retrospectively from hospital records, correspondence with treating physicians and through the civil registry. Mortality and other valve-related events were registered according to the guidelines for reporting morbidity and valve-related events.[18] Operative mortality was defined as death within 30 days or within any time interval after operation if the patient was still hospitalized.

The database was frozen on January 1st, 2007. Follow-up was 98.0% complete. Three patients were lost to follow-up due to emigration. Overall mean follow-up after RARR was 6.2 years (range 0-18.3 years), with total follow-up of 973 patient years.

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 associated with 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 6 weeks of antibiotics), cardiopulmonary bypass time (in minutes) and cross clamp time (in minutes). The variable valve prosthesis type used at reoperation was additionally analyzed 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. A p-value ≤ 0.05 was considered statistically significant. All testing was two-sided.

RESULTS

Preoperative patient characteristics are displayed in Table 1. The prosthetic valves in situ were bioprotheses (n=20) and mechanical prostheses (n=36). None of the patients with a mechanical prosthesis in situ had structural failure, in contrast to the biological prostheses. Perioperative details are displayed in Table 2. In 46 patients a pulmonary autograft was inserted, 56 patients underwent allograft root replacement, and in 54 patients an aortic valved conduit (Bentall procedure) was employed. Of the patients with etiology of aneurysm ascending aorta or root dilatation 8 patients had a bicuspid valve in history (16%).

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]	9% (n=15)	21% (n=12)	2% (n=1)	9% (n=2)	
Time interval previous -current operation (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)	
RD and/or AR	18% (n=28)	-	-	-	100% (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

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 valve 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	17% (n=26)	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)	-	-
Length of hospital stay (days, range)	15 (0-91)	22 (0-91)	12 (0-72)	10 (0-31)	10 (5-41)
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.

Characteristics of different valve substitute groups

Patients who received an allograft at RARR more often 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 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).

Table 3 Details on hospital deaths

Nr	In situ valve	Age RARR	Time sincepreviousoperation	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	Pulm. autograft	Heart failure	Peroperative
13	Native valve	40	9.2 years	SVD	Pulm. autograft	Heart failure	Peroperative
14	Native valve	24	13.7 years	SVD	Pulm. autograft	Mediastinitis + sepsis	13

NSVD= non structural failure, SVD= structural failure

Patients who received a Bentall procedure more often 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 younger than the allograft and Bentall patients (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

During hospital stay, 26 patients (17%) required a rethoracotomy for persistent bleeding, 3 patients (2.0%) had a stroke, of which one was lethal, one patient (1%) had a myocardial infarction, and one patient (1%) required a permanent pacemaker.

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

Table 4. Characteristics per valve substitute implanted at RARR

	All valves (n=156)	Bentall (n=54)	Allograft (n=57)	Autograft (n=46)
Mean age (yrs, (range))	37 (0.2-76)	42 (15-73)	45 (4-76)	21 (0.2-57)
Male gender	69% (n=107)	78% (n=42)	65% (n=37)	61% (n=28)
Systolic LVF				
Good	81% (n=126)	88% (n=47)	65% (n=37)	91% (n=42)
Impaired	13% (n=21)	8% (n=4)	24% (n=14)	7% (n=3)
Moderate/bad	6% (n=11)	4% (n=2)	11% (n=6)	2% (n=1)
Cardiac rhythm				
Sinus rhythm	93% (n=143)	88% (n=47)	88% (n=51)	98% (n=45)
Atrial fibrillation	3% (n=6)	6% (n=3)	6% (n=3)	-
Other	4% (n=7)	6% (n=3)	6% (n=3)	2% (n=1)
Creatinin (µmol/L)	79 (22-305)	82 (55-142)	88 (22-305)	64 (23-120)
NYHA				
I	37% (n=57)	37% (n=20)	30% (n=17)	43% (n=20)
II/III	51% (n=80)	59% (n=32)	44% (n=25)	50% (n=23)
IV/V	12% (n=20)	4% (n=2)	26% (n=15)	7% (n=3)
Hemodynamic diagnosis				
AR	52% (n=81)	81% (n=43)	47% (n=27)	22% (n=11)
AS	21% (n=32)	6% (n=3)	19% (n=11)	40% (n=18)
AR+AS	18% (n=28)	4% (n=2)	16% (n=9)	38% (n=17)
None	11% (n=15)	9% (n=5)	18% (n=10)	-
Time interval previous -current operation (years,(range))	8.3 (0-33)	9.7 (0.2-31)	7.5 (0-31)	7.6 (0.1-33)
Indication RARR				
SVD	60% (n=94)	59% (n=32)	37% (n=21)	89% (n=41)
NSVD	1% (n=2)	-	-	4% (n=2)
Endocarditis	14% (n=23)	2% (n=1)	33% (n=19)	7% (n=3)
Aneurysm/dissection	13% (n=21)	25% (n=13)	14% (n=8)	-
RD and/or AR	11% (n=15)	14% (n=7)	14% (n=8)	-
Valve thrombosis	1% (n=1)	-	2% (n=1)	-
Preop ventilation support	19% (n=30)	-	11% (n=6)	52% (n=24)
Type surgery				
Emergent	5% (n=8)	4% (n=2)	11% (n=6)	-
Urgent	30% (n=47)	26% (n=14)	45% (n=26)	15% (n=7)
Elective	65% (n=101)	70% (n=37)	44% (n=25)	85% (n=39)

CPB time (min, (range))	(79-685)	239 (115-660)	241 (79-485)	224 (129-685)
Cross clamp[a] (min, range))	(61-331)	146 (77-331)	158 (61-302)	144 (90-240)
Circulatory arrest	n=39	n=22	n=15	n=2
(min,((range))	(2-99)	22 (2-71)	47 (15-99)	(11, 64)
Concomitant procedures				
Planned CABG	3% (n=4)	2% (n=1)	5% (n=3)	-
Unplanned CABG	2% (n=3)	-	2% (n=1)	4% (n=2)
MVR	3% (n=4)	-	7% (n=4)	-
MVP	4% (n=6)	6% (n=3)	5% (n=3)	-
PVR	3% (n=5)	7% (n=4)	2% (n=1)	-
Extended root	17% (n=26)	22% (n=12)	19% (n=11)	7% (n=3)
Rethoracotomy	11% (n=17)	20% (n=1)	16% (n=9)	15% (n=7)
Length of hospital stay (days, range)	15 (0-91)	12 (0-72)	22 (0-91)	10 (0-42)
Hospital death	9% (n=14)	6% (n=3)	14% (n=8)	7% (n=3)

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. See also Table 4.

Follow-up and survival

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 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 5 shows details on deaths during follow-up.

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 96.3%±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 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

Table 5 Details on deaths during follow-up

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

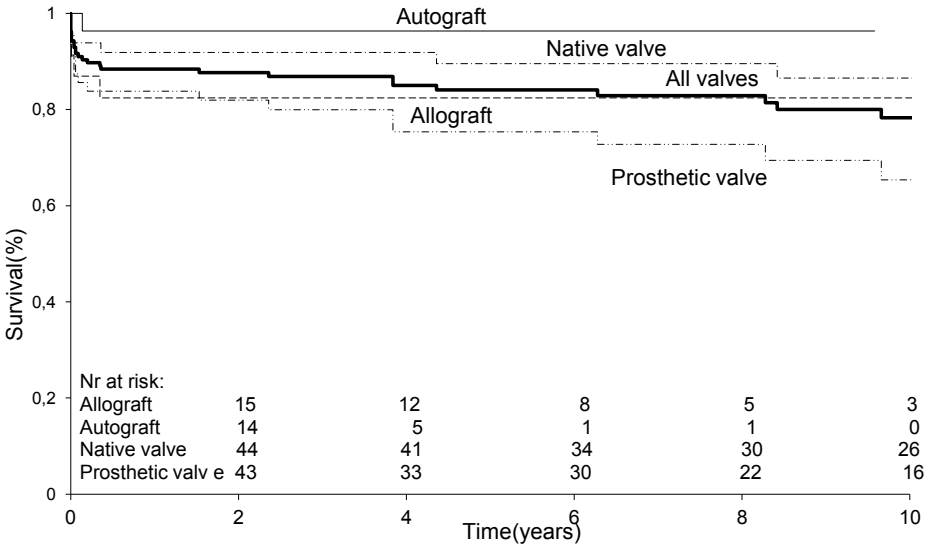

Figure 1. Patient survival after reoperative aortic root replacement per valve substitute in situ before RARR

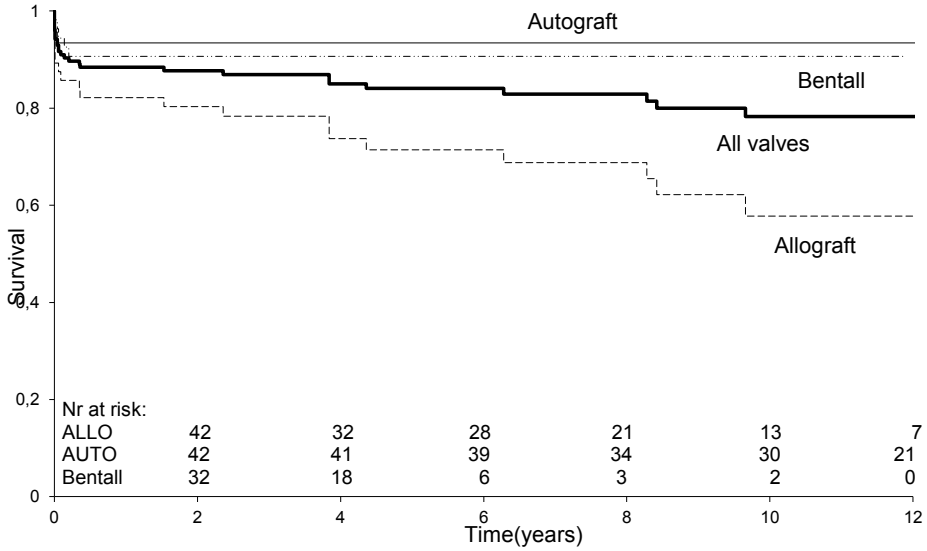

Figure 2. Patient survival after reoperative aortic root replacement per valve substitute inserted at reoperation

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 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.

DISCUSSION

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. Also, 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] This 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.[12] 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[15,25,26], but enthusiasm for this operation has been tempered in recent reports due to the high incidence of reoperations.[10,12,27] 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] Yet, at present in our institution we perform the Ross operation as a secondary operation after previous aortic valve operation in young patients. For these patients a third operation must be anticipated, probably at an age a Bentall operation will be chosen as a definitive procedure. For older adult patients requiring reoperation we tend to perform a Bentall procedure. Main indication for reoperation after the Ross operation was an aneurysmal dilatation of the aortic root causing aortic valve regurgitation. Although an aneurysmal aortic root is still difficult to reoperate on, it takes less 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.[14]

Although a reoperation after the pulmonary autograft procedure also requires reimplantation of the coronary arteries, the coronary buttons can be maintained to a larger size in absence of calcification, which necessitates resizing. However, reimplantation of the coronaries after a pulmonary autograft is 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 these patients 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.[6,29]

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.[4,6,7,20] 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 led 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.

CONCLUSIONS

Our study indicates that reoperation after previous surgery on the aortic valve, ascending aorta or both, can safely be performed. Although several patient factors play a 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 7.

Re-operations for aortic allograft root failure: experience from a 21-year single center follow-up study.

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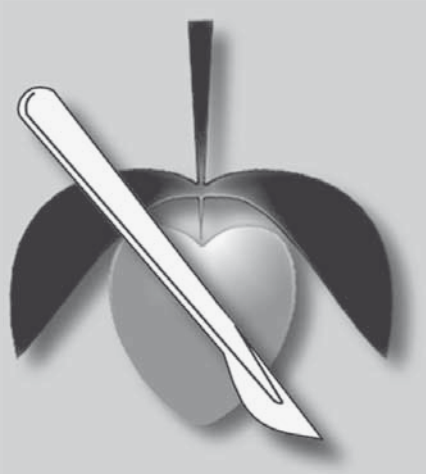

ABSTRACT

Objective: The study aims to report results of re-operations after aortic allograft root implantation.

Methods: All consecutive patients in our prospective allograft database, who underwent aortic allograft root implantation, were selected for analysis, and additional information for patients who subsequently underwent re-operation was obtained from hospital records.

Results: From 1989 to 2009, 262 aortic allograft root implantations were performed. Thirty-day mortality was 5.7%. During follow-up, 69 patients died. The actuarial survival was 77.0% (95% confidence interval (CI) 71–83%) after 10 years, and 65.1% (95% CI 57–74%) after 14 years. A total of 52 patients required re-operation. The actuarial freedom from allograft re-operation was 82.9% (Standard Error (SE) 2.9%) after 10 years and 55.7% (SE 5.7%) after 14 years. The actuarial median time to re-operation was 14.8 years. The indications for re-operation were structural valve dysfunction in 46 patients, endocarditis in two patients and non-structural valve dysfunction in four patients. The re-operations included 23 aortic valve replacements (mechanical prostheses 20 and bio-prostheses 3), 27 aortic root replacements (mechanical conduits 21, aortic allografts five, and biological conduit one), one trans-apical valve implantation and one primary closure of a false aneurysm. The additional procedures were mitral valve repair (*N*=5), mitral valve replacement (*N*=1), ascending aortic replacement (*N*=5), and coronary artery bypass grafting (CABG) (*N*=4; in two patients unforeseen). Thirty-day mortality after re-operation occurred in two patients (3.9%). Five patients died during follow-up. The survival after re-operation was 87.1% (SE 5.5%) after 1 year and 79.3% (SE 7.4%) after 9 years.

Conclusions: Re-operations after aortic allograft root implantation will be required in a substantial and growing number of patients. These re-operations, although technically demanding, can be performed with satisfying results.

Key words: Allograft aortic root replacement, aortic valve, re-operation.

INTRODUCTION

Aortic allograft implantation has been widely used for a variety of aortic valve or aortic root diseases. Initial reports on the use of either fresh or cryopreserved allografts date from the early years of heart valve surgery.[1-3] Major advantages ascribed to the use of an allograft are the excellent hemodynamic characteristics as a valve substitute; the low rate of thrombo-embolic complications, and, therefore, absence of the need for anticoagulant treatment; and the resistance to endocarditis. Furthermore, the aortic allograft has proven its value in complex aortic root pathology such as endocarditis with aortic annulus destruction. An aortic allograft can be used as a simple valve substitute, using a sub-coronary implantation technique or as a full root replacement with coronary artery reimplantation.

A major disadvantage of using human tissue valves, as with all biological valve substitutes, is the susceptibility to (tissue) degeneration and need for re-interventions. The durability of a cryopreserved aortic allograft is age dependent, leading to a high life-time risk for a re-operation, especially for young patients.[4-7]

Re-operations on the aortic root are complex, with substantial operative risks. Mortality rates of 5.4–18% have been reported.[8-12] More specifically, re-operations after previous aortic allograft implantation form a technical challenge to the surgeon. Calcification of allograft valve tissue and allograft aortic wall, and the need for repeat mobilization and reimplantation of the coronary arteries might complicate these procedures.[13-16]

In our institute, we started our experience with the use of cryopreserved allografts in 1988. In this report, we analyze the long-term results of the use of these allografts and focus on re-operations after allograft root implantation.

MATERIALS AND METHODS

Between July 1989 and January 2010, 257 consecutive patients underwent 262 allograft aortic root replacement procedures at Erasmus University Medical Center. All patients, who receive an allograft at our center, are enrolled in our ongoing, prospective, follow-up study.[17,18] Institutional Review Board (IRB) approval was obtained for this prospective follow-up study; the IRB waived informed consent. The preoperative patient characteristics are displayed in Table 1.

Primary operation

All 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 36 patients with ascending aorta or arch pathology. Root replacement was performed as a freestanding root with reimplanta-

Table 1. Preoperative patient characteristics

	All 262 patients	51 patients requiring allograft root reoperation*
Mean age (years (SD; range))	44(17; 0.06-76)	35 (14; 4-65)
Male/female ratio	185/77	39/12
Creatinin (µmol/L,N=322,(SD;range))	99 (76; 22-900)	85 (35; 29-305)
Prior cardiac surgery	29% (N=76)	26% (N=13)
Prior aortic valve surgery	22% (N=58)	14% (N=7)
Hypertension	14% (N=37)	12% (N=6)
Ischemic Heart Disease	8% (N=20)	4% (N=2)
Marfan	7% (N=18)	16% (N=8)
Diabetes Mellitus	3% (N=8)	-
Diagnosis		
Aortic valve regurgitation (AR)	58% (N=153)	63% (N=32)
Aortic valve stenosis (AS)	16% (N=43)	12% (N=6)
AR+AS	19% (N=51)	18% (N=9)
No AR and/or AS	6% (N=15)	8% (N=4)
Etiology		
Endocarditis	32% (N=84)	24% (N=12)
Active	26% (N=67)	*14% (N=7)*
Congenital (incl. bicuspid)	31% (N=81)	30% (N=15)
Other (mainly prosthetic valve)	10% (N=25)	8% (N=4)
Degenerative	8% (N=21)	6% (N=3)
Aneurysm	10% (N=25)	18% (N=9)
Rheumatic	3% (N=8)	6% (N=3)
Dissection	7% (N=18)	10% (N=5)
Sinus rhythm	92% (N=241)	100% (N=51)
Systolic LVF (N=259)		
Good	72% (N=187)	78% (N=39)
Impaired	19% (N=50)	16% (N=8)
Moderate/Bad	8% (N=22)	6% (N=3)
Preoperative NYHA class		
I	31% (N=80)	31% (N=16)
II	27% (N=70)	26% (N=13)
III	22% (N=59)	31% (N=16)
IV/V	20% (N=53)	12% (N=6)
Prior CVA	4% (N=11)	2% (N=1)
Ventilation support	8% (N=21)	8% (N=4)
Urgent operation (<24 hours)	14% (N=37)	14% (N=7)

LVF = left ventricular function, NYHA = New York Heart Association, CVA = cerebrovascular accident.
*Patient characteristics at the time of the primary allograft aortic root implantation.
One patient first had a reoperation for closure of a false aneurysm, and 4 years later replacement of the degenerated allograft, this patient is only counted once; 1 patient received 3 consecutive allografts and is counted 2 times, at the time of implantation of the 1st and 2nd allograft. This explains N=51.

Table 2. Perioperative data

	All 262 patients	51 patients requiring allograft root reoperation*
Valve requiring operation		
Bicuspid	33% (N=86)	37% (N=19)
Tricuspid	49% (N=129)	51% (N=26)
Quadriscuspid	1% (N=2)	-
Allograft	2% (N=6)	2% (N=1)
Prosthesis	15% (N=39)	10% (N=5)
Allograft characteristics		
Size (mean, (SD,range);mm)	22.4 (1.9;14-28)	22.8 (2.3; 18-28)
Aortic	99% (N=261)	100%
Cryopreserved	99% (N=261)	100%
Concomitant procedures		
No	45% (N=118)	37% (N=19)
Yes	55% (N=144)	63% (N=32)
Aortic cross clamp time (min (SD; range))	145 (64; 61-357)	143 (44;76-321)
Perfusion time (min (SD; range))	205 (86; 79-589)*	200 (75; 95-485)
Circulatory arrest (%)	14% (N=36)	22% (N=11)
(min (SD; range))	35 (31; 5-163)	29 (25; 5-73)
Procedure-related CABG	2% (N=6)	2% (N=1)
Bleeding requiring reoperation	12% (N=31)	12% (N=6)
Permanent pacemaker	4% (N=10)	4% (N=2)
Perioperative CVA	2% (N=6)	4% (N=2)
Early death (≤30 days)	5.7% (N=15)	-

LVOT = left ventricular outflow tract, CABG = coronary artery bypass grafting, SD = standard deviation, min = minutes, CVA = cerebrovascular accident..
*Patient characteristics at the time of the primary allograft aortic root implantation.

tion of the coronary arteries in all patients. The characteristics of implanted allografts are displayed in Table 2.

Follow-up

All patients who receive an allograft at Erasmus University Medical Center are followed prospectively by annual telephone interviews and through visits to their cardiologist. Valve-related complications were defined, according to the 2008 guidelines, for reporting morbidity and mortality after cardiac valvular operations.[19]

The study database was frozen for analysis on 1 March 2010. Follow-up was 94% complete: eight patients were lost to follow-up due to emigration. The mean follow-up duration was 8.6 years (range 0–20.9 years), with a total follow-up of 2260 patient years.

Re-operations

All re-operations were performed through a median sternotomy and on cardiopulmonary bypass with moderate hypothermia. We mostly used central cannulation in the ascending aorta and right atrium or caval veins. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Total circulatory arrest with deep hypothermia was needed in five patients with ascending aorta or arch reconstruction, necessary to correct ascending aortic or arch dilatation.

After preparing the aortic root, the aorta was cross-clamped and the aorta opened. If the allograft aortic wall was free of calcification, it was possible to extend the aortotomy to the allograft non-coronary sinus of Valsalva. After removal of the degenerated allograft valve leaflets and debridement of the annulus, an appropriately sized valve prosthesis was implanted. In patients with heavily calcified allograft roots, the complete allograft is dissected. The original coronary buttons were dissected and mobilized. When possible, a cleavage plane is developed between the allograft and the original aortic annulus and the allograft completely removed. An appropriately sized valved conduit is implanted, and the dissected coronary buttons are reimplanted.

Statistical methods

Continuous data are presented as means (standard deviation; range). Categorical data are presented as proportions. Univariable logistic regression analysis was used to study potential determinants of hospital mortality.

Cumulative survival and freedom from re-operation or re-intervention were analyzed using the Kaplan–Meier method. The estimated 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 re-operation (event) or last follow-up or patient death (censoring).

The Cox proportional hazards model was used for univariable and multivariable analysis of time-related events. First, all variables were entered into a univariable analysis. Next, all variables, that were significant in the univariable analysis or that showed a tendency toward significance ($p \leq 0.10$), were forced into the multivariable Cox regression analysis (the 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 through the partial residuals. There was no indication of violation of the assumptions. A p-value of ≤ 0.05 was considered statistically significant. All testing was performed two-sided. 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 (creatinine, continuous variable expressed in $\mu moll^{-1}$), 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 vs impaired/moderate/bad), prior cerebrovascular accident (CVA), preoperative New York Heart Association (NYHA) class, emergency of the procedure, and cardiopulmonary bypass time (continuous variable expressed in minutes). Factors that were tested as potential risk factors for re-operation for structural valve deterioration (SVD) were: patient age (continuous variable expressed in years), gender, severe renal disease requiring either dialysis or transplantation, prior cardiac surgery, prior aortic valve surgery, hemodynamic diagnosis (regurgitation vs stenosis vs combined regurgitation and stenosis), heart-valve disease etiology, preoperative hypertension, and allograft diameter (continuous variable expressed in millimeters). For all the analyses mentioned above, Statistical Package for Social Sciences (SPSS) 17.0 for Windows statistical software (SPSS, Chicago, IL, USA) was used.

RESULTS

Early morbidity and mortality

The perioperative data for all patients are shown in Table 2. Coronary artery bypass grafting (CABG) for complications related to reimplantation of the coronary arteries was necessary in six patients, of which two 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 were very thin layered and ruptured after reimplantation. A third patient had an active endocarditis of an aortic bioprosthesis with abscesses, and the edematous right coronary artery button ruptured after reimplantation. Another two 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.

During the procedure, six patients died, and nine more patients died within 30 days postoperation (early mortality, 5.7%). The six operative deaths were caused by persistent massive bleeding in three patients (one with an active endocarditis with abscesses, one with an acute dissection, and one patient who underwent a re-operation for paravalvular leakage of a Bjork–Shiley mechanical valve), left ventricular failure in two patients (one patient who presented with acute endocarditis with fistula to the left atrium, and another patient with active prosthetic-valve endocarditis), and, finally, prosthetic aortic valve endocarditis with extensive tissue destruction of the left ventricular outflow tract and proximal ascending aorta with abscesses in one patient, who died during a salvage procedure. The causes of death in the additional nine patients, who died within 30 days postoperation, were registered as ‘not valve-related’ in six patients. The three valve-related early deaths concerned one patient, who died of a major intracerebral bleeding; one patient with a myocardial infarction caused by

kinking of the reimplanted right coronary artery; and one patient with an acute endocarditis, who died as a result of a stroke caused by septic emboli. Potential risk factors for increased early mortality were older patient age (odds ratio (OR) 1.08, 95% confidence interval (CI) 1.03–1.13; p=0.001 (continuous variable expressed in years)), female gender (OR 2.95, 95% CI 1.03–8.44; p=0.04), severe renal disease (requiring either dialysis or renal transplantation) (OR 44.0, 95% CI 7.26–266.64; p<0.001), prior aortic valve surgery (OR 3.36, 95% CI 1.17–9.71; p=0.03), longer cardiopulmonary bypass time (OR 1.01, 95% CI 1.004–1.013; p=0.001 (continuous variable expressed in minutes)), emergent procedure (within 24h) (OR 6.33, 95% CI 2.14–18.71; p=0.001), abnormal preoperative cardiac rhythm (OR 13.44, 95% CI 4.06–44.49; p<0.001), preoperative ventilation support (OR 4.92, 95% CI 1.42–17.10; p=0.01), NYHA class>II (OR 5.99, 95% CI 1.65–21.73; p=0.007), active endocarditis (OR 3.64, 95% CI 1.27–10.47; p=0.02), and preoperative hypertension (OR 3.36, 95% CI 1.08–10.46; p=0.04).

Late survival

During follow-up, another 54 patients died (2.4% per patient year). Of these patients, 32 died of non-valve-related causes. In three patients, the cause of death could not be retrieved. The causes of valve-related death (N=19) were as follows: 11 patients died in sudden, unexpected, or unexplained ways; three patients died due to endocarditis, four patients who had structural allograft valve failure died of heart failure; and one patient died due to a major bleeding. The overall cumulative survival, including early survival, was 92.0% at 1 year (95% CI 89–95%), 77.0% at 10 years (95% CI 71–83%), and 65.1%

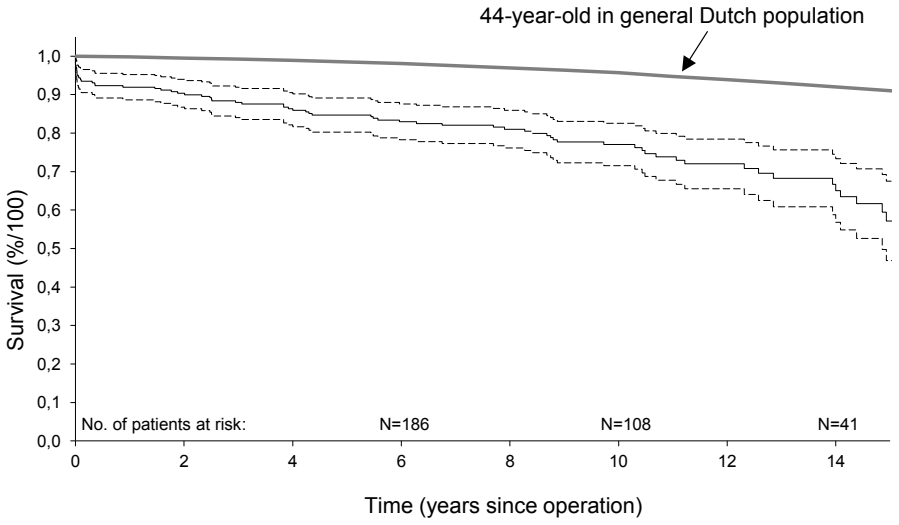

Figure 1. Observed cumulative survival after aortic allograft root replacement compared with a 44 years old dutch male with 95% confidence interval (- - - -).

at 14 years postoperation (95% CI 57–74%) (Figure 1). Independent predictors of late mortality were older patient age (hazard ratio (HR) 1.03, 95% CI 1.00–1.05; p=0.036 (continuous variable expressed in years)), preoperative ventilation support (HR 4.52, 95% CI 1.33–15.31; p=0.015), preoperative abnormal cardiac rhythm (HR 9.36, 95% CI 3.61–24.25; p<0.001), preoperative hypertension (HR 2.47, 95% CI 1.20–5.10; p=0.014), and preoperative NYHA class III or IV (HR 2.12, 95% CI 1.15–3.92; p=0.017).

Re-operation

During follow-up, 52 allograft root re-operations were performed in 50 patients. The actuarial median time to re-operation was 14.8 years. The indications for re-operation were structural valve dysfunction in 46 patients, endocarditis in two patients, and non-structural valve dysfunction in four patients. Estimating possible perforation of the heart or aorta when reopening the chest, we instituted cardiopulmonary bypass with cannulation of the femoral vessels in four patients before performing the sternotomy. An additional three patients required emergency institution of cardiopulmonary bypass, using femoral vessel cannulation after great vessel injury at re-sternotomy. In one patient, a lateral thoracotomy was done to release the adherent aorta from the sternum prior to sternotomy. Re-operations included 23 aortic valve replacements, 27 aortic root re-replacements, one trans-apical valve implantation, and one primary closure of a false aneurysm. The additional procedures were mitral valve repair (N=5), mitral valve replacement (N=1), ascending aortic replacement (N=5), and CABG (N=4; in two patients unforeseen). Table 3 shows the characteristics of the re-operations. In 23 patients, who underwent simple valve replacement, the mean size of the implanted prosthesis was 23.2 (21–27). In 21 patients, who received a mechanical conduit, the mean size of the implanted conduit was 25.4 (23–29). In the two patients, who required an unforeseen additional coronary bypass, this was due to disruption and perforation of the left coronary button and left main coronary artery during preparation and mobilization. In one patient, this was repaired using a saphenous vein patch. In the other patient, a vein graft to the anterolateral coronary artery and the anterior descending coronary artery was implanted. This patient was re-operated 10 months later for vein graft stenosis. Revascularization was performed using left and right internal mammary arteries. Another patient underwent revascularization of the anterior descending coronary artery for anterior wall ischemia 1 day postoperatively. Bleeding during sternal re-entry occurred in three patients (two bleeding events were from the ascending aorta, and one from the innominate vein). In these patients, the bleeding was temporarily controlled, followed by femoral vessel cannulation and institution of cardiopulmonary bypass. The actuarial freedom from allograft root re-operation was 82.9% (SE 2.9%) after 10 years and 57.8% (SE 5.7%) after 14 years (Figure 2). The actuarial freedom from allograft root re-operation for structural valve dysfunction was 85.0% (SE 2.8%) after 10 years and 59.3% (SE 5.8%) after 14 years. Younger patient age at the time of the allograft implantation was the only

Table 3. Reoperation characteristics

	N
Indication for reoperation	
Structural valve dysfunction	46
Endocarditis	2
Non-structural valve dysfunction	4
Reoperation	
Aortic valve replacement	23
Mechanical prosthesis	20
Bioprosthesis	3
Aortic root replacement	27
Mechanical conduit	21
Aortic allograft	5
Biological conduit	1
Transapical valve replacement	1
Primary closure false aneurysm	1
Additional procedures	
Mitral valve repair	5
Mitral valve replacement	1
Ascending aortic or arch replacement	5
CABG	4

CABG=coronary artery bypass grafting

factor associated with increased re-operation rates for structural valve dysfunction (HR 0.96, 95% CI 0.94–0.98; $p<0.001$). Thirty-day mortality after re-operative allograft root procedure occurred in two patients (3.9%). Both patients died of low output failure in the operation theater. One of these patients underwent a fourth operation for allograft SVD after previous aortic valve replacement, aortic allograft implantation, and mitral valve replacement combined with tricuspid valve plasty. At re-operation, a valved conduit was implanted. The left coronary button and the left main coronary artery were reconstructed with a saphenous vein patch required for left main perforation during preparation. The second patient underwent a third operation for severe heart failure due to allograft SVD after CABG and allograft implantation for an acute type I dissection. At re-operation, a valved conduit was implanted combined with ascending aortic and partial arch replacement. After a complex and time-consuming operation, the patient could not be weaned from extracorporeal circulation (ECC). Postoperative morbidity included a rethoracotomy for persistent blood loss in five patients (9.8%), myocardial infarction in one patient (1.9%), respiratory insufficiency in three patients (5.9%), and deep sternal infection in one patient (1.9%). One patient was re-operated 2 weeks after implantation of a size 25 mechanical

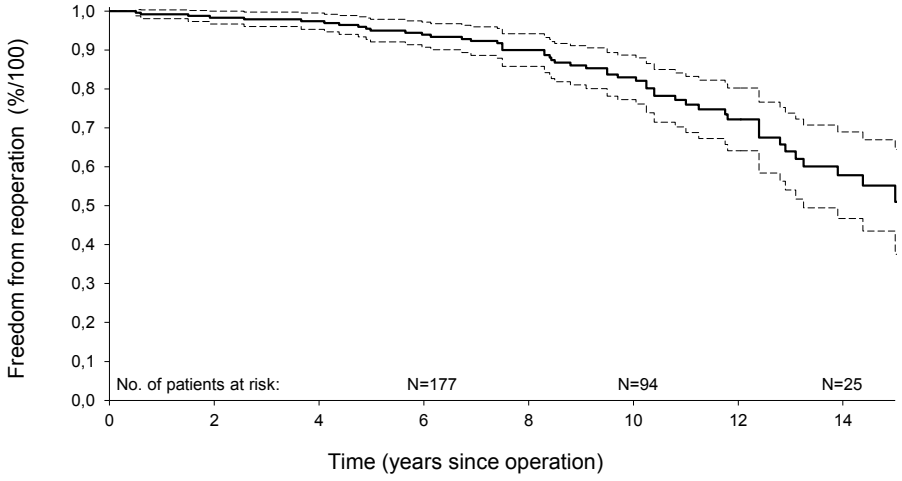

Figure 2. Freedom from allograft related reoperation with 95% confidence interval (- - - -).

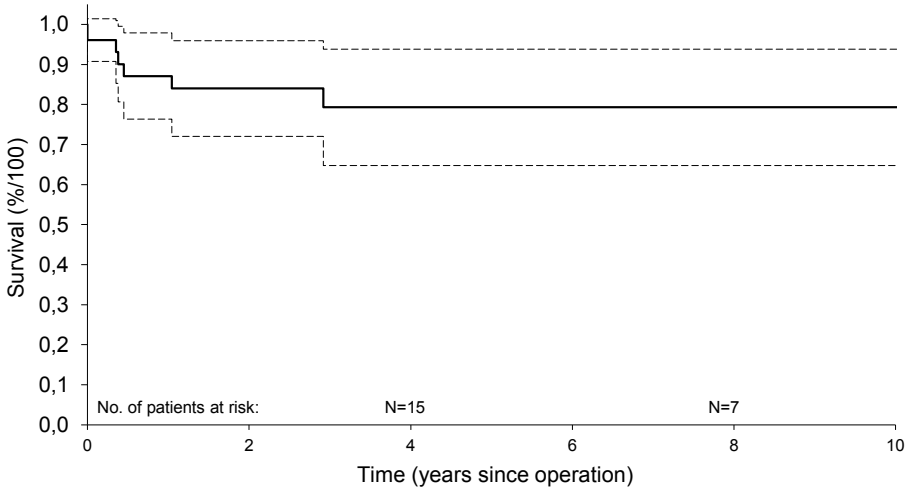

Figure 3. Cumulative survival after 52 allograft reoperations with 95% confidence interval (- - - -).

prosthesis for a postoperative obstruction with a gradient over 100mmHg. At re-operation, a mechanical conduit of size 29 was implanted with a minimal postoperative gradient.

During follow-up after the re-operative allograft root procedure, five patients died: one patient habituated to drugs died of recurrent endocarditis 4 months after re-operation for allograft endocarditis, one patient died of heart failure 4 months after replacement of a degenerated allograft root with another allograft root (procedure complicated by a

perioperative myocardial infarction), two patients died of unknown causes 6 months and 1 year after re-operation, and one patient died of cancer 2.9 years after re-operation. The survival after re-operation was 87.1% (SE 5.5%) after 1 year, and 79.3% (SE 7.4%) after 9 years (Figure 3).

DISCUSSION

After initial enthusiasm for the use of allografts as an aortic valve substitute, we have learned from our own and other's experiences that, although patient survival after aortic allograft implantation is acceptable, the durability of these prostheses is limited. The cumulative survival in our study after 10 years was 77%, and 65% after 14 years. These results are comparable to other series reporting on long-term results.[6,7] We have learned from previous reports that SVD is the Achilles' heel of the use of a cryopreserved allograft in the aortic position. Especially in the second decade after implantation, the incidence of SVD increases. In the present study of 262 patients with aortic allograft root replacement, 52 re-operations had to be performed. The actuarial freedom from re-operation was 83% after 10 years and 58% after 14 years. The median time to re-operation was 14.8 years. These results are comparable to other reports on long-term results using allografts. When comparing these results to other possible valve substitutes, the incidences of SVD and re-operations are comparable to results reported for stented or stentless bioprostheses.[5-20] In a previous study, we used a microsimulation model to compare lifetime risks of re-operation for allografts and stented bioprosthesis.[18] We found the risk of re-operation to be comparable for these types of valve replacement. We concluded from this study that there is no benefit in using allografts as an aortic valve substitute, except for patients with complicated endocarditis or an absolute contraindication for anticoagulation. Others also argued against the use of allografts for aortic valve replacement, except for specific indications.[21-22] Most patients surviving long enough after allograft aortic root replacement will require a re-operation, almost uniquely for SVD. In our series, 46 patients (90%) were re-operated for SVD. We analyzed possible risk factors for SVD. Only younger patient age at the time of allograft implantation was associated with an increased re-operation rate for SVD. In a previous report on our total series of both allograft root replacements and sub-coronary implantations, we found a larger allograft size to be associated with a higher rate of allograft-related re-operations.[17] In the present series, however, we did not find a larger allograft size to be a risk factor for re-operations (p=0.11). It might be that this association is only present in sub-coronary implanted allografts, but not in full root replacement.

Re-operations after a previous aortic root are technically demanding. More specifically, re-operations after allograft root implantation confront the surgeon with some specific conditions. The allograft aortic wall shows a strong tendency to calcification, already oc-

curring shortly after allograft implantation. Contrary to the pulmonary autograft, there is no tendency to root dilatation. Nevertheless, can the allograft be strongly adherent to the posterior sternum, which will be a risk factor for severe bleeding at reopening the chest. In three patients, we encountered severe bleeding upon reopening the chest (in two patients, originating from the aorta). Preoperative computed tomography (CT) scanning of the chest might be helpful in determining the relation of the aorta and the allograft root to the sternum. When a specific risk for bleeding at re-entry is anticipated, the choice for elective femoral vessel cannulation and institution of cardiopulmonary bypass before opening the chest might be a strategy to prevent this complication. In one patient, we chose to release the allograft and the aorta using an anterolateral thoracotomy. Preparation and mobilization of the coronary arteries is another specific challenge to the surgeon re-operating on the aortic root. After allograft root implantation, the original coronary buttons usually consist of non-diseased aortic wall. These buttons can usually be found to be surrounded by severely calcified allograft aortic wall tissue. To facilitate detachment of the coronary buttons and subsequent reimplantation at re-operation, we advocate the use of generously sized coronary buttons at the initial operation. Preparing the coronary arteries might lead to accidental perforation or damage to the coronary buttons or proximal coronary arteries. In two patients (3.9%), we encountered coronary artery complications at re-operation. In one patient, this complication could be successfully treated by CABG; in the other patient, reconstruction of the left mean coronary artery was unsuccessful. One other patient underwent revascularization of the anterior descending coronary artery 1 day postoperatively. Kirsch and colleagues reported an incidence of 25% of unplanned coronary artery revascularizations in 56 re-operations after previous aortic valve or aortic root operations.[12] Mortality after these unplanned coronary artery revascularizations was 36%.

When, after preparation of the aorta and the allograft root, allograft wall disease is limited, it is often possible to leave the allograft root in place and insert a valve prosthesis into the allograft after excision of the deteriorated valve leaflets. This simple valve replacement may be attractive, as this obviates the need for coronary artery reimplantation. It must be realized, however, that parts of the implanted allograft, already implanted inside the original aortic annulus will stay in place, possibly reducing the size of the prosthesis to be implanted. When the allograft root, however, is severely calcified, there will be no alternative than to completely remove all allograft tissue. Usually, it will be possible to develop a cleavage plane between the original aortic annulus and left ventricular outflow and the allograft root. This will usually provide a large-sized, flexible, aortic annulus, able to accommodate an adequately sized valved conduit.[16] An additional advantage of complete aortic root re-replacement, using a valved conduit, is that this provides the most radical solution for the aortic root. There will be little chance of new pathology, requiring further re-operations. In our series, 46% of patients underwent simple valve implantation. The

mean size of the implanted valves was 23, opposed to a mean size of 25 for the implanted valved conduits. In one patient, a mechanical valve had to be replaced by a valved conduit due to an unacceptable gradient over the valve.

Mortality after these complex re-operations occurred in two patients (3.9%). Both were very complicated patients, requiring a fourth and third heart operation, respectively. One patient was in severe heart failure before re-operation. Although the mortality after primary operation was 5.7%, patients in the primary operation group showed a higher preoperative risk profile, with more acute endocarditis, a higher NYHA class, and more emergency operations. Several authors report on mortality after previous surgery on the aortic valve, aortic root, or ascending aorta. In these series, often combining different types of index operations prior to the re-operation, mortality is reported to be 5.4–18%.[8-12] Most of these series contain only few patients with previous allograft implantations. Sadowski and colleagues report on 139 re-operations after aortic allograft implantation.[13] The ratio between root replacement and sub-coronary implantation is not clear. In most patients, a valve prosthesis was implanted. Their re-operative mortality was 4.31%. Joudinaud and colleagues report on 20 patients re-operated, all after previous allograft root implantation.[15] Mortality occurred in two patients (10%), both after very complicated re-operations. Nowicki and colleagues report on 130 first-time re-operations after aortic allograft implantation.[14] Most of their patients underwent simple valve replacement, mortality being 3.8%.

LIMITATIONS

Our study reports on a single-center experience on aortic allograft root implantations. The size of the study and the number of re-operations is limited; therefore, we were not able to identify specific risk factors for re-intervention, neither in preoperative patient status nor in allograft characteristics at implantation, other than patient age.

CONCLUSIONS

Re-operation after aortic allograft root implantation will be required in a substantial number of patients, especially in the second decade after initial operation. Careful patient monitoring is therefore essential in detecting allograft dysfunction in an early stage. Re-operation can then be performed before the onset of severe symptoms or before heart failure develops. Both simple valve replacement and repeat root replacement can be the optimal technique of operation, mostly depending on the local findings at re-operation. These re-operations, although technically demanding, can be performed with satisfying results, regarding mortality and morbidity.

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CONFERENCE DISCUSSION

Dr W. Harringer (*Braunschweig, Germany*): I completely agree with your conclusions; it reflects my personal experience with the use of allograft root replacements in re-operations. Your group has achieved very good results in these challenging re-operations as reflected by a rather low mortality. Your study is a profound evaluation of long-term allograft performance and contributes significantly to the proper indications for usage of such conduits.

There are three questions I would like to ask you. Firstly, did you analyze the influence of allograft characteristics such as donor age, ischemic time or preservation techniques? Do you have these data, on the difference between valve deterioration only versus root calcification as a whole, as this makes a significant difference in re-operation?

Dr Bekkers: We tried to analyze those, but it didn't affect the rate of re-operations. As for preservation type, these were all cryopreserved allografts, so we couldn't distinguish with this.

Dr Harringer: Secondly, what is your opinion on the potential and the risk of replacing the aortic valve with catheter-based prostheses, as you have done in one patient, especially with regard to calcification of the whole aortic root versus structural valve disease alone, and what is your future perspective on managing these patients?

Dr Bekkers: That is a bit of a philosophical question and I think this whole convention is flooded with presentations on the indications for transcatheter valve replacement, but I can add a little philosophy to that.

These re-operations are difficult, but, on the other hand, very do-able and we can perform them. The patients in whom we did these re-operations had a mean age of 44 years. That is, I think, by current standards, a young group to manage with transcatheter

valve replacement. So I think at present it depends on the risk of patients; we had one patient in a very bad condition where the choice was made to perform a trans-apical valve replacement, but I don't think I would recommend this as routine in current practice. I would prefer to proceed with the old-fashioned operations.

Dr Harringer: And thirdly, what are the current indications in your institution for the use of aortic allografts nowadays?

Dr Bekkers: We started using allografts in 1988 and we did a lot of them, because we believed at that time that it would be a valuable and long-term solution for patients with aortic root pathology, and also for patients with only aortic valve disease. Nowadays we are more reluctant to use allografts, and we restrict the indications to complex aortic root pathology like complex endocarditis but do not use them routinely for valve replacement or for the simpler root replacements.

Dr Harringer: Basically for endocarditis cases with a lot of abscesses and destruction of the LVOT?

Dr Bekkers: Those are the patients who get allografts in current practice, yes.

Dr C. Yankah (*Berlin, Germany*): I would like you to comment on the patients' characteristics, in particular on the age of those patients who had their homografts explanted, as well as the size of these homografts. We have shown in our early publication that mismatch of homografts could also result in early degeneration due to high transvalvular gradients. Further, do you have age group stratification to analyse and differentiate among the groups time-related incidence of degeneration? Because the older age patients might not experience degeneration so early?

Dr Bekkers: What we found in our series is that indeed younger age of the patient at the initial implant was associated with a higher chance of valve deterioration and re-operation. I think there was one more question, but I forgot it.

Dr Yankah: Sizes, valve sizes.

Dr Bekkers: I have not yet analyzed the valve sizes, if that is important.

Dr Yankah: Because in our published series we clearly identified that a mismatch of patient/homograft size could lead to early degeneration.

Dr Bekkers: Okay.

Chapter 8

Aortic root reoperations after pulmonary autograft implantation

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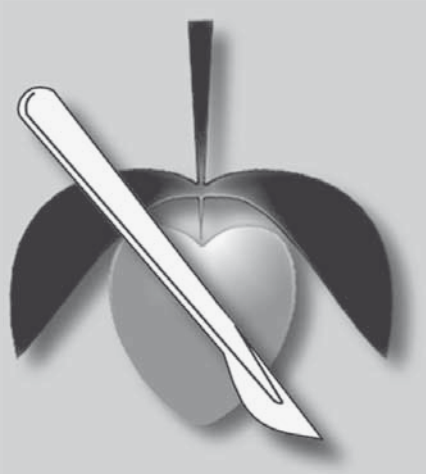

ABSTRACT

Objective: To report the results of aortic root reoperations after pulmonary autograft implantation.

Methods: All consecutive patients in our prospective Ross research database were selected for analysis, and additional information for patients requiring reoperation was obtained from the hospital records.

Results: From 1988 to 2009, 155 pulmonary autograft operations were performed. During this period, 41 patients required reoperation for aortic root dilatation and/or autograft valve insufficiency, in 8 patients combined with pulmonary allograft dysfunction. The freedom from autograft reoperation rate was 86% (standard error, 3.3%) after 10 years and 52% (standard error, 6.6%) after 15 years. The median interval to reoperation was 15.3 years. During reoperation, 39 patients underwent aortic root replacement (mechanical conduit, 31; stentless root, 2; allograft, 3; and valve sparing, 3), and 2 patients underwent valve replacement. In 8 patients this was combined with pulmonary allograft replacement. The technical difficulties encountered included bleeding at the sternal re-entry in 5 patients. No 30-day mortality occurred. The postoperative complications included reexploration for persistent blood loss in 3 patients and cerebrovascular accident in 3 patients. Two patients died during the follow-up period. The survival rate after reoperation was 94% (standard error, 4.1%) at 5 years.

Conclusions: An increasing number of patients requires reoperation after pulmonary autograft implantation. These reoperations can be done with very low mortality and morbidity and excellent follow-up results.

INTRODUCTION

Pulmonary autograft implantation (the Ross operation) is an attractive option for aortic valve replacement, especially in children and young adults.[1] The operative mortality and longer term results have been very satisfactory. A major drawback of this operation, however, is the progressive dilatation of the autograft root, often combined with autograft valve insufficiency, necessitating reoperation. Reoperations after previous aortic root surgery are complex and carry increased operative risks.[2-5] In particular, reopening the chest, with the possible adherence of the dilated aorta to the sternum and the need for mobilization and reimplantation of the coronary arteries might contribute to the high-risk character of these reoperations and, therefore, the greater expected mortality risk in reoperative patients. In our center, a high volume of pulmonary autograft procedures was performed in the past 2 decades.[6] Re-replacement of the aortic root will usually be performed using implantation of a valved conduit; however, recently, valve-sparing procedures after previous aortic root replacement have also been introduced.[7]

The purpose of the present study was to analyze the need for aortic root reoperations after pulmonary autograft implantation and to report our experience with these reoperations.

MATERIALS AND METHODS

Patients

From 1988 to 2009, 155 consecutive patients underwent the Ross operation at our institution. In 149 patients, we performed a full root implantation; in 6 patients, an inclusion cylinder was implanted. The preoperative patient characteristics are listed in Table 1. Twelve patients underwent previous aortic valve replacement: 6 subcoronary homografts, 3 biologic prostheses, and 3 mechanical prostheses were used. The institutional review board approved the present prospective follow-up study and waived the need for informed consent.

Primary Operation

The perioperative data are listed in Table 2. All surgical procedures were performed with 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 used, and the pulmonary autograft was inserted at the level of the annulus, with care taken to reduce the subannular muscular rim of the autograft to 3 to 4 mm. The proximal suture line of the autograft

Table 1. Preoperative patient characteristics

	N=155
Mean age (years (SD; range))	21.4 (13.7; 0.05-52)
Age 0-16	39% (n=61)
Age >16	61% (n=102)
Male gender	66% (n=96)
Prior cardiac surgery*	33% (n=51)
Prior aortic valve replacement	8% (n=12)
Prior valvulotomy	18% (n=28)
Prior balloon dilatation	22% (n=33)
Aetiology	
Endocarditis	5% (n=8)
Congenital (incl. bicuspid)	75% (n=117)
Other (mainly prosthetic valve)	12% (n=18)
Degenerative/Rheumatic	7% (n=11)
Aneurysm/Dissection	1% (n=1)
Diagnosis	
Aortic valve regurgitation (AR)	29% (n=45)
Aortic valve stenosis (AS)	32% (n=50)
AR+AS	39% (n=60)
Systolic LVF[§] (n=148)	
Good	83% (n=124)
Impaired	12% (n=16)
Moderate/Bad	5% (n=8)
Sinus rhythm	100%
Creatinin (µmol/L (SD; range), n=145)	62 (24; 12-157)
NYHA class (n=148)	
I	42% (n=62)
II	36% (n=54)
III	16% (n=24)
IV/V	5% (n=8)
Ventilation support	3% (n=4)
Type operation	
Emergency (<24 hrs)	1% (n=2)
Urgent	16% (n=25)
Elective	83% (n=128)

*Some patients had other prior cardiac surgery, i.e. VSD closure, subvalvular membrane resection
[§]Systolic left ventricular function based on qualitative echocardiographic estimations.

Table 2. Perioperative details

	All patients (n=155)
Aortic valve	
Bicuspid	60% (n=93)
Tricuspid	32% (n=49)
Prosthesis	8% (n=12)
Surgical technique	
Autograft root replacement	96% (n=149)
Inlay autograft	4% (n=6)
Concomitant procedures	
CABG	2% (n=3)
LVOT enlargement	12% (n=19)
Mitral valve surgery	1% (n=2)
Other*	12% (n=18)
CPB time (min)	201 (114-685)
Cross-clamp time (min)	141 (90-240)
Circulatory arrest (N=3, min)	30 (11-64)
Complications	
Bleeding/Tamponade	13% (n=20)
Pacemaker	1% (n=1)
Perioperative MI	1% (n=1)
Early mortality	2.6% (n=4)

CABG=coronary bypass operation, LVOT=left ventricular outflow tract, CPB=cardio-pulmonary bypass, MI=myocardial infarction.
*Includes patients requiring tailoring of the ascending aorta or subvalvular membrane resection.

was constructed, with interrupted sutures in 21% (n = 30) of the procedures and 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 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 because of a procedural complication. The details of these patients have been previously reported.[6]

Reoperations

All reoperations were performed through a median sternotomy, with cardiopulmonary bypass and moderate hypothermia. We mostly used central cannulation in the ascending aorta and right atrium or caval veins. To anticipate possible perforation of the heart or aorta when reopening the chest, we instituted cardiopulmonary bypass with canulation of the femoral vessels and deep cooling in 4 patients before performing the sternotomy. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Total

circulatory arrest with deep hypothermia was needed in 11 patients, with ascending aorta or arch reconstruction, necessary to correct ascending aortic or arch dilatation.

In patients without aortic root dilatation, the valve leaflets were excised, followed by mechanical valve implantation. 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 inspected, and most of them were excised and the coronary buttons mobilized. Excess autograft wall tissue was removed, leaving parts of the autograft at the annular level in situ. Standard valved conduit implantation was performed. When appropriate, the valve leaflets were spared, using the aortic valve reimplantation technique.[8]

Follow-up

All patients were followed up prospectively and annually contacted and interviewed by telephone. Patients older than 16 years underwent standardized echocardiography biannually.[9] In the case of suspected complications, the attending physician was contacted for verification. Valve-related events were defined according the 2008 guidelines for reporting morbidity and mortality after cardiac valvular operations.[10] Failure of the autograft or pulmonary allograft was determined at reoperation or death. The recording of patient survival was started at the Ross operation and ended at death or the last follow-up visit. Survival of the autograft or pulmonary allograft was started at surgery and ended when reoperation or reintervention was necessary, the patient died, or the last follow-up visit. Two patients moved abroad and were lost to follow-up.

The database was frozen on December 1, 2009. The total follow-up was 1694 patient-years and was 97% complete. The mean follow-up duration was 11.0 years (range, 0-20.4 years).

Statistical Analysis

Descriptive statistical analysis of the perioperative data was done. Continuous data are displayed as mean ± 1 standard deviation. Discrete data are presented as proportions. Cumulative survival and freedom from reoperation or reintervention were analyzed using the Kaplan-Meier method. Survival is displayed as the proportion ± standard error. The log-rank test was used to compare the 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, surgical technique used (root replacement versus inclusion cylinder technique), and hemodynamic diagnosis (regurgitation versus stenosis versus combined regurgitation and stenosis). First, all variables were entered into a univariate analysis. Next, all variables that were significant on univariate analysis or showed a tendency toward significance ($P \leq .20$) were forced into the multivariate Cox regression analysis (enter method). The proportional hazards assumption was assessed for each vari-

able through graphic inspection of the log minus log survival and the linearity assumption for continuous variables though the partial residuals. No indication was seen of a violation of the assumptions. All testing was performed 2-sided. For all data analysis, the Statistical Package for Social Sciences, version 15.0.0, for Windows (SPSS, Chicago, Ill) was used.

RESULTS

Early Mortality After Primary Operation

The early mortality rate at 30 days was 2.6% (4 patients). Two patients, both female, died during surgery. Of these 2 patients, 1, a 40-year-old patient, died of low output failure and the other patient (4 months old) died of heart failure and severe arrhythmias. A third patient, a 26-year-old man, died of massive pulmonary emboli shortly after surgery. Finally, a 24-year-old female patient with Turner syndrome and extreme left ventricular hypertrophy died of mediastinitis and sepsis 13 days after surgery.

Late Survival After Primary Operation

During follow-up, 7 more patients died. Of the 7 deaths, 3 were valve-related and 4 were nonvalve-related deaths. One 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 surgery of recurrent rheumatic disease.[11] The other 2 valve-related deaths were both sudden, unexpected, and unexplained deaths. One adult patient died 13.8 years after autograft implantation, and one died 10.8 years after autograft implantation and 1 year after autograft replacement for progressive neo-aortic dilatation and regurgitation.

The causes of the nonvalve-related deaths included septic shock *(Candida albicans)* in 1 infant 51 days after autograft implantation, heart failure resulting in cardiogenic shock in another infant 1.7 years after autograft implantation, acute myocardial infarction in 1 adult patient 4.7 years after autograft implantation and 2 months after autograft replacement for progressive neo-aortic dilatation and regurgitation, and heart failure with normal functioning autograft in 1 adult patient 16.2 years after autograft implantation.

The overall 15-year survival rate was 92% ± 1.8% (Figure 1).

Reoperation

A total of 41 patients underwent reoperation on the autograft, of which 3 were in other institutions. All patients who required reoperation of the autograft had originally undergone full root implantation. The mean age was 36 years (range 16-64 years) at reoperation. Of these 41 patients, 33 required isolated pulmonary autograft reoperation, 8 required simultaneous replacement of both the pulmonary autograft and the allograft.

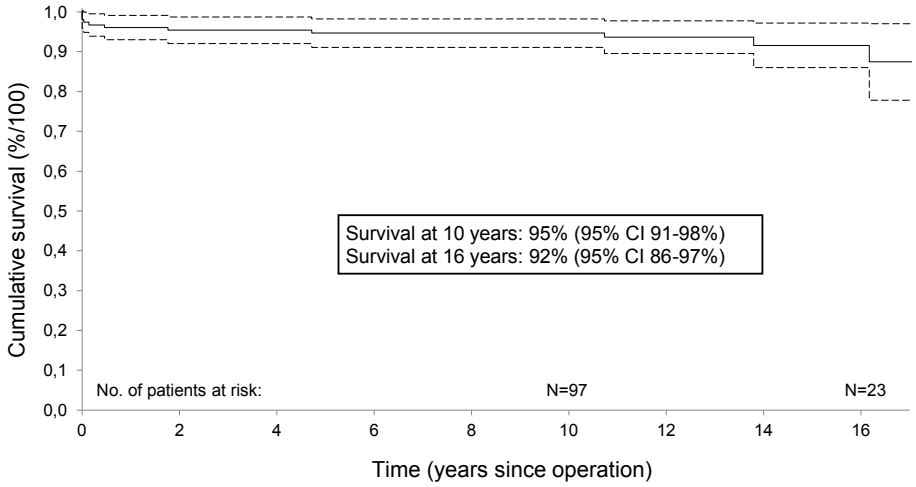

Figure 1. Observed cumulative survival after the Ross operation.

Progressive dilatation of the neo-aortic root combined with aortic regurgitation was the main cause for autograft reoperation. The causes for allograft replacement were mainly structural failure, calcification, or senile degeneration of the valve. The details of the re-operative procedures are listed in Table 3. In 1 patient, an aortic valve replacement was performed 8 years after the primary Ross operation for neo-aortic regurgitation with a moderately dilated neo-aorta, followed by mechanical conduit implantation 4 years later for progressive ascending aortic dilatation. The technical difficulties encountered at these reoperations were accidental injury of the aorta or pulmonary artery at reopening the chest in 5 patients, in 3 patients requiring emergency institution of cardiopulmonary bypass using the femoral vessels. No reoperative mortality occurred. Postoperative morbidity included rethoracotomy for persistent blood loss in 3 patients (7.3%) and stroke in 3 patients (7.3%). In 1 patient, the stroke was related to accidental injury of the pulmonary allograft and hypovolemic shock at reopening of the chest.

Two patients died after these reoperations. One patient died 3 months postoperatively of a myocardial infarction. The second patient died 17 months postoperatively; the death was sudden and unexplained. The freedom from reoperation for autograft failure rate at 10 years was 86% ± 3.3% and was 52% ± 6.6% at 15 years (Figure 2). The rate of freedom from autograft reoperation was comparable between patients younger than 16 years and those aged 16 years or older at surgery (log-rank test, chi-square 2.288; $P = .13$).

The only univariate predictor of autograft reoperation was preoperative pure aortic regurgitation (hazard ratio [HR], 1.86; 95% confidence interval [CI], 0.99-3.49; $P = .05$). Adult patient age showed a tendency toward greater autograft reoperation rates (HR, 1.73; 95% CI, 0.84-3.56; $P = .14$). After multivariate analysis, the adult patient age was no longer significant (HR, 1.53; 95% CI, 0.72-3.21; $P = .26$), and pure aortic regurgitation

showed a trend toward greater autograft reoperation rates (HR, 1.70; 95% CI, 0.89-3.24; $P = .11$).

Table 3. Reoperation characteristics

	N
Indication for reoperation	
Aortic root dilatation with AR	34
Isolated aortic root dilatation	5
Isolated aortic regurgitation	2
Aortic root procedure	41
Aortic root replacement	39
Allograft	3
Valved conduit	31
Stentless root	2
Valve sparing	3
Aortic valve implantation	2
Additional procedures	
Pulmonary allograft replacement	8
Allograft	7
Valved conduit	1
Mitral valve repair/replacement	4

Other Valve-Related Events

During follow-up, 2 patients developed endocarditis (0.11%/patient-year), complicated by a stroke in 1 patient. In 1 patient, allograft endocarditis occurred and was treated with antibiotics (0.06%/patient-year). One patient developed pulmonary emboli (0.06%/patient-year). Bleeding events, valve thrombosis, or nonstructural failure was not observed.

Functional Status at Follow-up

At the last follow-up visit, 95% of the patients were in New York Heart Association class I or II, and 5% of patients (n = 6) were in New York Heart Association class III-IV owing to aortic regurgitation or heart failure. Finally, 5% of the patients had moderate to severe aortic regurgitation, 1% had moderate to severe pulmonary regurgitation, and 7% of the patients had moderate to severe pulmonary stenosis.

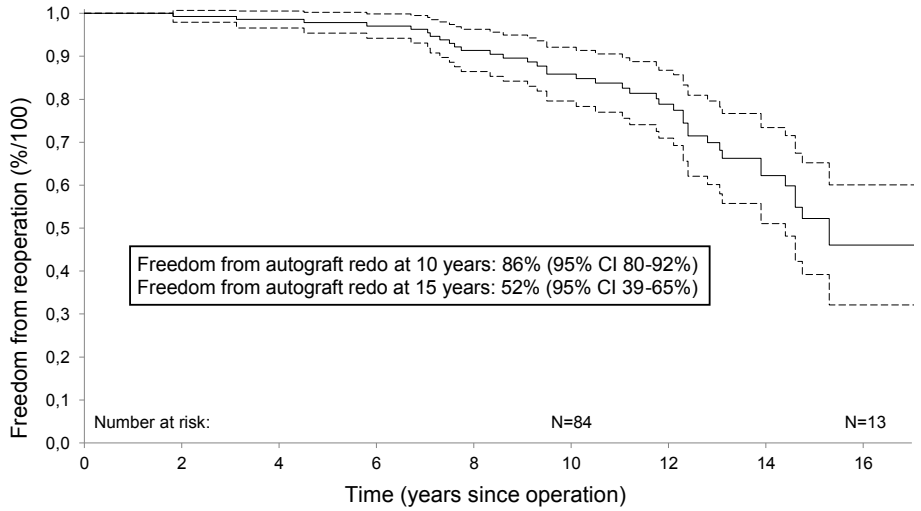

Figure 2 Overall freedom from autograft reoperation.

DISCUSSION

Although the Ross operation has provided very satisfactory results in the first postoperative decade, over time an increasing number of patients will require reintervention. Of our series of 155 primary Ross operations, 41 patients underwent reintervention on the aortic root with a median interval to reintervention of 15.3 years (range, 1.8-18.7 years). Since the completion of the present study, 4 additional patients were scheduled for reoperation. The freedom from reoperation rate at 10 years was 86%. These results are comparable to those of other series.[12,13] Most of our reoperations occurred in the second decade after the Ross operation. In a meta-analysis of 17 consecutive series of both children and adults, the yearly rate of structural valve deterioration or nonstructural valve deterioration for the autograft valve was estimated to be 1.15% (95% CI, 1.06-2.06%).[1] In our series, with a longer follow-up than other series in the meta-analysis, we found a yearly rate of structural valve deterioration or nonstructural valve deterioration of 1.81%, well within the 95% CI of the pooled series.[6]

Given that in our institution, none of the autograft roots were implanted in an intra-annular method and no proximal support was used, technical adaptations of the pulmonary root implantation might be helpful in preventing, or at least delaying, these reoperations. Charitos and colleagues[14] reported on the results of the German-Dutch Ross Registry. They found that reinforcement of the proximal suture line in a full root Ross operation leads to a reduction of the reoperation rate at 10 years of follow-up.[14] In their series, the mean follow-up duration of only 8 years in the patients with a reinforced proximal suture line was shorter than in patients without reinforcement. Conceptually, it is hard to understand by

which mechanism, that the reinforcement of the proximal suture line only will prevent the sinuses of Valsalva and distal parts of the pulmonary autograft root from dilation. Others have advocated reinforcement of the entire pulmonary root with a prosthetic graft.[15,16] These advanced techniques for the Ross operation might be attractive additions to the operation in an adult patient population. In growing children, however, some degree of dilatation or growth of the autograft will be advantageous to the patient. It is hard to foresee what technical modifications of the operation would allow for some degree of diameter augmentation of the implanted root but would prevent aneurysmal dilatation and subsequent valve dysfunction.

In the present series, we had no mortality in 41 reoperations. The operative mortality rate after previous ascending aortic or aortic valve surgery is reported to be 5.4% to 17.9%.[2-5] Most of these series are combined series of patients with different types of previous aortic root procedures. The risk factors for mortality are mostly advanced age and the need for coronary revascularization, either planned or unforeseen.[3-5] In our series of exclusively reoperations after pulmonary autograft implantation, the patients were relatively young, and no coronary revascularization was necessary. In these reoperations, the coronary buttons are usually relatively easy to prepare, because, in contrast to reoperations after previous allograft implantation, aortic wall calcification is absent.

Our experience has shown that the reoperations can be performed safely with little morbidity and no reoperative mortality, but with a few surgically challenging technical difficulties, the consequences of which can be avoided by paying particular attention to the reopening of the chest. Because in most patients, the aortic root and ascending aorta are dilated, these structures can become adherent or very close to the posterior aspect of the sternum. Preoperative computed tomography scanning might help identify patients at risk of aortic injury at reopening the chest. In these patients, elective femoral vessel canulation will allow safe entry into the chest. Nevertheless, we encountered accidental aortic or pulmonary artery injury in 5 patients, requiring emergency installation of cardiopulmonary bypass with femoral vessel canulation. From this experience, we routinely performed computed tomography of the chest in the preoperative workup of these patients.

Because the most prominent indication for reoperation is aortic root dilatation, aortic root replacement is required. Only 2 patients in our series had structural valve dysfunction without severe aortic dilatation. In these patients, insertion of an aortic valve prosthesis in the pulmonary autograft root was possible. In 1 of these patients, a moderately dilated ascending aorta was untouched at reoperation, but progressive ascending aortic dilatation necessitated ascending aortic replacement 4 years later. In patients with aortic root dilatation without structural aortic valve dysfunction, a valve-sparing root replacement might be possible. Our systematic biannual echocardiographic follow-up protocol helps in identifying asymptomatic patients with significant aortic root dilatation. These patients can undergo elective reoperation before the onset of potentially lethal aortic complica-

tions, such as aortic dissection. Performing reoperation before severe aortic insufficiency has developed could enhance the possibilities for valve-sparing procedures and prevent irreversible myocardial damage.

The indication for a Ross operation has been a matter of debate, and recent reports have shown an increasing incidence of reoperations after pulmonary autograft implantation.[1,6,17] Our results have shown a substantial proportion of patients requiring reoperation after a Ross operation. The present report provides information about the risks of these reoperations and might therefore be useful in determining the preferred choice for a valve substitute in patients with aortic valve disease. In adult patients, our initial enthusiasm for the Ross operation has tempered. We have not performed a Ross operation in an adult patient in the past 7 years. In children and young adults, however, the pulmonary autograft might still be the preferred valve substitute, given the excellent short- and long-term results and the lack of a reasonable alternative. The decision for a valve substitute should take into account, weighing the risks and benefits of the available treatment strategies, combined with careful elicitation of patient preferences to ascertain patient-tailored optimal treatment selection.

CONCLUSIONS

In our prospective cohort, reoperation of the autograft root was observed increasingly in the second decade after the Ross operation. Careful monitoring of patients over time and adequate timing of the reoperation and a surgical strategy tailored to the mode of autograft failure are the basic requirements for a safe and successful reoperation.

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Chapter 9

Discussion on: Aortic root reoperations after pulmonary autograft implantation

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H.J. Safi, H. Ogino,; J.E. Bavaria, R. Di Bartolomeo.

J Thorac Cardiovasc Surg 2010;140:S86-91.

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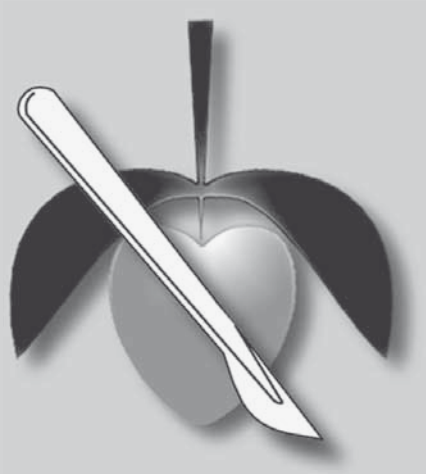

DISCUSSION

Dr F. Meadors*(Little Rock, Ark)*. I have a question for you, Dr Miller, and the panel. If you have a patient who is going to require graft replacement in the ascending aorta, how big does the true transverse aortic arch have to be before the panelists would convert from a hemiarch replacement to either a conventional open arch, total replacement, or a hybrid?

Dr Miller. Is it a bicuspid aortic valve or a trileaflet aortic valve? I think that makes a very important difference.

Dr Meadors. I think it is certainly pertinent to pose the scenario of the patient with bicuspid valve because that denominator is going up with the baby boomers coming into middle age. Therefore I would take the easy way out and ask for answers to both scenarios.

Dr Miller. Therefore the question is how big does the arch have to be to make you go beyond a simple open distal or hemiarch to a total arch in both trileaflet and bicuspid aortic valve disease. My response would be to parrot back what I learned at this meeting over 20 years ago from E. Stanley Crawford and that is to use the patient's own meter stick or yardstick when the aneurysm or what you are thinking about replacing exceeds the normal contiguous aorta by a ratio of 2. E. Stanley used this rule of thumb for patients with Marfan syndrome way back when, and I have found it to work pretty well. But he admitted, and I will admit also, that we do not have one shred of scientific evidence to back that up. However, this barometer of 2× works pretty well, remembering that the denominator for a patient with a bicuspid aortic valve cannot be the distal ascending aorta because it way too often tends to be dilated. It has to be the distal arch for the denominator on a patient with a bicuspid valve, whereas the distal ascending or proximal arch might be okay in a patient with a trileaflet valve. Therefore it does not take much in my book, especially for young elective cases because it does not add to the risk. For the patients with trileaflet valves, probably I would be a little less aggressive, but patients with bicuspid valves tend to be younger, and I think we have to do a better job up front to confer the most durable repair we can.

Dr Stewart. I would agree with you. With patients with bicuspid valves, we tend to be a bit more aggressive and move to a total arch when you exceed 2 to 1. You have to make the patient's operation individual as well, though, and in some of the older patients, you can generally almost perform a total arch by using a method I think you described, a peninsula operation in which you can just leave the greater curve and take the whole arch essentially off and reconstruct it with a very aggressive hemiarch. We do that more often than not for patients with trileaflet valves.

Dr Bavaria. I think there is some science to the bicuspids. I think a total arch operation with a bicuspid valve is almost never necessary. It is backed up by the fact that if you look at data from embryology and arch development from lots of basic scientists, the whole

bicuspid valve gene penetration is about at the proximal and middle arch. It does not go much more distal than that. Therefore I almost never do a full-blown aortic arch procedure.

Dr Miller. Wait a minute. Neural crest development starts at the ligamentum and goes retrograde. You said proximal arch?

Dr Bavaria. No. There are data that suggest that bicuspid aortic valve pathology ends at the mid arch, and the only exception to that is when you start having coarctation issues. Therefore I do not do very many full arch procedures in patients with bicuspid valves because I do not think they really need that. To answer your question about tricuspid atherosclerotic disease, if you start having 5- or 5½-cm aortas, you should probably go down and do kind of a first-stage elephant trunk type of procedure to get rid of the full arch in cases like that.

Dr Di Bartolomeo. Sometimes, in patients with bicuspid aortic valves, the aortic arch is small or hypoplastic. In these cases I am very aggressive and replace the ascending and the full arch. In cases of tricuspid aortic valve, the extension of the arch replacement depends on the size of the aneurysm, the age, the etiology, and so on.

Dr Miller. Do I interpret your remarks correctly by saying you are more aggressive in the younger patients with bicuspid valves than you are in the older patients with trileaflet valves?

Dr Di Bartolomeo. Yes.

Dr Safi. Dianna Milewicz, with her work on the bicuspid aortic valve gene, thinks they have a transforming growth factor β2 mutation. You operate on them, even at 4 cm, because they are prone to dissection and rupture. With regard to the elephant trunk procedure, if the descending thoracic aorta is big or it is going to dilate because of dissection, I would use the standard elephant trunk procedure. Otherwise, I will resect most of the lesser curvature and the lateral wall of the aorta, and it seems this is very stable.

Dr Spielvogel. I tend to agree with Dr Safi. If the descending aorta is really normal and you just have sort of a dilatation at the proximal aorta into the arch, I think you can resect most of the underside of the aortic arch with an extended hemiarch and remove the pathology without resorting to a full arch. My only question is this: What was the descending aorta like? Was there aneurysmal disease there where you did not expect to be coming back? In that case, I think you would like to put in an elephant trunk and do a full arch replacement.

Dr Ogino. I think total arch replacement is not necessary in most patients with bicuspid aortic valves because the dilated part is limited to the proximal arch. Therefore I think hemiarch replacement is a good operation for patients with bicuspid aortic valves.

Dr Bekkers. I think it is nice to make an anastomosis on a rather normal-sized aorta, and therefore I try to resect or remove as much as needed until the aorta returns to normal. Whether that is some kind of an extended hemiarch or needs to be a full arch with an

anastomosis either distal to the subclavian artery or at the level of the subclavian artery can be decided during the operation.

Dr Di Luozzo. Basically if a patient has a bicuspid aortic valve and a normal-sized descending thoracic aorta, data from our institution indicate that just a hemiarch replacement is good enough. The need for a distal aortic reoperation is very, very low. I think in our series it might be 1 of more than 200 patients who required a distal aortic reoperation. Therefore based on our data, I think just a hemiarch is all that is needed.

Dr Stulak. Having presented a congenital topic, and this admittedly not being an area of expertise for me, what I have seen at Mayo Clinic with Dr Sundt is basically the same as what Gabe has said. If there is a normal distal aorta, then he can do most of his resections with a hemiarch.

Dr Wheatley. I agree, a hemiarch would be our approach as well.

Dr N. Kouchoukos*(St Louis, Mo)*. I have a question for Dr Bavaria. Some of the 3-dimensional reconstructions you showed of these distal arch aneurysms suggest that they could be easily dealt with from a left thoracotomy, resecting only the very distal part of the aortic arch. You might have to reimplant the subclavian artery, but you would not have to do anything to the left carotid or innominate arteries. Why not use that procedure? You indicated that there was a 20% stroke rate associated with open operation, and I would take strong issue with that. Some of Dr Stanley Crawford's data from the 1990s, when he was putting clamps on the aorta, indicated a 20% stroke rate. With circulatory arrest, however, you do not need to place any clamps on the aortic arch, and the prevalence of stroke is quite low. I would suggest that hybrid procedures are unnecessary for these cases in which the aneurysm is in the very distal arch.

Dr Bavaria. I think if you can get into a zone 2 landing with a regular thoracic endovascular aortic repair (TEVAR), then you would do that. Therefore we would never operate on any of those cases if we can get into zone 2 with a stent. To do a thoracotomy on a patient who has a proximal descending aortic aneurysm with an adequate zone 2 landing is something I would avoid: I would stent in every case. Therefore the question is this: What about something that precludes landing in zone 2, which then means you have to come in and maybe do a left chest case? These patients all have big atherosclerotic aneurysms, and most of those patients have very high atherosclerotic burdens and are really bad smokers. We believe that a fourth interspace, high reverse, hemiarch distal arch procedure from the left chest or from an anterior clamshell is just not appropriate in these cases. We have learned from the volume reduction data in thoracic surgery that a sternotomy compared with a thoracotomy in patients with chronic obstructive pulmonary disease is so much better tolerated. Therefore a proximal median sternotomy-based solution, in our opinion, is a better option here.

Dr Kouchoukos. But you really have not shown that the mortality rate or the stroke, renal failure, or paraplegia rates are any better.

Dr Bavaria. I do not even think you need to show that they are any better. Even if they are the same, it is still probably preferable for the patients to go in from the front compared with the back. We are still early in this business. I just showed you the meta-analysis. I think the world literature only shows about 180 cases. We will have to see how it goes, but noninferiority is really all you need here.

Dr Miller. Let me ask a few zingers here. Allen, in the first session you were telling us about your neat 3f valve in a De Paulis graft. You are too young probably to know that Christian Cabrol in Paris did all of his composite valve grafts for 30-plus years, even going back to the Starr–Edwards ball valve days, sewing the valve way up, leaving a cuff, and then sewing the cuff of the graft to the annulus. But that is what led him to have to create, out of misery, the Cabrol II mustache coronary revascularization when the coronaries would not reach because it was too high. Have you seen that with your new technique?

Dr Stewart. Interestingly, Dr Coselli just reminded me that Dr Cabrol did that. We have not had a problem. I mobilize the button from the bottom up and do not spend too much time mobilizing the sides. I just have not had that problem.

Dr Miller. Yet.

Dr Stewart. Well, we have done a good number now, and we have not had any difficulties. That skirt at the bottom is not very long. We usually go about 3 rings up with our sutures, and therefore really it is not a long skirt underneath the valve.

Dr Miller. Maybe the examples we saw in the movies were before you cut them down.

Roberto, you talk about paraplegia of 7.5% with the long frozen trunk with the E-vita, and I do not know whether that is chronic A, acute A, or B dissection, but you are covering a lot of intercostals, and I am worried that the paraplegia rate might be excessively high. I am also worried about the chronic dissections, A or B, in which you are stuffing an E-vita into a very tiny frozen true lumen. Tell us how you avoid trouble there.

Dr Di Bartolomeo. We had 1 episode of paraplegia in a 52-year-old patient with chronic type A dissection. Two weeks after the operation, we performed magnetic resonance imaging, and we found that the patient had an angioma at T5; we do not know whether the cause was this angioma. Another episode of paraplegia occurred in a patient undergoing intervention for a very bad atherosclerotic aorta with 3 large aneurysms involving the arch, the proximal descending aorta, and more distally the infrarenal aorta. The endograft was deployed at T6. It is difficult to find a reason in these cases. Embolism? Insufficient spinal circulation?

Dr Miller. Therefore your advice to us would be to study the intercostals carefully and only go as far you need to distally? Would that be the safest course of action?

Dr Di Bartolomeo. Generally we use only the angio–computed tomographic scan and sometimes an aortogram, but it is difficult preoperatively to stabilize the patient.

Dr Miller. The open E-vita, which we do not have in this country, does it come in different lengths for the stent graft part? Do you have a choice of length for the stent?

Dr Di Bartolomeo. The length is 15 or 16 cm, but it is also possible to get a shorter stent graft of 10 cm.

Dr Miller. A custom-ordered shorter stent graft.

Dr R. Griepp*(New York, NY)*. I don't like to speak up, but with the degree of ignorance about spinal cord perfusion, I think I have to say something. I can guarantee you that I can take a patient and ligate T3, which is usually the first intercostal artery coming off the aorta, to T7 a hundred times and never get a spinal cord injury, and I challenge those of you who do descending thoracic aortic surgery to remember the last time you had a paraplegia if your distal anastomosis ended above T8 or T10. Nonetheless, this phenomenon of paraplegia in frozen elephant trunks has been reported by a lot of practitioners. I am not sure of the reason. One thing I am confident about is that it is not taking those intercostals out of the circulation. It might well be embolization down one: if you embolize an intercostal artery and obstruct an end artery into the cord, you will have a localized infarct and possibly paraplegia or paraparesis. But I do not think depriving the body of the upper few intercostal arteries in itself will cause a neurologic injury. I would be curious to hear whether anyone else has an explanation for why you can resect the aorta from the left subclavian artery to the mid and lower descending thoracic aorta almost every time without a neurologic injury, but when you do this with a frozen elephant trunk procedure or TEVAR, you see neurologic injury in a significant percentage.

Dr Miller. The skeptics would say because your technique involves progressive ischemic preconditioning of the cord as you sequentially work down, and you do not have that advantage with sudden TEVAR coverage. Any other theories of why there is a difference from the panelists?

Dr Ogino. Regarding spinal cord injury after open stent grafting, I try to demonstrate the Adamkiewicz artery by means of computed tomographic scanning or magnetic resonance imaging preoperatively, particularly in operations on the descending and thoracoabdominal aorta. In most the Adamkiewicz artery originates between T8 and L1, but in a few patients it originates at the level of T6 or T7. Therefore I think we have to be more careful about the level of the Adamkiewicz artery in endovascular settings. Too long an elephant trunk or too long a stent graft can be very dangerous in terms of spinal cord injury.

Dr Bavaria. We have done a lot of stents with hybrids and standard endovascular deployment up to about T7. We have had no paraplegia except in one subcategory, which is with intramural hematoma cases, which might be because you are throwing a kind of junk into the spinal arteries.

Dr Miller. Does that include the traumatic tears?

Dr Bavaria. We have never had a spinal injury from a traumatic tear. We have had strokes but not spinal injury.

Dr Miller. The paper presented in Banff by your younger faculty colleague?

Dr Bavaria. We had a stroke, and we had some intramural hematoma cases.

Dr Miller. I recall it was a traumatic tear.

Dr T. Hanke*(Luebeck, Germany)*. I have a question for Dr Bekkers from The Netherlands. You conclude that there is a high number of reoperations in the Ross patient population. Do you think, as does one of your Dutch colleagues in a comment in the *Annals*, that almost 100% will undergo reoperation? Do you agree with me that with special surgical maneuvers like the subcoronary technique or the reinforced full root, we can decrease this dramatic reoperation rate into more of a normal range?

Dr Bekkers. One thing for sure is that we are going to see more patients coming out having dilated aortas. Whether it will be all those patients remains to be seen, but there will be more. Of course, I am aware that a lot of colleagues advocate reinforcement either only at the site of the proximal anastomosis or as a full jacket around the whole aorta. The latter I can imagine will prevent the root from dilatation. If one reinforces only the proximal part of it, it is conceptually difficult for me to understand why that should prevent the whole aorta from dilating and not only the annulus.

Dr Miller. Dr Bekkers, were all of your Ross procedures done as a full root?

Dr Bekkers. No, they were not, but this report was only for the full roots. We had some dilatation, but not as much as seen with either a cylindrical inclusion or other techniques. This was a report only on 155 roots.

Dr Miller. I think that was Thorsten's point: if you do them the way the operation was designed to be done, as a subcoronary scalloped operation way back when, as Hans Sievers and you just reported (the article will be out next month), you would not see these dilatation problems.

Dr Bekkers. That might be. The other thing is that nowadays we reserve these operations especially for younger growing patients, and then it is hard to use any reinforcement with material that will not grow. We are hoping to see how the aorta and components can grow as the patient grows. Our experience is that whether it is a young patient or an old patient, they all receive these dilatations, and we think it will be hard to prevent that, especially in the younger group.

Dr Miller. Tell us about the Luebeck series, which is phenomenal. I think you were a coauthor?

Dr Hanke. Yes. With the subcoronary technique and the reinforced root, we were able to show that freedom from reoperation, at least after 10 years, was 94% and not 88% as with the nonsupported root. Therefore with the special surgical maneuvers, with a full root or the subcoronary technique, it seems, at least in the midterm, that there are better results. We do not know much about 15 years, and your data are great for all these 15-year survivors, so we will have to wait. However, we think with the original Donald Ross technique, we might be able to get better results.

Dr J. Bachet*(Abu Dhabi, United Arab Emirates)* My comments are addressed to Dr Spielvogel. You have shown us a very elegant technique, and I will not be critical of this,

although in many instances I think that the conventional arch replacement with an island reimplantation of the vessels is easier. However, I think that your outstanding results could be improved. I was very happy to hear that Dr Kouchoukos already told you several times that you could perfuse the brain continuously without interrupting cerebral perfusion because you are cannulating the subclavian artery. Why do you not perfuse the brain continuously? Second, I think that you could improve your results by getting rid of deep hypothermia. Why do you not do the procedure with moderate hypothermia? Do the distal anastomosis. Then when you have anastomosed the main prosthesis to the distal aorta, reimplant your trifurcated prosthesis into this main prosthesis, reperfuse the patient, rewarm the patient, and during the rewarming, do the proximal repair. You will save time on bypass and degrees in temperature, and your results will most probably be a little better.

Dr Spielvogel. Thank you for your suggestions. In many patients, particularly patients with degenerative aneurysms and dissections, you can occlude the brachiocephalic vessels. However, in those patients with extensive atherosclerotic burden, there are times we have had to resect, particularly in the innominate artery, almost up to the bifurcation to clear it of atherosclerotic disease. In those patients you cannot occlude the innominate artery and begin selective cerebral perfusion. Therefore I think in the atherosclerotic subset you have to be particularly careful about doing any instrumentation or clamping of those vessels, and that is one of the reasons why we have stayed away from the approach you suggest. However, there are patients in whom you can certainly do it.

In terms of the issue with hypothermia, if you look at the history of those who presented today, several have created very complex methods for perfusing the head and the lower body in an attempt to avoid using hypothermia. What we have found is that to preserve end organs in the lower body, it is very simple: just cool to a sufficient degree, and then, with the protection of hypothermia, you can go about your repair in an unhurried fashion and not worry that you are going to have renal failure, paraplegia, or some kind of ischemic event to the liver. As you saw, our reoperation rate for bleeding was not particularly high for this kind of operation. Although you can do it as you describe, we have stayed away from elaborate perfusion schemes and kept it as simple as possible. I always believe that if someone is going to adopt your procedure, it will be because they can understand it and perform it on an occasional basis without the requirement that they be in a major center that does a lot of similar cases. I guess that is part of the reason why we have not added those additional maneuvers. But thank you for your comment.

Dr Bachet. If you allow me, Craig, I have another question for the panelists. Why do you use so much Teflon felt in chronic patients? I have seen videos in which you could make the patient a Stetson with the felt that was used.

Dr Miller. I have not used Teflon felt in16 years, and that is why I have so many hats.

Dr Stewart. I do not use any felt.

Dr Bavaria. I use no felt.

Dr Miller. No felt.

Dr Di Bartolomeo. I use it.

Dr Safi. Well, I use Teflon felt and pledgeted sutures, and I call them the home team. I want to go home. And I do not use the French glue or the cryo glue.

Dr Bachet. But in chronic patients we do not use the glue either. We just use the patient's aorta.

Dr Safi. In the chronic patient, the chronic dissection or medial degenerative aneurysm, if you put in real stitches—2–0 or 3–0 polypropylene sutures—sometimes there is a tear in the intima. I promise you, I spend days and nights trying to stop bleeding from outside. If you put felt in prophylactically, you go home, and there is no problem with it, and there is no incidence of infection. The biggest patch is the graft: Why are we worried about the Teflon patch?

Dr Miller. Hazim, try some 4–0 or 5–0 sutures. David, we know what you are going to say: felt, lots of it.

Dr Ogino. For 70% or 80% of my cases, I use felt. We have more than 3,000 cases at the National Cardiovascular Center. The frequency of pseudoaneurysm formation is quite low. I think the Teflon felt contributes to the prevention of pseudoaneurysm formation.

Dr Bekkers. I like 4–0 Prolene sutures without felt.

Dr Di Luozzo. I use felt.

Dr Stulak. Dr Sundt uses felt.

Dr Wheatley. No shortage of felt in Arizona.

Dr Griepp. I would like to see publication on the rate of false aneurysm formation from those who do not use felt. We have published our incidence; it is in the literature. With felt, the rate is something like 1 false aneurysm per 357 patient-years looking back at all of our computed tomographic scans. Therefore if you do not use felt, fine, but give us some idea of how well it works.

Dr Miller. While we have Dr. Spielvogel here, let's talk about your elephant trunk procedure: 7% stroke rate for the first stage, and then up to a year, there was another 7% stroke rate, and you said most of those occurred during the second-stage operation. How can that be when it takes just a few seconds or a minute to reach in and grab the trunk and clamp it? Why are the patients exposed to such a high risk of stroke at the second stage?

Dr Spielvogel. That is a very good question. We had a number of patients who had strokes not so much as the result of the proximal reconstruction but in whom their habitus affected their cerebral perfusion. For example, we had a very obese patient, and the positioning in the right lateral decubitus position resulted in a very high central venous pressure during the thoracotomy with an inadequate arterial pressure, and therefore there was relative hypoperfusion of the brain, causing cerebral injury. We now recognize that we have to be very careful in maintaining adequate blood pressure in patients in that position.

Also, once you clamp proximally, the central pressure can go very high, and patients who have undiagnosed cerebral aneurysms can have an intracerebral bleed.

Dr Miller. Is that why you are on the pump, to keep them decompressed?

Dr Spielvogel. That is the case, but we unfortunately had a few patients in whom that happened.

Dr J. Appoo*(Calgary, Alberta, Canada)*. I have one point and a question for the panel. My point is about paraplegia with short stent grafts and why that might occur even though you are not sacrificing intercostals below T7 or T8. It could be due to spinal cord steal, which you do not see when you actually tie off the intercostals. However, maybe if you put in a stent graft, you actually have backward steal from the spinal cord.

I was interested in hearing that they use the E-vita graft for chronic dissections. I wanted to ask the panel how they handle the sort of patient we see a lot: the 70-year-old man who is 5 or 10 years out after a type A repair who has had a hemiarch done but still has a dissection flap in the arch. The aorta has grown over the last 5 to 10 years, and the distal arch is aneurysmal; the proximal middescending thoracic aorta is aneurysmal, perhaps 6½ or 7 cm; and there is a true and a false lumen and multiple fenestrations. How many people would re-enter, do a median sternotomy, and do some sort of hybrid approach with an E-vita type of graft or something else, as opposed to trying to manage this patient with circulatory arrest from the left chest to repair his distal arch and thoracic aneurysm?

Dr Miller. My answer is simple. It depends on how pathologically damaged the arch is. If there is going to be very little to sew up there, I would not want to be looking up through a left thoracotomy, hoping to do something quick. I would stage it with a total arch and a full surgical trunk, followed by whatever later.

Dr Stewart. I agree.

Dr Bavaria. I agree, for the most part, and that is the reason why when we do these type A dissections to begin with, we should be doing operations in which we do not leave a whole lot of arch and distal false lumen, so that we do not have this situation. There is one caveat: if you have a reasonable proximal landing zone of some sort, which might or might not be the case, and you have the celiac artery, superior mesenteric artery, and both renal arteries coming off the true channel, I would stent those cases. Those cases do really, really well.

Dr Di Bartolomeo. A chronic dissection?

Dr Miller. Chronic type A dissection with a previous ascending hemiarch.

Dr Di Bartolomeo. This is a perfect indication for the frozen elephant trunk procedure.

Dr Appoo. Do you find that there is still perfusion in the false lumen when you do that?

Dr Di Bartolomeo. I do not perfuse the false lumen.

Dr Miller. Do you see it later?

Dr Appoo. Because of fenestrations. If the patient has a 7-cm aneurysm, part is true lumen and part is false lumen, and the graft sits in the true lumen. If you still perfuse the false lumen through fenestrations below, is that a concern for you?

Dr Di Bartolomeo. I do not understand.

Dr Miller. You still have persistent flow in the large distal false lumen below your elephant trunk.

Dr Di Bartolomeo. In most cases we have observed complete thrombosis of the false lumen. In case of retrograde perfusion at the false lumen, an additional stent can be placed 1 or 2 months afterward.

Dr Miller. This is a major difference in philosophy and maybe the laws of the country. In Italy it is legal to stent graft a chronic dissection. Be careful in North America: you will go to jail. I do not think it works, I do not think it is very effective, and it is futile because of that exact point. You are going to have far too many fenestrations, and even if the false lumen does thrombose, there is going to be endotension in the false lumen. You have not conferred protection from rupture.

Dr Safi. Well, I do exactly what you said: a classic elephant trunk procedure and wait for 6 weeks and do the thoracoabdominal procedure, and my associate, Dr Tony Estrera, is going to explain our recent results.

Dr Spielvogel. Again, I think I would follow your tack with a redo arch elephant trunk procedure, and then, depending on how the distal aorta looks, an open completion or endograft. However, one thing we have forgotten is that if it is accessible in the left chest, Dr Kouchoukos has operated on a number of patients like this with a thoracosternotomy or a clamshell incision. Doing it all in one stage, you might be able to resect from your previous graft down to your distal extent, and Dr Kouchoukos has had excellent results. Therefore that is also an option if you think the patient can tolerate that type of procedure.

Dr Miller. I am glad you brought up Nick's thoracosternotomy, which was just updated and published recently.

Dr Ogino. I prefer a 2-stage approach with total arch replacement initially, with an elephant trunk procedure in the elderly. The second procedure actually depends on the patient's condition. If the patient can tolerate a thoracotomy, I prefer an open repair, but if that is not possible, I do a TEVAR, as Dr Bavaria said.

Dr Bekkers. I would preferably go through the left chest under deep hypothermic circulatory arrest and do some kind of a hemiarch from the other side.

Dr Stulak. Dr Sundt would do a total arch elephant trunk procedure, and then stage II would be through the left chest.

Dr Wheatley. I am going to side with our international colleagues: we would do a hybrid debranching and stenting, obviously under institutional review board approval as part of a research study.

Dr Di Luozzo. I would do a 2-stage approach. I did not understand Dr Appoo's first point about the steal phenomenon with the stent. Can you clarify that?

Dr Appoo. The question was this: Why were some of these patients with short stent grafts having paraplegia when Dr Griepp said you could ligate all the intercostals down to T10 and not get spinal cord ischemia? Maybe when you put in a stent graft you are covering the intercostals but the orifices are still open, so there is actually retrograde flow. Instead of the vessels perfusing the spinal cord, the intercostals are actually stealing blood from the spinal cord. With time, those intercostals could thrombose, but in the acute setting they might actually be patent.

Dr Bavaria. What you are saying is that there are small type II endoleaks?

Dr Appoo. Yes, in theory.

Dr C. Young*(London, United Kingdom)*. We heard 2 articles today looking at long, thin, small grafts going up to the cerebral vessels, and this worries me: I wonder what the rest of the panel thinks about it. With the ones that we have done before, using reverse transit grafts, we have had a lot of blockages, and we would aim to go with individual grafts, probably 12 mm, up to the underside of the subclavian. The other aspect that Dr Bavaria did not mention is that most of the patients we see for hybrid procedures have had previous TEVARs, and the problem is that they are left with endoleaks, type I endoleaks, into the arch. They are going back in this sort of redo setting. You did not mention that, and I wonder what your experience was.

Dr Miller. I think Joe has an extensive experience with that problem: going back in the arch for a proximal 1A endoleak after TEVAR.

Dr Bavaria. The second question is about the cases in which we performed the hybrid procedure. We do a lot of secondary procedures for type I endoleaks, which is pretty common. However, for this particular series, we only had 1 patient who underwent intervention elsewhere; it was a traumatic case. Therefore we only had 1 of the 27 cases that was a proximal endoleak disaster. The other 26 cases were actually classic hybrid procedures. And we have had no—zero—zone 0 endoleaks, which we think is because, if you look at Czerny's paper from Vienna, you get type I endoleaks in zone 0 if you put stents in overly large aortas. We do not do that. I tried to point that out: when we do zone 0 landings, we do not do them in 4-cm aortas.

Dr Miller. You made that quite clear. You said 3.5 cm, and if it is bigger than that, you are going to replace it at zone 0.

Dr Bavaria. That is correct. We have had zero type I endoleaks in our hybrid procedures. Your first question, about small grafts into the cerebral vessels, I thought was very significant. I happen to agree with you completely. It is a little bit worse to have a single-branch 14-mm graft come off to the whole brain and arms. I am wondering whether the 7% stroke rate in the second stage of an elephant trunk procedure is related to some sort of issue regarding low flow, or maybe there is also some compression of the airway. Fear of

low flow through small grafts is the reason why the vascular surgeons who do debranching operations come off with a single graft. I tend to not do that and come off with multiple grafts to the cerebral circulation.

Dr Miller. David, you gave us what long-term follow-up you had, admitting that it was neither complete nor very long term, but I think you were quite honest. We do not know, but you are not aware of any problems yet?

Dr Spielvogel. No. Actually, I recently got a call from a referring doctor who had a patient with a problem. The first hybrid procedure that I did was in 1999 in an elderly woman in whom I moved the left carotid and innominate arteries to the ascending aorta because of occlusive disease and then stented the arch retrograde with the old excluder. She is actually now more than 10 years out, and both of those grafts are widely patent. This doctor had to put another stent graft below the old one because she dilated her distal aorta and had a type I endoleak. We are following these patients very closely, and we have patients out over 10 years with grafts that are widely patent. Clearly this is a concern of ours. I think you should try and keep the limbs as short as possible. When you measure them, and we do, the average limb length is quite short. Again, we will continue to follow these patients, and we will see.

Dr Miller. Maybe that multibranch graft, when you turn these heavy people on their side for the second stage, might be where you are having an issue. I have to correct myself (which is common because I make a bunch of errors), but the Japanese study was not the first randomized controlled study of cerebral protection in arch surgery. Dr Griepp reminded me that Professor Bonser in Birmingham did a small one, and also Lars Svensson, when he was at the Lahey Clinic, did one looking at S100. Again, small numbers, but the Japanese, we commend you: that is what we need. That is real evidence, but the numbers are so small that even had you seen a difference, it might have been suspect. Is there hope that this JSTAR2 study can be continued? Is there funding to get bigger numbers?

Dr Ogino. That is a good question. Time is limited, and funding is also limited. Therefore we have discontinued the randomized controlled study. The power analysis regarding the JSTAR1 suggested that we should have 50 patients in each limb, but as you know, we had fewer than 50% of this number: this is a weakness.

Dr Miller. So your funding dried up and you cannot continue to randomize?

Dr Ogino. It is quite difficult to continue it. At the moment, our patient age has increased: the patients are 75 or 80 years old, and their aortic pathology is also quite complex. This study is just for isolated total arch replacement without any concomitant procedures for low-risk patients having simple aortic pathology. In 2004, when we planned this study, 50% of the patients had simple disease, but in 6 years, the aortic pathology has become more complex. Therefore it is quite difficult to continue the randomized controlled study for patients having simple disease.

Dr Miller. And the surgeons do moderate or more deeply hypothermic cerebral perfusion depending on how they feel about each patient? Some will go very cold and some will stay warm depending on the patients at the various hospitals? Have the results of the study changed their practice patterns? They probably do what they did anyway.

Chapter 10.

Aortic dissection, a vascular emergency

J.A. Bekkers, J.J.M. Takkenberg, A.J.J.C. Bogers.

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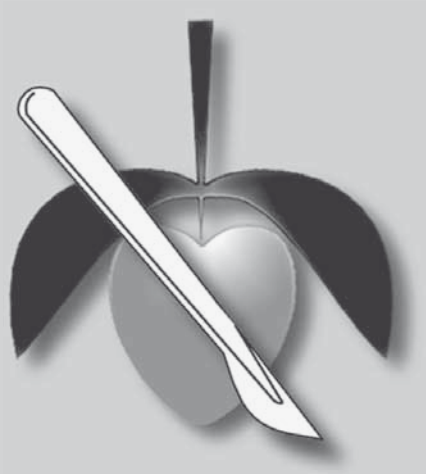

SUMMARY

When the ascending is aorta involved in a proximal aortic dissection (DeBakey type I or II or Stanford type A) emergency surgery is warranted, since mortality in the first hours after the onset of the dissection is high. The diagnosis can be made by trans-oesophageal echocardiography or CT-scanning. Overall operative mortality used to be high, but showed a steady decline over time. Long-time survival of our patients is acceptable. Multivariate logistic regression analysis showed aetiology, date of operation, pre-operative mechanical ventilation and pre-operative pericardial drainage to be independent risk factors for mortality.

INTRODUCTION

Aortic dissection is an acute disease in which splitting in the medial layer occurs, thereby creating two lumina, true and false. The primary origin of the dissection (the primary intimal tear), may occur at varying sites of the aorta, most commonly just above the aortic valve or just distally of the left subclavian artery. The extent of the dissection may vary from a few centimetres to the total length of the aorta from just above the aortic valve to the abdominal aorta. Classification of the dissection is determined by the site and extent of the dissection, using the DeBakey or Stanford classification. Both classifications are depicted in Figure 1.

The most prominent presenting symptom is acute severe chest or back pain, usually accompanied by hypotension. Other symptoms may be signs of pericardial tamponade or

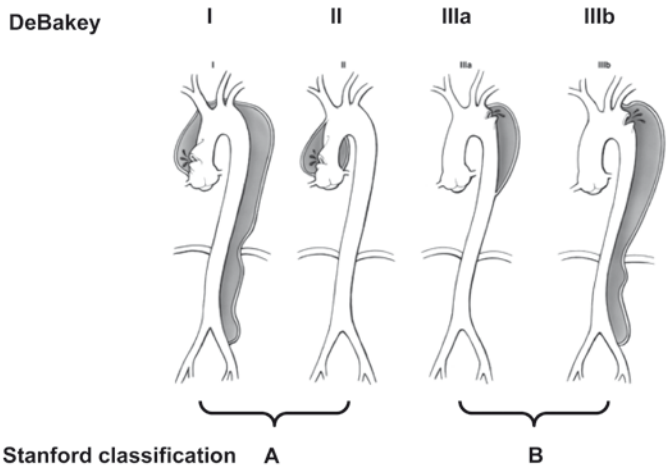

Figure 1. Classification of dissections.

aortic insufficiency, central or peripheral neurological deficit or vascular insufficiency.

Acute aortic dissection is usually a consequence of arterial hypertension but other etiological factors may be present as shown in Table 1.

The diagnosis can be made by trans-oesophageal echocardiography or CT-scanning. The key issues in determining the correct diagnosis are the presence of an intimal flap in the aorta, the finding of a true and a false lumen, involvement of the ascending aorta, pericardial effusion with possible tamponade and aortic insufficiency.

When the ascending is aorta involved in the dissection (DeBakey type I or II or Stanford type A) emergency surgery is warranted, since mortality in the first hours after the onset

Table 1. Etiology of aortic dissection

Etiology of Aortic Dissection
Hypertension
Connective tissue disease: M. Marfan, M. Ehlers-Danlos
Congenital aortic valve disease: bicuspid aortic valve
Aortic aneurysm
Atherosclerosis
Pregnancy

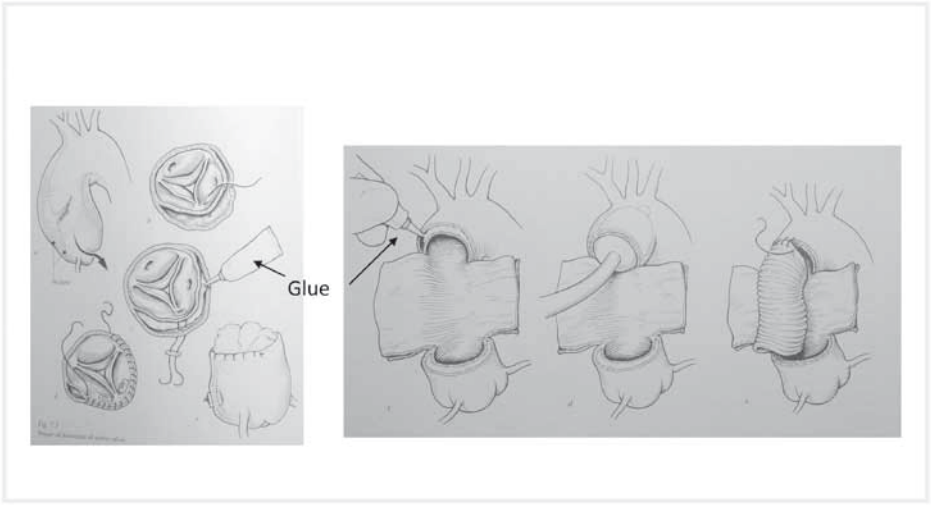

Figure 2. Reconstruction of the proximal aorta in acute dissection.

of the dissection is high, accumulating to 70% after 48 hours. For distal aortic dissection (DeBakey type III or Stanford type B) medical therapy is preferred and surgery only indicated in complicated cases.

Surgical therapy for acute DeBakey type I or II dissection consists of resection of the aortic part with the intimal tear (usually the ascending aorta) and replacement with vascular prosthesis. If the aortic root and aortic valve show no pre-existing pathology or irreparable lesions the aortic root is reconstructed and anastomosed to the prosthesis (Figure 2). If the aortic root or valve cannot be preserved, root replacement by means of a valved conduit or allograft is indicated. Usually the aortic arch can be reconstructed. Alternatively the aortic arch is replaced partially or completely by means of a vascular prosthesis.

Table 2. Patient characteristics

Factor	N
Sex (m/f)	99/46
Age (mean, range)	56 (21-78)
Aetiology	
Idiopathic	126
Marfan	13
Other CTD	4
DeBakey type	
I	111
II	34
Aortic insufficiency	
Grade 0	54
Grade I-II	44
Grade III-IV	47
Urgency (time after onset)	
< 24 hours	132
24 hours- 14 days	13
Main presenting symptom	
Acute pain	115
Stroke	8
Paraplegia	2
Limb ischemia	9
Pre-operative resuscitation	9
Pre-operative pericardial drainage	7
Pre-operative ventilation	13

MATERIALS AND METHODS

We analysed data regarding all patients operated for acute proximal aortic dissection in the Erasmus University Medical Center in Rotterdam, The Netherlands from 1972 to 2003. Patients with chronic dissection, traumatic dissection or iatrogenous dissection were excluded. 145 patients were operated. Patient characteristics are shown in Table 2.

All patients were operated emergently after diagnosis. Operative procedures are shown in Table 3.

For aortic valve replacement a valved conduit containing a mechanical prosthesis was used in 30 patients and 16 patients received a cryopreserved allograft.

Operative mortality was analysed related to 5 year time periods. Operative mortality was defined as mortality within 30 days of operation or during hospitalisation. Risk factors for operative mortality were determined by multivariate logistic regression.

Long term survival was determined by Kaplan-Meier methods.

Table 3. Operative procedures

Procedure	N
Ascending aorta replacement and aortic valve preservation	83
Ascending aorta replacement and aortic root replacement	39
Ascending aorta and arch replacement	16
Ascending aorta, arch and aortic root replacement	7

Additional procedures were mitral valve repair (n=1) and CABG (n=9)

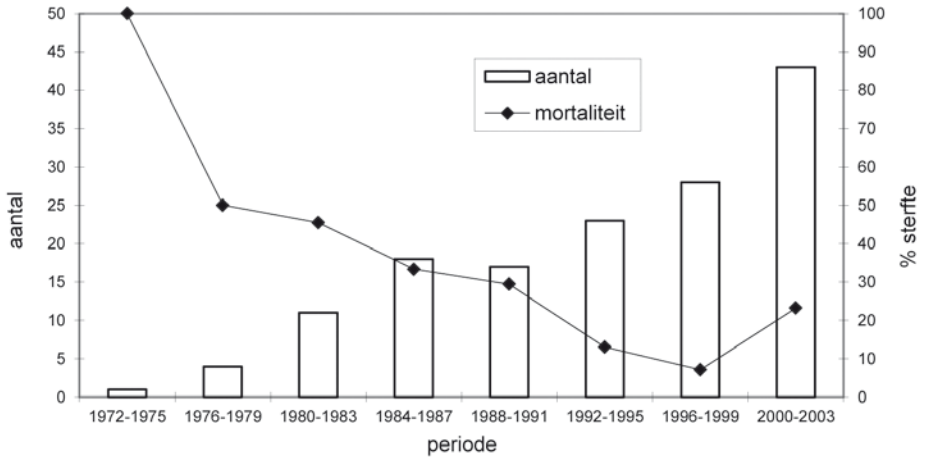

Figure 3. Number of operations and mortality per 5 year period.

RESULTS.

Overall operative mortality was 23% (34 patients). By analysing mortality for 5 year periods we found a steady decline in mortality over time, as shown in Figure 3.

Multivariate logistic regression analysis showed aetiology, date of operation, pre-operative mechanical ventilation and pre-operative pericardial drainage to be independent risk factors for mortality. Whether the aortic valve was preserved or was replaced, or whether aortic arch replacement was performed was no risk factor for mortality.

Long time survival determined by Kaplan-Meier methods was 63%, 50% and 26% at 5, 10 and 15 years respectively.

Reoperation for aortic valve incompetence after repair or valve replacement was necessary in 10 patients after a mean interval of 5.8 years (3 months-11 years). Reoperation for distal aortic complications was performed in 11 patients, most frequently for thoraco-abdominal aneurysm (n=5), abdominal aneurysm (n=2) or arch re-dissection/rupture (n=3).

CONCLUSIONS

Acute aortic dissection is a potential life threatening disease. Symptoms may vary and mimic other conditions, leading to a delay in diagnosis. Since mortality of untreated proximal dissection is high, emergency operation is warranted. In most patients the ascending aorta only needs to be replaced combined with restoration of the native aortic valve. In 32% of patients additional aortic valve replacement was necessary; the aortic arch was replaced in 11% of patients.

Overall operative mortality used to be high, but showed a steady decline over time. Long-time survival of our patients is acceptable. The incidence of late complications, leading to reoperations for aortic valve replacement or aortic reoperations is acceptable.

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Chapter 11

Acute type A aortic dissection; long term results and reoperations

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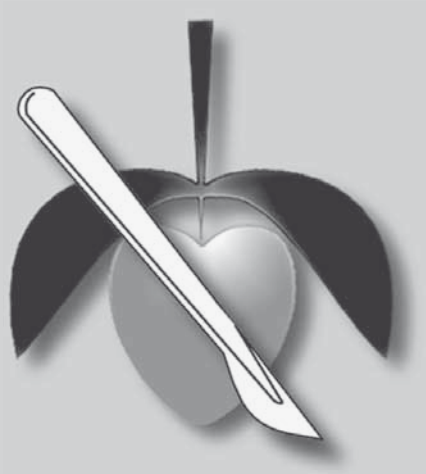

ABSTRACT

Objectives: The objective of this study was to report long-term results and incidence of reoperations after surgery for acute type A dissection.

Methods: All 232 consecutive patients who underwent surgery for acute type A aortic dissection from 1972 to April 2011 were included. Patient, procedural and follow-up information was obtained from hospital records.

Results: Mean age was 57.9 years (standard deviation 13.4 years), 64% were male. In 157 patients, the native aortic valve was preserved, 75 underwent aortic valve replacement (valved conduit 49, aortic allograft 16, mechanical prosthesis 8 and bioprosthesis 2). Thirty-, 60- and 90-day mortalities were 18.1% (*n* = 42), 19.8% (*n* = 46) and 21.6% (*n* = 50), and decreased over time. Thirty-day mortality in the period 2007–11 was 12.5%. During follow-up of hospital survivors (mean duration 7.2 years, range 0.2–25.7 years), 64 patients died. Risk factors for 30-day mortality were preoperative resuscitation and longer cardiopulmonary bypass time. The use of circulatory arrest and biological glue was associated with a lower 30-day mortality. Actuarial survival was 53.4% (95% confidence interval [CI] 45.8–61.0%) after 10 and 29.3% (95% CI 29.9–48.7%) after 15 years. Late survival was comparable for patients with preserved native valves versus patients with various types of valve replacement. Forty-three patients underwent 47 reoperations; for aortic valve insufficiency in 17 patients (12 native valve, 5 allograft), recurrent aortic dissections or aneurysms in 27 and other cardiac operations in 3. Actuarial freedom from aortic valve reoperation at 10 years was 85.6% for patients with a preserved native aortic valve, 84.8% after allograft implantation and 100% after prosthetic replacement (Tarone–Ware test *P* = 0.13). Aortic valve preservation in patients presenting with severe aortic insufficiency was associated with an increased risk of aortic valve reoperation.

Conclusions: Acute type A dissection in the current era is associated with a decreasing acceptable operative mortality risk and has a satisfactory long-term survival for hospital survivors. The use of circulatory arrest and biological glue were both involved were associated with a lower 30-day mortality. A substantial proportion of patients will require reoperations on the aortic valve or the aorta.

Key words: Aortic dissection, allograft, aortic root, aortic valve repair, aortic reoperation.

INTRODUCTION

Acute ascending aortic dissection (classified as DeBakey type 1 or 2) is a severe condition, with a high risk of a fatal outcome, unless emergency surgery is performed. Although substantial improvement has been accomplished over time, early mortality after emergency operations remains high.[1-4]

The principal element in the operative treatment of acute ascending aortic dissection is reconstruction and replacement of the ascending aorta to prevent a fatal rupture.[5] Aortic valve incompetence can usually be corrected by the repair of the aortic root and resuspension of the aortic valve commissures.[6] Alternatively, aortic root replacement, often by means of a composite graft or a biological conduit may be required. After successful initial treatment secondary aortic valve incompetence or residual pathology of the descending aorta or thoraco-abdominal aorta may require later reintervention.[7-9]

Due to the emergent nature of aortic dissection, much attention is paid to acute phase and early treatment results. Because the majority of patients will survive the initial treatment, information on the long-term outcome becomes relevant.

In this study, we analyse our results of the surgery for acute ascending aortic dissection. We study the early patient outcome, as well as long-term results, with an emphasis on the durability of valve-preserving operations, valved conduit implantation or allograft root replacement. Finally, the incidence of interventions for residual distal aortic pathology is studied.

MATERIALS AND METHODS

From our institutional Aortic Surgery Database, we extracted 232 consecutive patients operated upon for acute (within 14 days after the onset of complaints) DeBakey type 1 or 2 dissection between August 1972 and April 2011. The arrival of the patient in the aesthetic room was considered to be the start of the operation. We excluded patients with a traumatic or iatrogenous dissection. The Institutional Review Board (IRB) approval was obtained for this retrospective follow-up study (MEC number 2011-064); the IRB waived informed consent. Preoperative patient characteristics are displayed in Table 1.

Primary operation

The operations were performed by 16 attending staff surgeons. Over time, aesthetic and extracorporeal circulation management and preferred surgical procedures evolved, as detailed below. Two patients early in the series were operated on by a lateral thoracotomy approach. In these patients, the proper diagnosis and nature of the disease were poorly understood and a part of the descending aorta was replaced. All other patients were

Table 1. Pre-operative patient characteristics.

Characteristic	N=232
Mean age (years (SD; range))	58 (13; 19-81)
Male/female ratio (%/%)	149/83 (64.2/35.8)
Creatinin (µmol/L,N=227,(SD; range))	112 (70; 25-842)
Prior cardiac surgery/PCI	10.3% (N=24)
Prior aortic surgery	5.6% (N=13)
Hypertension	52.2% (N=121)
COPD	6.9% (N=16)
Prior CVA	1.7% (N=4)
Diabetes Mellitus	1.3% (N=3)
Prior myocardial infarction	3.4% (N=8)
Dissection type	
DeBakey type 1	76.7% (N=178)
DeBakey type 2	23.3% (N=54)
Etiology	
Idiopathic	93.1% (N=216)
Marfan or other CTD	6.9% (N=16)
Main presenting symptom	
Acute pain	84.9% (N=197)
Collapse/Stroke	11.6% (N=27)
Dyspnea	1.7% (N=4)
Other/unknown	1.7% (N=4)
Malperfusion symptoms	22.0% (N=51)
Cardiac ischemia	6.0% (N=14)
Central neurological deficit	5.6% (N=13)
Peripheral vascular dysfunction	9.9% (N=23)
Paraplegia	1.7% (N=4)
Peripheral neurological dysfunction	1.3% (N=3)
Systolic LVF (N=96)	
Good	81.3% (N=78)
Impaired	4.2% (N=4)
Moderate/Bad	7.3% (N=7)
Aortic insufficiency	
None	43.1% (N=100)
Grade I-II	31.5% (N=73)
Grade III-IV	25.4% (N=59)
Shock	23.7% (N=55)
Tamponade	30.6% (N=71)
Resuscitation	3.9% (N=9)
Pericardial drainage	3.9% (N=9)
Ventilation support	6.0% (N=14)
Urgent operation (<24 hours)	93.5% (N=217)

SD: standard deviation, PCI: percutaneous catheter intervention, COPD: chronic obstructive pulmonary disease, CVA: cerebro vascular accident, CTD: connective tissue disease, LVF: left ventricular function,

operated on by median sternotomy, using cardiopulmonary bypass. In most of the patients, remote arterial canulation in the femoral artery was performed before sternotomy. In 2 patients, we used subclavian artery canulation and in 2 patients, the innominate artery was used. Early in the series, patients were operated on using moderate hypothermia and aortic cross-clamping high in the ascending aorta. After 1985, we used deep hypothermia and circulatory arrest, with additional retrograde or antegrade cerebral perfusion, introduced in 1997. Patients were cooled to 18–20°C nasal temperature. In patients who required multiple periods of circulatory arrest, the total time of circulatory arrest was calculated by adding up these periods. We did not clamp the aorta before circulatory arrest, unless left ventricular dilatation occurred. For myocardial protection, we used cold crystalloid cardioplegia and topical cooling, except in the first patient. The ascending aorta and the aortic arch were opened and after resection of the area of the intimal tear, if present, the aortic arch was reconstructed or replaced. If possible, only the inner curvature of the aortic arch was resected and a bevelled anastomosis with a vascular graft was constructed (hemi-arch replacement). For distal aortic reconstruction, biological glues [Gelatin–resorcinon–formalin glue (Colle biologique, Fii, Saint Just Malmont, France), Bioglue (Cryolife Inc., Kennesaw, GA, USA)], introduced in 1987, or felt strips were utilized. Alternatively, a complete arch replacement was performed. The aortic root and aortic valve leaflets were reconstructed by resuspension of the aortic valve commissures, using pletgetted sutures and biological glues or felt strips if possible. When the aortic valve or aortic root was found to be unsuitable for reconstruction, the aortic valve was replaced, mostly in conjunction with the aortic root and ascending aorta. Finally, the reconstructed aortic root was anastomosed to the vascular prosthesis.

Follow-up

All patients were followed at our institution or by their referring cardiologist. Early in the series, only the clinical follow-up was available. Since 1988, we used protocolled CT scanning after 3 and 6 months and yearly thereafter. In 1990, we instituted a dedicated aortic surgery outpatient clinic. From hospital records or referring cardiologists, we collected information on vital status, reoperations and complications. In addition, we consulted the municipal civil registries to ascertain vital status of all patients. Valve-related complications were defined according to the 2008 guidelines for reporting morbidity and mortality after cardiac valvular operations.[10]

The study database was frozen for analysis on 30 April 2011. The follow-up was 97.8% complete: 5 patients were lost to the follow-up. The mean follow-up duration of hospital survivors was 7.2 years (range 0.2–25.7 years), with a total follow-up of 1331 patient-years.

Reoperations

Indications for reoperation are symptomatic aortic valve insufficiency or allograft deterioration, patients with symptomatic aortic dilatation or an aortic diameter of 6 cm or more during follow-up.

Reoperations on the ascending aorta or aortic valve were performed through a median sternotomy. For reoperations on the descending or thoraco-abdominal aorta, we used a lateral thoracotomy or thoraco-abdominal approach. Replacement of the descending aorta or thoraco-abdominal aorta was performed using deep hypothermia and circulatory arrest or left heart bypass.

Statistical methods

Continuous data are presented as means [standard deviation (SD); range]. Categorical data are presented as proportions. Univariable and multivariable logistic regression analyses were used to study potential determinants of 30-day mortality. The Cox proportional hazards model was used for univariable and multivariable analyses of time-related events. For the analysis on 30-day mortality and time-related events, using the multivariable Cox regression analysis (stepwise backward method), inclusion criteria were $P \leq 0.10$. Criteria for exclusion were $P \geq 0.10$. Variables that were tested as potential risk factors for hospital and late mortality are available as supplementary material.

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 primary operation and ended at the time of death (event) or at the last follow-up (censoring). The comparison of Kaplan–Meier estimates was done using the Tarone–Ware test. Late survival of hospital survivors was compared with age-matched survival in the general population and after aortic valve replacement, using a microsimulation model, described previously.[11]

A *P*-value ≤ 0.05 was considered statistically significant. All testing was performed two-sided.

For all analyses, SPSS 17.0 for Windows statistical software (SPSS, Chicago, IL, USA) was used.

RESULTS

During the study period, 232 consecutive patients underwent surgery for acute ascending aortic dissection. Figure 1 presents the number of operations per 6-year time periods, showing a steady increase of the number of procedures over time.

The perioperative data for all patients are shown in Table 2. In 4 patients, no procedure on the ascending aorta was performed: 2 patients were operated by a lateral thoracotomy

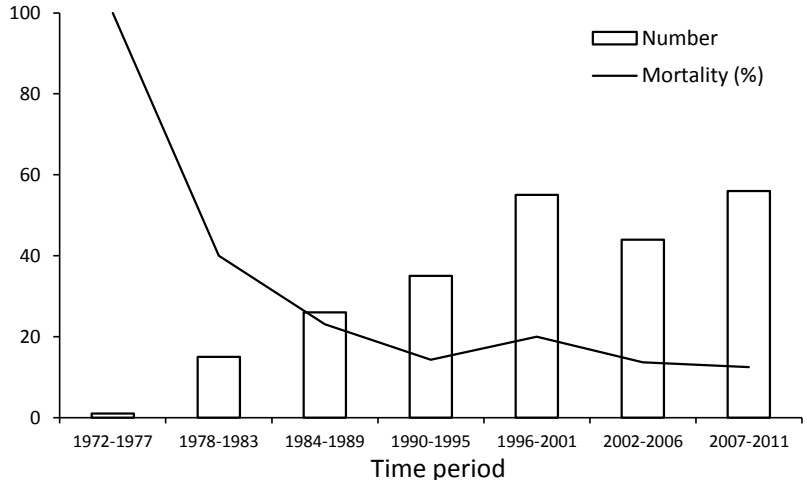

Figure 1. Number of operations for acute type A dissection and 30-day mortality per 6 years period.

approach, and 2 patients could not be stabilized during extracorporeal circulation and, the procedure was terminated.

In 197 patients, we used deep cooling and hypothermic circulatory arrest, allowing the construction of an open distal anastomosis or the replacement of (a part of) the aortic arch. In 2 patients, retrograde brain perfusion was used and in 43, antegrade cerebral perfusion was used. In 9 patients, additional coronary bypass grafting was performed. In 8 patients, this was necessary for coronary ostium disruption due to the dissection, while in 1, a previously placed occluded coronary artery bypass was replaced.

Early morbidity and mortality

Forty-two patients (18.1%) died within 30 days postoperative. In-hospital mortality occurred in 47 patients (20.3%), 6 of them died after 30 days. Twenty-one patients died during the operation. Four of these patients died of uncontrollable bleeding before the institution of extracorporeal circulation or exsanguinated on extracorporeal circulation. Over time, the mortality risk decreased from more than 50 to 12.5% in the time period 2007–11 (Figure 1). Mortality within 60 days was 19.8% (46 patients) and mortality within 90 days was 21.6% (50 patients). Table 3 shows the causes of early mortality.

Factors that were potentially and independently associated with increased 30-day mortality are displayed in Table 4.

Twenty-four patients (10.4%) were found to have a post-operative cerebrovascular incident (CVA). In patients operated without circulatory arrest, we found 17.1% CVA's; in patients operated using circulatory arrest, we found 9.1% CVA's (P = 0.152). The use of antegrade cerebral perfusion in patients operated with circulatory arrest was not associ-

Table 2. Perioperative data.

	N=232
Ascending aorta	
Replacement	97.3% (N=227)
Repair	0.4% (N=1)
None	1.7% (N=4)
Aortic valve	
Preservation	67.6% (N=157)
Valved conduit	21.1% (N=49)
Mechanical prosthesis	3.4% (N=8)
Allograft	6.9% (N=16)
Bioprosthesis	0.9% (N=2)
Aortic arch procedure	
No	13.4% (N=31)
Open distal anastomosis/hemi-arch	70.3% (N=163)
Replacement	16.4% (N=38)
Concomitant procedures	
CABG	3.9% (N=9)
Mitral valve repair	0.9% (N=2)
Tricuspid valve repair	0.4% (N=1)
Atrial septal defect closure	0.4% (N=1)
Cardiopulmonary bypass time (min. (SD; range)) (n=230)	254 (110;30-762)
Aortic cross clamp time (min. (SD; range)) (n=228)	131 (64;25-335)
Circulatory arrest time (min. (SD; range)) (n=197)	50 (36;4-232)
Cerebral perfusion time (min. (SD; range)) (n=43)	78 (46;14-218)
Intensive care stay (days) (median (SD: range))	4 (10.9;1-81)
Time on ventilator (days) (median (SD: range))	2 (10.0;1-76)
Bleeding requiring re-operation	23.3% (N=54)
Post-operative myocardial infarction	4.3% (N=10)
Post-operative renal dysfunction	
No dialysis	19.8% (N=46)
Temporary dialysis	5.6% (N=13)
Permanent dialysis	4.7% (N=11)
Post-operative CVA	10.4% (N=24)
Post-operative paraparesis/paraplegia	2.2% (N=5)
Post-operative recurrent nerve dysfunction	3.4% (N=8)
Post-operative psychiatric disorder	23.7% (N=55)
Early death (≤ 30 days)	18.1% (N=42)

CABG: coronary artery bypass grafting, min.: minutes, SD: standard deviation, CVA: cerebro vascular accident.

Table 3. Causes of 30 day mortality (N=42) and late mortality (N=64).

Cause of mortality	30 day mortality (N=42)	Late mortality (N=64)
Bleeding	14	
Cardiac failure	13	18
Sepsis/multiple organ failure	8	
Aortic rupture/vascular	4	13
Neurological	2	2
Respiratory failure	1	1
Malignancy		11
Other		2
Unknown		17

Table 4. Univariable and multivariable analysis on factors for 30 day mortality and late mortality in hospital survivors

	30 day mortality		Late mortality	
Factor	**Univariable OR (95% CI); p value**	**Multivariable OR (95% CI); p value**	**Univariable HR (95% CI); p value**	**Multivariable HR (95% CI); p value**
Era before 1990	2.5 (1.2-5.4); 0.02	-	1.7 (1.0-2.9) 0.05	-
Collapse main presenting symptom	2.6 (1.1-6.3); 0.03	-		
Pre-operative AI grade 3/4	2.1 (1.0-4.3); 0.04	2.0 (0.9-4.5); 0.089		
Pre-operative resuscitation	6.3 (1.6-24.5); 0.008	5.0 (1.1-22.4); 0.035		
Pre-operative pericardial drainage	3.9 (1.0-15.2); 0.05	-		
Malperfusion	2.4 (1.1-4.9); 0.02	-		
Cardiopulmonary bypass time	1.005 (1.002-1.008); 0.001	1.007 (1.003-1.010); <0.001		
Aortic cross clamp time	1.006 (1.001-1.011); 0.01	-		
Use of circulatory arrest	0.3 (0.2-0.8); 0.009	0.2 (0.1-0.6); 0.004		
Use of biological glue	0.4 (0.2-0.7); 0.003	0.3 (0.1-0.6); 0.002		
Age			1.037 (1.015-1.060); 0.001	1.031 (1.007-1.055); 0.01
Prior aortic surgery			2.1 (0.9-4.8); 0.1	-
Prior myocardial infarction			6.8 (2.8-16.2); <0.001	3.9 (1.6-9.8); 0.003
Hypertension			2.0 (1.2-3.4); 0.007	1.6 (0.9-2.7); 0.09
Pre-operative creatinin			1.004 (1.002-1.006); 0.01	1.004 (1.001-1.006); 0.002
Pre-operative COPD			2.7 (1.1-6.9); 0.04	3.8 (1.4-10.2); 0.007
Pre-operative CVA			2.6 (.09-7.3); 0.07	-
LV function impaired/poor/bad			4.5 (1.3-15.3); 0.02	4.5 (1.2-16.3); 0.02

OR: odds ratio, HR: hazard ratio, AI: aortic insufficiency, COPD: chronic pulmonary obstructive disease, CVA: cerebro vascular accident, LV: left ventricular

ated with an increased postoperative CVA rate ($P = 0.57$), although the circulatory arrest time was significantly longer (39.9 min versus 88.7 min; $P < 0.001$).

Late mortality

During follow-up, 64 patients died. The causes of late death are presented in Table 3. Overall, cumulative survival (including 30-day mortality) was 53.4% (95% confidence interval [CI] 42.2–58.4%) after 10 years and 29.3% (95% CI 19.9–38.8%) after 15 years (Figure 2A). For the 185 hospital survivors, late survival was 67.5% (95% CI 58.8–76.2%) after 10 years and 37.0% (95% CI 25.3–48.8%) after 15 years, this was impaired compared with

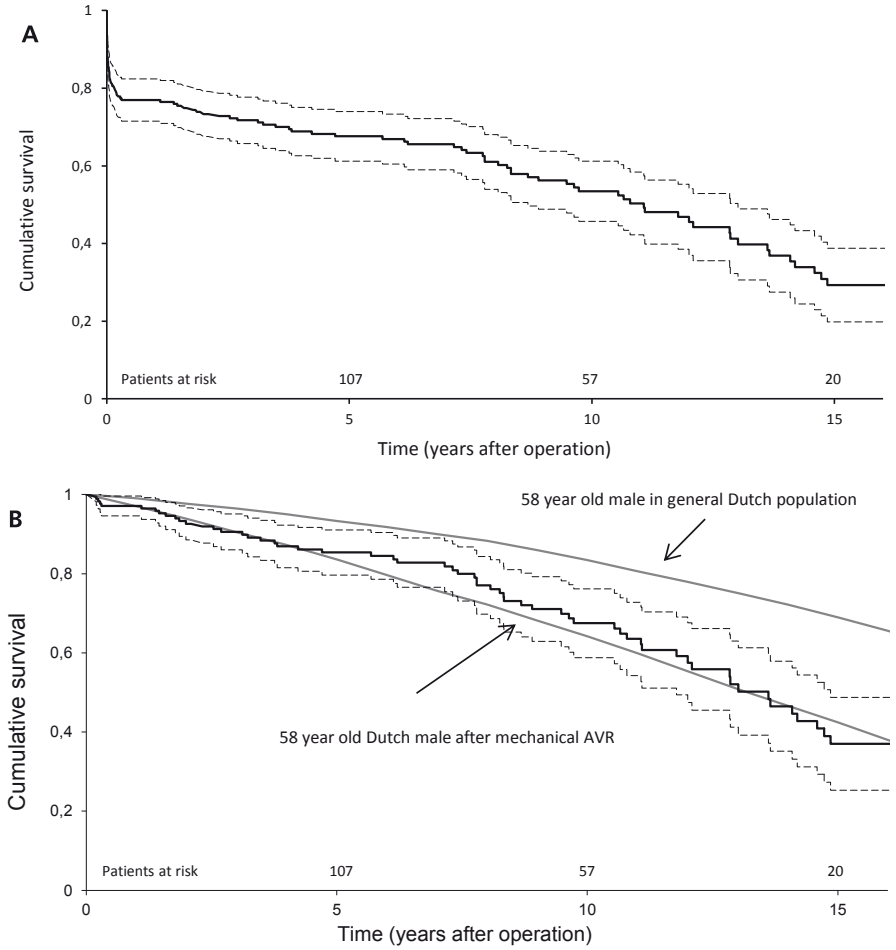

Figure 2. Observed cumulative survival after surgery for acute type A aortic dissection with 95% confidence interval (- - - -) in all patients (A) and in 185 hospital survivors compared with a 58 years old Dutch male in the general population and a 58 year old Dutch male after mechanical aortic valve replacement. (B).

the age-matched Dutch population, but comparable with an age-matched patient after aortic valve replacement with a mechanical prosthesis (Figure 2B). Factors that were potentially and independently associated with increased late mortality are displayed in Table 4. Dissection type (DeBakey type 1 or 2) and the type of aortic valve procedure (preservation, allograft implantation or mechanical conduit implantation) were not associated with late mortality.

Reoperations

Out of 185 hospital survivors, 43 patients underwent a total of 47 reoperations on the heart, the aorta or both. Table 5 presents details on these reoperations.

Reoperations for valve dysfunction

Seventeen patients were reoperated for aortic valve dysfunction. Five patients were reoperated for allograft structural valve deterioration (SVD) after 5.0–12.8 years. In 12 patients, the native aortic valve, preserved or repaired at primary operation, was reoperated after 2 weeks to 14.3 years. In 3 patients, reoperation was necessary within 1 year of the initial

Table 5. Reoperations after acute type A dissection.

Segment	Indication	N	Reoperation	N
Aortic valve	Preserved valve incompetence	12	Valved conduit implantation	6
			Aortic valve replacement	5
			Allograft root replacement	1
	Allograft SVD	5	Valved conduit implantation	3
			Aortic valve replacement	2
Ascending aorta/arch	(false) aneurysm	5	Valved conduit implantation	2
			Ascending aortic/arch replacement	3
	Re-dissection/rupture	4	Ascending aortic/arch replacement	3
			Ascending-descending aortic conduit	1
	Graft infection	1	Allograft arch replacement	1
Distal aorta	Distal sutureline disruption	1	Descending aortic replacement	1
	Descending aortic aneurysm	5	Descending aortic replacement	4
			Descending aortic stent-graft	1
	Thoraco-abdominal aneurysm	7	Thoraco-abdominal aortic replacement	7
	Abdominal aortic aneurysm	3	Bifurcation prosthesis	3
	Coarctation aortae	1	Descending aortic replacement	1
Other cardiac	Atrial septal defect	1	Device closure	1
	Mitral insufficiency	2	Mitral valve repair	1
			Mitral valve replacement + tricuspid repair	1

SVD: structural valve deterioration

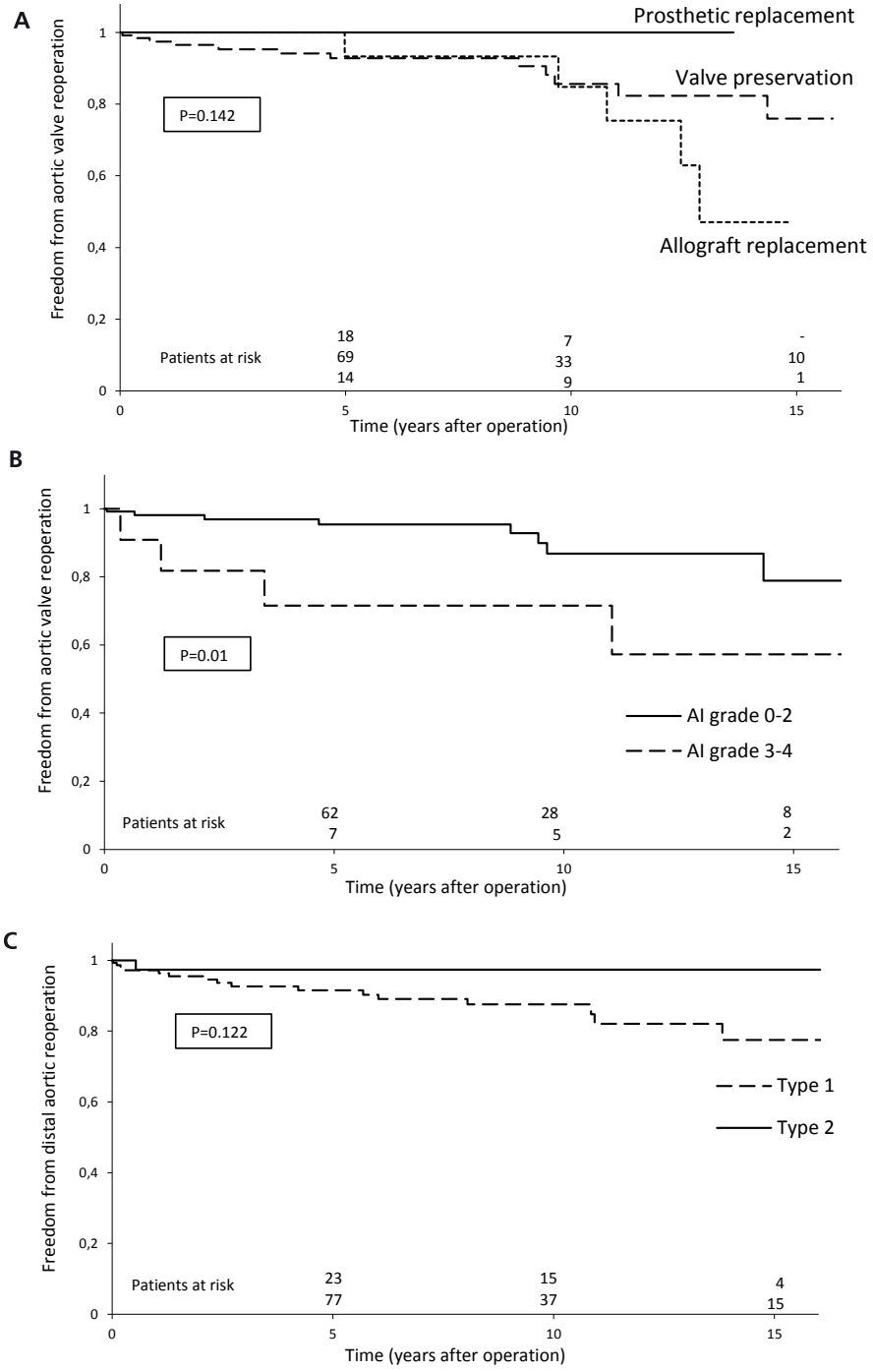

Figure 3. Freedom from reoperation for aortic valve dysfunction by type of valve procedure (A), for aortic valve dysfunction in patients with aortic valve preservation by grade of aortic insufficiency (AI) (B) and freedom from distal aortic reoperation by type of dissection (C).

operation. Freedom of reoperation for aortic valve dysfunction at 10 years was 85.6% (95% CI 76.4–94.8%) for preserved aortic valves and 84.8% (95% CI 65.2–100%) for allografts (Fig. 3A). For the allografts, freedom of reoperation for SVD at 15 years was 47.1% (95% CI 12.0–82.2%; Figure 3A).

For patients presenting with preoperative aortic insufficiency (AI) Grade 0–II who had their aortic valves preserved (n = 157), the freedom of reoperation for aortic valve dysfunction at 10 years was 86.8% (95% CI 76.6–97.0%). Four of 19 patients with preoperative AI Grade III or IV who had their aortic valves preserved had to be reoperated. This led to a freedom from reoperation for aortic valve dysfunction at 10 years of 71.6% (95% CI 44.2–99.0%), which is significantly reduced compared with patients with less severe aortic valve insufficiency preoperatively (Tarone–Ware test P = 0.01; Figure 3B).

Six of these 17 reoperative patients required additional replacement of the ascending aorta or the aortic arch. Early reoperative mortality occurred in 1 patient. There were no reoperations after implantation of a mechanical valved conduit or valve prosthesis.

Reoperations on the ascending aorta and aortic arch

Ten patients underwent reoperations on the previously operated ascending aorta or aortic arch. The indications for reoperations were recurrent dissections, rupture of the aorta or (false) aneurysms. In 1 patient, a chronically infected aortic arch prosthesis was replaced by a cryopreserved aortic allograft arch. Deep hypothermia with total circulatory arrest was employed in 7 patients with ascending aorta or arch reconstruction. Two patients died early after reoperation. No specific risk factors for proximal aortic reoperations were identified.

Reoperations for distal aortic pathology

Seventeen patients underwent reoperation for distal aortic pathology. The interval between primary operation and reoperation ranged from 1 day to 13.8 years. One patient was reoperated on 1 day after ascending aortic and aortic arch replacement for persistent distal sutureline bleeding. In this operation, the descending aorta was replaced. In 1 patient, a previously undiscovered aortic coarctation was corrected. All other patients were operated on for descending, thoraco-abdominal, abdominal or abdominal aortic aneurysms, mostly in a chronically dissected aorta. Figure 3C shows an actuarial freedom from distal aortic reoperation at 10 years postoperatively of 87.6% (95% CI 80.9–94.3%) for patients after type 1 dissection and 97.4% (95% CI 92.3–100%) for patients after type 2 dissection (Tarone–Ware test P = 0.12). Early reoperative mortality occurred in 3 patients.

DISCUSSION

Acute aortic dissection with involvement of the ascending aorta, classified as DeBakey type 1 or 2 or Stanford type A, is a vascular emergency. The mortality of untreated patients is high, although the exact mortality risk is difficult to determine, since pre-hospital mortality is already considerable. Additional mortality occurs during the initial evaluation and preparation for the surgical treatment of these patients. The mortality rate in the early hours after the onset of the dissection is estimated to be 1–2%/h.[12,13]

In this report, we present our total experience of 232 consecutive patients treated surgically for acute ascending aortic dissection over nearly four decades, beginning in 1972. Our results show an overall 30-day mortality risk of 18.1%. Before 1985, 30-day mortality was >30%. Over time, 30-day mortality steadily declined to 12.5% in the present era (2007–11). Several reports on acute aortic dissections have published hospital mortality rates of 13–25%.[2-4,14-16] The International Registry of Acute Aortic Dissection (IRAD) reports in a combined series of 682 patients operated upon in 18 hospitals, an overall in-hospital mortality of 23.9%.[17]

In our series, preoperative resuscitation and longer cardiopulmonary bypass time were independent risk factors for 30-day mortality. The use of circulatory arrest and biological glue were associated with a reduced 30-day mortality risk. Tan *et al.*[3] also found preoperative cardiopulmonary resuscitation and longer duration of cardiopulmonary bypass to be risk factors for operative mortality. Pompilio *et al.*[15] found in addition prior myocardial infarction, preoperative renal insufficiency, preoperative shock and age >70 years to be risk factors for hospital mortality. Others found preoperative malperfusion to be a predictor for early mortality.[2,16] In the IRAD, risk model for early mortality after surgery for acute type A dissection age >70 years, prior aortic valve replacement, preoperative hypotension, shock or tamponade, migrating chest pain, any pulse deficit, intraoperative hypotension, right ventricular dysfunction and coronary bypass surgery were risk factors for mortality, while partial arch replacement was associated with lower mortality.[17] The large number of reported risk factors for early death after surgery for acute aortic dissection illustrates the complexity of these critically ill patients.

Over time, our surgical approach changed significantly from using femoral artery perfusion throughout the operation, moderate hypothermia and aortic cross-clamping to our current practice of initial femoral artery perfusion, avoidance of aortic cross-clamping, deep hypothermic circulatory arrest, with the possibility of antegrade cerebral perfusion allowing for thorough inspection of the aortic arch and proximal descending aorta with adequate reconstruction of the aortic layers and an open distal anastomosis. And finally, we reinstitute cardiopulmonary bypass by the antegrade route, utilizing a vascular prosthesis with a prefabricated side branch. These technical modifications have improved our results remarkably in more recent years, as is reported by others.[4,18,19] At present, we prefer the

use of deep hypothermic circulatory arrest alone for patients in whom reconstruction of the distal aorta is relatively simple, and usually requires an arrest time of <30 min. In more complex patients, we use additional antegrade cerebral perfusion. With this approach, we did not find an increased mortality rate, or postoperative CVA rate, despite significantly longer circulatory arrest times in these patients.

Long-term survival of patients surviving surgery for acute aortic dissection is impaired compared with the general population as is reported by others.[15,20] Reduced long-term survival, however, is also found after other cardiac operations. As an example, by using our microsimulation model, we found a comparable reduction in long-term survival in patients after aortic valve replacement. These patients may have a different general risk profile compared with the general population. We found older patient age, prior myocardial infarction, a higher preoperative creatinin, preoperative COPD and impaired left ventricular function to be risk factors for late mortality. In addition, these patients may have residual aortic pathology, especially after DeBakey type 1 dissection surgery. However, in our experience, we could not demonstrate a difference in early- or late mortality between type 1 and 2 dissection.

In two-thirds of our patients, we were able to preserve or reconstruct the native aortic valve. For patients without severe preoperative aortic valve insufficiency, the incidence of reoperation for AI was low and statistically not different from patients who underwent valve replacement. Although some authors advocate an aggressive policy of root replacement[21], we concur with others that making an effort to spare these valves is worthwhile and yields a satisfactory long-term result.[6,22] Therefore, we advocate aortic valve preservation whenever possible for patients without severe AI. In patients with pre-operative severe aortic valve insufficiency who had their valves preserved, however, we found a decreased freedom from reoperation of 71.6%, although this observation was based on only 4 reoperations in a small subgroup of patients. For patients with severe pre-operative AI, the operating surgeon has to consider the increased risk of a reoperation after valve preservation in deciding whether or not to attempt to preserve the aortic valve. Alternatives are more complex reconstructions by means of implantation of a valved conduit or David type of reconstruction or aortic valve replacement within the reconstructed aortic root, both with the inherent risks of valve replacement. For patients who received an allograft root, freedom from allograft reoperation at 15 years was a little <50%, comparable with our total experience of aortic allograft root replacements.[23] At present, we do not advocate the use of an aortic allograft for aortic root replacement in acute aortic dissection and prefer the use of a valved conduit.

Patients may require repeat operations on the aorta after successful initial operation. The incidence of proximal reoperations is rather low and in concurrence with other authors.[7,24] Given our low observed aortic reoperation rate, we find that a more aggressive approach to the aortic arch, as sometimes advocated[8,25] is not warranted.

Most patients operated upon for a DeBakey type 1 dissection are at risk for progressive dilatation of the chronically dissected downstream aorta. In contrast, patients operated

on for a type 2 dissection undergo a 'radical' operation, in which all aortic pathology is completely removed, leaving them without residual aortic pathology. For patients operated upon for DeBakey type 1 dissection, the freedom from distal reoperation at 10 years was 88%. Interestingly, the late survival of types 1 and 2 patients did not differ, indicating a limited influence of this residual pathology on late survival. Some authors advocate a more aggressive approach to the descending aorta, utilizing covered stent grafts into the descending aorta during the primary operation.[25] Although these advanced techniques are theoretically attractive, further experience will have to discover whether these more extensive approaches result in better long-term outcomes, without compromising the early results in these often complicated patients, who need emergency operations, sometimes at inconvenient hours and not always performed by the most experienced surgeons. We believe that one of the key factors in achieving the best possible results for these patients is to perform a well standardized and straight forward procedure to save the patient's life. With this approach, a relatively good long-term prognosis can be achieved for patients surviving a potential lethal condition despite a risk of additional operations.

LIMITATIONS

This study reports the results of a retrospective analysis of a single centre experience over a very long time period with major modifications in preoperative patient management, operative strategy and techniques and follow-up over time. Although we find important changes over time concerning the outcome of these operations, only limited conclusions can be drawn by the nature of this study. In this study, only patients who underwent operations for acute type A aortic dissection were analysed. Patient who died preoperatively or with contraindications were not analysed.

CONCLUSIONS

Acute type A aortic dissection is a severe condition for patients and a challenge for surgeons. Over time, there has been a great improvement in the surgical approaches and patient management, resulting in a decrease of the 30-day mortality from over 30 to 12.5% in recent years. Survival after successful operation is satisfactory, given the disastrous nature of the disease, although it was reduced compared with the general population. The reduced long-term survival is related to general cardiovascular risk factors for late mortality. With the use of modern surgical techniques, the need for reinterventions on the aortic valve and the proximal or the distal aorta is acceptably low.

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Chapter 12

Progression rate and early surgical experience in the new aggressive Aneurysms-Osteoarthritis Syndrome

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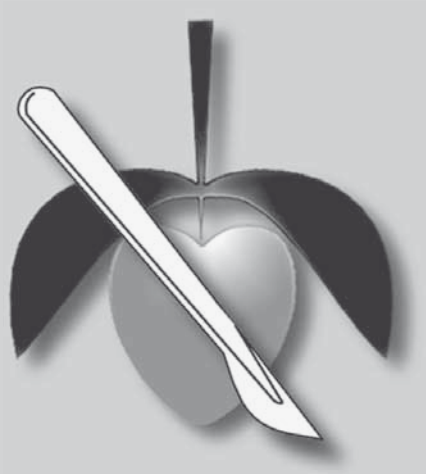

ABSTRACT

Background: Aneurysms-Osteoarthritis Syndrome (AOS), caused by *SMAD3* mutations, is a recently described autosomal dominant condition characterized by aneurysms throughout the arterial tree in combination with osteoarthritis. The objective of the present study was to evaluate progression rate of aortic dilatation and surgical outcome in AOS patients.
Methods: All AOS patients are regularly monitored according to our clinical AOS protocol. Patients with at least two follow-up visits or who underwent aortic root surgery during follow-up were included in this cohort study. Clinical and surgical data were obtained from chart abstraction.
Results: We included 22 patients (age 38±15 years, 41% male) with the molecular diagnosis of AOS. Follow-up duration was 3.3 (1.6-5.1) years. In the 17 patients, who were managed conservatively, aortic root diameter increased from 37.5±5.1 at baseline to 40.3±6.2 mm at follow-up (p=0.008). Progression rate of aortic dilatation was highest at the level of the sinus of Valsalva (2.5±5.8 mm/year) and significantly correlated with the initial diameter (r=0.603, p=0.017). Ten patients successfully underwent valve sparing aortic root replacement, of whom five patients after previous watchful waiting. Mean pre-operative aortic diameter was 46.6±4.0 mm. The operations were not complicated by fragility of tissue. After a post-operative period of 2.8 (0.7-5.4) years, no mortality or reoperations had occurred and all patients remained asymptomatic.
Conclusions: Aneurysm growth in AOS patients can be fast and unpredictable, warranting extensive and frequent cardiovascular monitoring. Valve sparing aortic root replacement is a safe and effective procedure for the management of aortic root aneurysms in AOS patients.

INTRODUCTION

Aortic aneurysms and dissections are common conditions, ranking as the 19th most common cause of death in the US in 2007.[1] The predilection for thoracic aortic aneurysms and dissections (TAAD) can be inherited in an autosomal dominant manner.[2] Familial TAAD is subdivided into non-syndromic and syndromic forms. Non-syndromic familial TAAD can be associated with bicuspid aortic valve and/or patent ductus arteriosus.[3,4] Syndromic familial TAAD includes several systemic connective tissue disorders, such as Marfan syndrome, and Loeys-Dietz syndrome.[5,6]

Recently, our group described a new syndromic familial TAAD form: Aneurysms-Osteoarthritis Syndrome (AOS), caused by mutations in the *SMAD3* gene.[7-11] Key features of this syndrome are arterial aneurysms and tortuosity, early-onset joint abnormalities and mild cutaneous and craniofacial features.[7-9] AOS is an autosomal dominant disorder and is found to be responsible for approximately 2% of familial TAAD.[7-12] Aneurysms most commonly occur at the level of the sinus of Valsalva, but can be present throughout the entire arterial tree.[7-11] Aortic dissections can occur in relatively mildly dilated aortas and are associated with high mortality.[7-9] Moreover, cerebrovascular abnormalities are encountered in the majority of patients.[8,9] The best discriminating feature between AOS and other connective tissue disorders is the presence of early-onset osteoarthritis, which is often the first reason to seek medical advice.[7-9]

The cardiovascular phenotype of *SMAD3*-related AOS has extensively been described[7-9], however, knowledge about the progression of the aneurysms over time and outcome after surgery in this patient group, is lacking. In other disorders affecting the aorta, for example vascular type Ehlers-Danlos syndrome, fragility of aortic tissue may complicate surgical intervention.[13] When considering prophylactic surgery to prevent aneurysms from rupturing, it is important to know whether friable vascular tissue is also present in AOS patients. Therefore, the purpose of this study was to evaluate the progression rate of aortic dilatation and surgical outcome of valve sparing aortic root replacement in AOS patients.

PATIENTS AND METHODS

All previously identified AOS patients[9] are intensively monitored at regular intervals according to our clinical AOS protocol.[8] Only alive patients with at least 2 follow-up visits with radiologic evaluation and those who underwent aortic root surgery were included in this cohort study. AOS patients without follow-up visits at our centers or who had already died, were excluded. The diagnosis of AOS was confirmed by molecular and clinical genetic analysis.[7] The study was approved by the institutional review board and ethical commit-

tee of the Erasmus MC in Rotterdam. Written informed consent was obtained from each patient.

Data collection

Data were abstracted from electronic patient records. Collected variables included demographics, medical history, family history, cardiovascular imaging, operative details, and complications. ECG-gated computed tomography angiography or magnetic resonance angiography from head-to-pelvis were used to evaluate presence, size and location of arterial aneurysms, dissections and tortuosity. Aortic dimensions were repeatedly measured at 8 standardized levels and the annualized growth rate was calculated. The follow-up period of this study was defined as the time between first and last radiographic evaluation. Transthoracic echocardiography was used to evaluate presence of valvular or congenital pathology and left ventricular hypertrophy and function. N-terminal pro brain natriuretic peptide (NT-proBNP) was measured by a radioimmunoassay (Phoenix Pharmaceuticals, Inc). Arterial stiffness was assessed by aortic pulse wave velocity (SphygmoCor® system, ArtCor, Sydney, Australia) and carotid distensibility (Wall Track System, Pie-medical Esaote).

Operative technique

In patients requiring surgical intervention, valve sparing root replacement (VSRR) with the David procedure is our technique of choice.[14] The native aortic valve is resuspended within a Dacron tube graft with prefashioned pseudosinuses (Gelweave Valsalva graft; Vascutek, Renfrewshire, Scotland, UK).

Data analysis

For the statistical analyses, the Statistical Package for Social Sciences, version 17.0 (SPSS, Inc., Chicago, Illinois) was used. All statistical tests were 2-sided; $p<0.05$ was considered statistically significant. The one-sample Kolmogorov-Smirnov Test and histograms were used to check normality. Normally distributed continuous data are presented as mean ± standard deviation (SD) and categorical variables as frequency (n) and percentages. Non-normal distributed data are presented as median with interquartile range (IQR). For comparison within subjects over time, the paired t-test and signed-ranks Wilcoxon test was used. For correlation analysis, the Pearson r correlation coefficient and Spearman correlation test were used.

RESULTS

A total of 22 patients (age 39±15 years, 41% male) from three families with the diagnosis of AOS were included in this study. Longitudinal natural history data were available for

17 patients. Five patients underwent surgery immediately after initial screening, and another five patients underwent surgery after previous watchful waiting (Figure 1). Median

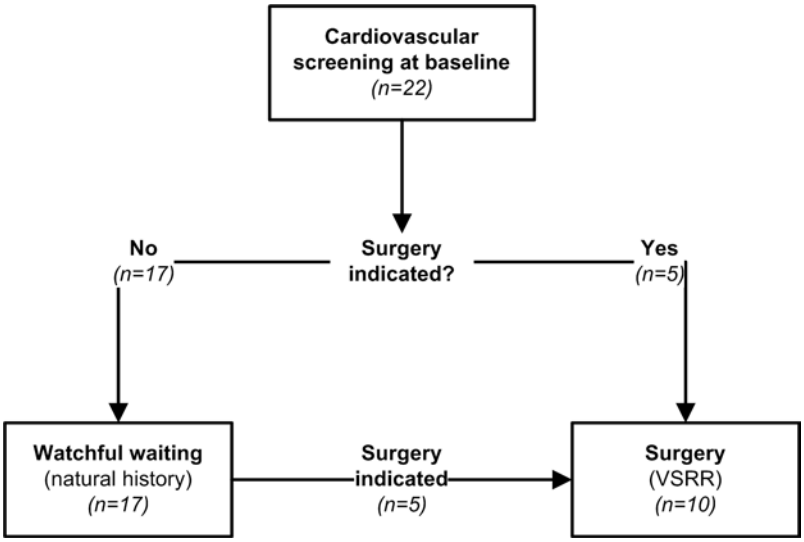

Figure 1. Flowchart demonstrating the number of Aneurysms-Osteoarthritis Syndrome patients included in this study. (VSRR = valve sparing aortic root replacement.)

Table 1. Baseline characteristics.

	AOS patients (n=22)
Age, years	39±15
Gender (male)	9 (41)
Body mass index, kg/m²	24±4
Arterial tortuosity thorax/abdomen	8 (18)
Mitral valve abnormalities	
Billowing	5 (23)
Prolapse	1 (5)
Mild mitral valve regurgitation	5 (23)
Moderate mitral valve regurgitation	2 (9)
Severe mitral valve regurgitation	0 (0)
Congenital heart defects	
Persistent ductus arteriosus	2 (9)
Pulmonary valve stenosis (mild)	1 (5)
Atrial septal defect	1 (5)
Left ventricular hypertrophy	3 (14)
Fractional shortening, %	36±7

Values are expressed as n(%) or mean±SD. AOS, Aneurysms-Osteoarthritis Syndrome

Table 2. Progression rate of aortic dilatation measured by computed tomography angiography (n=17).

	Baseline aortic diameter (mm)	Follow-up aortic diameter (mm) *	p-value	Progression rate (mm/year)
Annulus	27.9±5.2	28.2±5.0	0.842	+0.9±3.7
Sinus of Valsalva	37.5±5.1	40.3±6.2	0.008	+2.5±5.8
Sinotubular junction	30.7±3.5	30.9±4.6	0.659	+0.2±1.7
Ascending thoracic aorta	29.9±4.3	31.2±4.0	0.004	+0.6±0.7
Aortic arch	24.7±4.7	26.4±4.0	0.164	+1.4±5.3
Descending thoracic aorta	24.4±3.4	25.6±4.3	0.095	+0.9±2.9
Diaphragmatic level aorta	21.9±3.9	22.5±3.3	0.542	+0.4±1.7
Abdominal aorta	18.6±3.2	20.6±3.3	0.063	+0.8±3.7

Values are expressed as mean±SD.
** Follow-up period: 3.3 (1.6-5.1) years.*

follow-up period was 3.3 (1.6-5.1) years. Baseline characteristics are shown in Table 1. All patients were in New York Heart Association (NYHA) class I and in sinus rhythm at baseline. No deaths or aortic dissections occurred during follow-up. No aortic valve pathology was found.

Progression rate of aortic dilatation

Table 2 shows the progression rate of aortic dilatation in the 17 conservatively managed patients. Statistically significant progression occurred at the level of the sinus of Valsalva and in the ascending thoracic aorta (respectively p=0.008 and p=0.004). The highest progression rate was found at the level of the sinus of Valsalva (2.5±5.8 mm/year; range -1.4-20.9 mm/year), which significantly correlated with the initial sinus of Valsalva diameter (r=0.603, p=0.017). No correlations were found between aortic progression rate and baseline age (r=0.261; p=0.368), low-density lipoprotein cholesterol (r=-0.214; p=0.463), systolic blood pressure (r=-0.280; p=0.332) or left ventricular mass (r=0.264; p=0.383). Furthermore, gender did not influence aortic progression rate (p=0.240).

Arterial stiffness and NT-proBNP measurements

No statistically significant changes in aortic pulse wave velocity, NT-proBNP or blood pressure were observed within a time interval of 11.2 (6.1-15.3) months (Table 3). Carotid stroke change and distensibility coefficient significantly decreased over time (respectively p=0.035 and p=0.004). No correlations were found between progression rate at the level of the sinus of Valsalva and NT-proBNP (r=0.243; p=0.423), carotid distensibility coefficient (r=0.191; p=0.533), aortic pulse wave velocity (r=0.110; p=0.748) or augmentation index (r=0.050; p=0.871).

Table 3. Arterial stiffness and N-terminal brain natriuretic peptide at baseline and during follow-up (n=17).

	Baseline	Follow-up	p-value
Heart rate, bpm	65.8±12.3	62.9±15.4	0.347
Pulse wave velocity, m/s *	9.7±3.0	9.5±3.1	0.782
Transit time, msec	166.1±65.5	173.1±66.0	0.566
Augmentation index @HR75, %	24.2±17.3	18.6±21.9	0.145
Systolic blood pressure, mmHg			
Brachial	127.1±15.0	125.8±10.4	0.680
Central	117.1±12.9	113.5±10.1	0.252
Diastolic blood pressure, mmHg			
Brachial	73.5±8.6	73.5±8.2	0.970
Central	75.0±8.8	74.6±7.9	0.816
Mean arterial pressure, mmHg			
Brachial	93.2±8.9	90.9±8.4	0.353
Central	93.2±8.9	90.9±8.4	0.353
Pulse pressure, mmHg			
Brachial	53.5±7.9	52.3±7.0	0.640
Central	42.1±8.0	38.9±6.3	0.182
Carotid intima-media thickness, μm	609.8±183.6	593.4±107.4	0.764
Carotid end-diastolic diameter, mm	6.8±1.4	6.5±1.2	0.546
Carotid stroke change, μm	403.1±140.3	303.4±137.5	0.035
Distensibility coefficient, 10^{-3}/kPa	27.5±10.1	16.9±5.4	0.004
NT-proBNP, pg/ml	101.7 (55.1-169.5)	102.5 (44.9-184.8)	0.778

Values are expressed median (IQR) or mean±SD.
@HR75 = at a heart rate of 75 beats per minute; NT-proBNP = N-terminal Pro Brain Natriuretic Peptide.

Elective valve sparing aortic root replacements

Ten patients underwent elective VSRR in our centers (age 38.4±14.7 years, 60% male) (Table 4 provides details for each patient). Pre-operative aortic root diameter at the level of the sinus of Valsalva was 46.6±4.0 mm (range 39-57 mm). Mean cardiopulmonary bypass and cross-clamp times were 168±12 and 141±17 minutes, respectively. During surgery aortic fragments from seven patients were obtained (unfortunately not in the first three operated patients). Histopathological examination showed characteristic loss and fragmentation of elastic fibers, and mucoid medial degeneration in five fragments (71%). No abnormalities were observed in the aortic tissue specimens from the other two patients.

The operation was uncomplicated in all patients, apart from one patient who developed a complete AV block perioperatively, requiring a permanent pacemaker implantation. In none of the patients a rethoracotomy was necessary. One patient experienced two episodes of paroxysmal atrial flutter three weeks postoperatively, treated successfully with

Table 4. Surgical details per patient.

Age at time of surgery (years)	Gender	Time since surgery (years)	Pre-operative aortic root diameter (mm)	Pre-operative degree of aortic regur-gitation	Type of operation	Additional surgical procedures	Prosthetic diameter (mm)	Post-operative degree of aortic regur-gitation	Cardio-pulmonary bypass time (minutes)	Cross-clamp time (minutes)	Length of hospital (ICU) stay (days)	Post-operative compli-cations
57.9	female	7.2	48	mild	VSRR	none	24	mild	---	---	--	none
32.0	male	1.0	57	trace	VSRR	none	30	trace	178	159	6 (1)	none
20.3	male	1.5	46	none	VSRR	none	28	none	158	137	15 (1)	Complete AV-block
39.9	male	4.4	47	none	VSRR	none	26	none	158	124	6 (1)	none
41.1	female	1.7	39	trace	VSRR	none	26	mild	165	123	5 (1)	none
34.0	female	6.5	45	none	VSRR	none	24	none	---	---	---	none
31.2	male	3.9	46	none	VSRR	none	28	none	172	131	6 (1)	AF
45.3	female	5.5	49	none	VSRR	none	26	mild	---	---	--	none
64.2	male	1.0	45	none	VSRR	none	30	trace	158	144	7 (1)	none
18.3	male	0.1	46	none	VSRR	none	28	none	189	168	7 (1)	none

AF = atrial flutter; AV = atrioventricular; ICU = intensive care unit; VSRR = valve sparing aortic root replacement.
--- = information could not be retrieved.

beta blockade. No patients experienced postoperative infections, thromboembolism or endocarditis.

After a post-operative period of 2.8 (0.7-5.4) years, no mortality or reoperations had occurred and all patients remained in NYHA class I.

COMMENT

The present study provides data on the progression of aortic dilatation and early surgical experience in patients with AOS.

Key clinical features of Aneurysms-Osteoarthritis Syndrome

AOS is a recently described autosomal dominant disorder that predisposes patients to widespread arterial aneurysms, dissections and tortuosity.[7-9] It is caused by mutations in the *SMAD3* gene, which likely causes loss of function and a paradoxical increase in TGF-β signaling in the aortic wall.[7] On histology of aortic wall specimens, disorganization of the tunica media with fragmentation and loss of elastic fibers, as well as characteristic mucoid medial degeneration and accumulation of collagen in media can be encountered.[7]

While aneurysms are most frequently localized in the aortic root, they can be found throughout the arterial tree, including the iliac, visceral and intracranial arteries.[8-11] Since dissections can occur at relatively mildly dilated aortic diameters, early elective surgical repair should be considered.[8] Extensive cardiovascular evaluation using computed tomography or magnetic resonance angiography from head-to-pelvis and echocardiography is recommended in every AOS patient at baseline and after one year.[8] Hereafter, progression rate, location and size of aneurysms and presence cardiac abnormalities should guide individualized frequency of imaging.[8]

Although AOS might resemble other TAAD syndromes such as Marfan and Loeys-Dietz syndrome[5,6], it can be discriminated by the presence of early onset joint anomalies such as osteoarthritis, osteochondritis dissecans and meniscal abnormalities.[9] Other features that are frequently related to AOS include hypertelorism (widely-spaced eyes), uvula abnormalities (broad or bifid), umbilical and inguinal hernias, pelvis floor prolapse, varices, scoliosis and velvety skin.[7-9]

Aortic aneurysm progression in AOS patients

Annualized progression of aortic dilatation in AOS patients was found to be highest in the sinus of Valsalva with approximately 2.5 mm/year. Although this estimate is based on a small number of AOS patients and should be confirmed in the future by larger studies with longer follow-up intervals, it has become clear that aortic growth in AOS patients can be fast and unpredictable. The annual progression rate seems comparable to or even higher

than in Marfan patients with progression ranging from 0.4 to 2.1 mm/year.[15-19] In patients with a bicuspid aortic valve the progression of ascending aortic dilatation seems to be lower, with a large variety ranging from 0.2 to 1.9 mm/year.[20-23] Unfortunately we could not find any longitudinal studies in Loeys-Dietz or vascular type Ehlers-Danlos syndrome patients to compare our results to. Similar to Marfan patients, in AOS patients the baseline aortic diameter was also correlated to progressive aortic dilatation.[24]

Interestingly, we noted that carotid distensibility significantly decreased, indicating increased arterial stiffness. However, the aortic pulse wave velocity did not change over time. Arterial stiffness depends on structural and functional properties of the arterial wall. The measure of carotid distensibility is a local measure of stiffness that provides information on elastic arteries, while aortic pulse wave velocity reflects the arterial wall stiffness of a larger part of the arterial tree providing information on both elastic and muscular arteries.[25] Although these findings need to be confirmed in a larger patient sample after a longer follow-up period, we speculate that early signs of degeneration in AOS patients might be more prominent in elastic arteries. For future research directions, it would be interesting to evaluate whether this might significantly impact in which type of arteries aneurysms develop and whether there is a difference in aneurysm growth between elastic and muscular arteries.

Early surgical experience in AOS patients

AOS patients tolerated VSRR well and excellent early results were achieved. No mortality occurred and 2.8 years post-operatively all patients remained in NYHA class I. No significant aortic regurgitation developed and no reoperations were required. Furthermore, all aortic valves could be saved. These favorable preliminary results seem comparable to the excellent results of VSRR in other patients with aortic aneurysms, including Marfan and Loeys Dietz syndrome patients, but need to be confirmed in larger series.[26-31] Unlike patients with vascular type Ehlers-Danlos syndrome who have a high incidence of intraoperative and early postoperative vascular events due to fragile arterial tissue[13], this was not encountered in AOS patients. The aortic tissue of AOS patients did not feel extremely thin or fragile, as is the case in Ehlers-Danlos syndrome.

Since growth of aortic root aneurysms in AOS patients can be fast and unpredictable, aortic dissections have been reported to occur in relatively mildly dilated aortas[7-9], and elective VSRR shows favorable results, early prophylactic surgical intervention should be considered to avoid vascular catastrophes. As AOS highly resembles Loeys-Dietz syndrome with regard to aortic aneurysms and dissections, we suggest applying the current surgical recommendations for Loeys-Dietz Syndrome.[32] Individualized assessment of risk versus benefit, based upon family history and/or patients' characteristics, should always be taken into account. For postoperative surveillance, we recommend transthoracic echocardiography six months post-operatively and annually thereafter to monitor aortic root diameter and valve competence. Given the widespread involvement of the arterial tree in AOS patients,

repeated head-to-pelvis imaging in patients after VSRR remains crucial to evaluate other large and medium-sized arteries.

STUDY LIMITATIONS

The main limitations of this study are the small number of patients with AOS and the relatively short follow-up period. This was inevitable, since this syndrome is only recently discovered and relatively unknown. To control for differences in follow-up length, the annual rate of progression was calculated. Due to the limited number of patients, we were not able to check whether progression is correctly described in a linear way and which factors could influence progression rate. Despite our efforts to measure aortic diameters repeatedly in a standardized way with optimal imaging, we have to acknowledge the limitations of the imaging techniques to accurately detect small changes in diameters. Selection bias certainly plays a role in this study, because this is a highly selected population of alive AOS patients with follow-up visits.

Despite these limitations, this study adds important clinical information for the management of this patient group. Definitive recommendations regarding management of AOS patients will require longer follow-up studies in a larger sample of patients.

CONCLUSIONS

AOS is known to predispose patients to aggressive and widespread cardiovascular disease. Progression rate of aortic dilatation in AOS patients is highest at the level of the sinus of Valsalva with approximately 2.5 mm/year and correlated with the initial aortic diameter. VSRR is a safe and effective surgical option for the management of aortic root aneurysms in AOS patients. Certainly, as more patients with AOS will be identified in the future, a better understanding of the natural history and surgical outcome will become evident. For now, cardiologists and (cardio)vascular surgeons should be aware of this new syndrome and its aggressive behavior.

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DISCLOSURES

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Chapter 13

Thoracic aortic surgery; an overview and long term results

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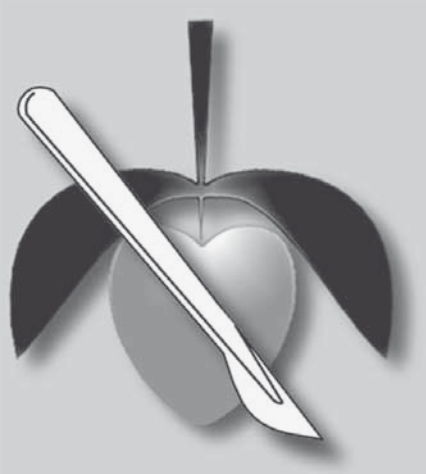


ABSTRACT

Objectives: To report on the total experience in thoracic aortic surgery over a 40 year time period in a single institution.

Methods: All 1075 patients who underwent surgery for thoracic aortic pathology from 1972- 2011 (N=1159) were included. Patient, procedural and follow-up information was obtained from hospital records and the civil registry. Patients were grouped in 4 categories: 1: acute type A dissection (N=261); 2: other ascending aortic/arch surgery (N=626); 3: descending aortic surgery (N=175); 4: thoraco-abdominal surgery (N=97). Risk factors for early and late mortality and the incidence of reoperations were analyzed.

Results: The annual number of operations increased significantly over time. In all 4 patient groups the early mortality (in hospital or within 30 days of operation) decreased significantly over time to 15.3% in Group 1, 1.9% in Group 2, 0% in Group 3 and 10.5% in Group 4 in the contemporary time period 2007-2011. Overall actuarial survival was 54.3% (95% CI 50.7%-57.9%) after 10 years and 27.8% (95% CI 26.4%-38.3%) after 20 years. Late survival improved over time, but was reduced compared to the general population and predominantly related to pre-existing risk factors. In 80 patients 111 reoperations were necessary, most frequently in Group 1 patients and patients with connective tissue disease.

Conclusions: Thoracic aortic operations are being performed increasingly over a 40 year time period. Early mortality decreased and late survival increased significantly in all patient groups. A significant proportion of patients requires multiple operations.

INTRODUCTION

Thoracic aortic aneurysm is a frequently encountered condition, potentially leading to lethal complications or serious morbidity.[1-3] The exact prevalence of thoracic aortic aneurysms is not known. In the USA aortic aneurysms were 19th in rank in the 2007 mortality statistics, with13,000 deaths (0.5% of all deaths). (http://webappa.cdc.gov/cgi-bin/broker.exe.) Once dissection or rupture occurs as complication of a thoracic aneurysm, emergency surgical treatment is most often the only available option to save a patient's life. Because these emergency operations have considerable operative mortality and complication rates, and because patients might be confronted with potential long-term consequences, elective surgery even in asymptomatic patients with aortic dilatation is recommended in recent guidelines.[4] The aortic dimension warranting operation depends on the underlying diagnosis.

In this setting surgery of the thoracic aorta has evolved from a small, but high impact part in terms of mortality and morbidity of the total cardio-thoracic surgical workload to one of the major subspecialties in cardiovascular surgery.

In this study we report our total experience with thoracic aortic surgery since 1972, specifically early patient outcome as well as long-term results in 4 major subgroups. Furthermore we analyze evolution over time in timing and characteristics of operations and operative results.

PATIENTS AND METHODS

From our institutional Aortic Surgery Database we extracted 1159 consecutive procedures for thoracic aortic pathology in 1075 patients between 1972 and 2011. We excluded patients with primary aortic coarctation and patients who underwent aortic root replacement for pure aortic valve pathology (endocarditis, aortic allograft root replacement or pulmonary autograft replacement for isolated valve pathology) or complex congenital pathology. Finally, patients who underwent thoracic stent-graft procedures were excluded. Patients were categorized in 4 groups: Acute type A dissections (Group 1), ascending aortic and/or arch procedures, excluding acute type A dissections (Group 2), descending aortic procedures (Group 3) and thoraco-abdominal procedures (Group 4). Institutional Review Board (IRB) approval was obtained for this retrospective follow-up study (MEC number 2011-064); the IRB waived informed consent. The indications for operation are displayed in Table 1. Preoperative patient characteristics are displayed in Table 2. Operations within 24 hours of onset of complaints are classified as acute, operations within 14 days or during the initial hospital admission are classified as urgent. The other operations were elective.

Table 1. Indications for thoracic aortic surgery and procedures performed.

Group	Indication/etiology	N	Procedure	N
Group 1. Acute type A dissection (N=261)	Acute type A dissection	261	Ascending aorta	
	Idiopathic	231	Replacement	252
	Marfan/CTD	17	Repair/patch	5
	Iatrogenic (CABG/AVR)	9	No ascending aortic procedure[a]	4
	Iatrogenic (PCI)	4		
			Aortic arch	
			No arch procedure	37
			Hemi-arch/open distal anastomosis	187
			Replacement	41
			Repair/patch	1
			Aortic valve	
			Repair/preservation	177
			Mechanical prosthesis	11
			Bioprosthesis	3
			Allograft	16
			Valved conduit	53
			T.David/Yacoub	1
Group 2. Ascending aorta/aortic arch (N=626)	Chronic type A dissection	46	Ascending aorta	
	Idiopathic	42	Replacement	591
	Marfan/CTD	3	Repair/patch	21
	Iatrogenic	1	No ascending aortic procedure	14
	Aneurysm	538	Aortic arch	
	Idiopathic	430	No arch procedure	279
	Marfan/CTD	40	Hemi-arch/open distal	283
	Infectious	10	Replacement	48
	Traumatic	1	Replacement with elephant trunk	11
	Iatrogenic	4	Repair/patch	5
	Allograft failure	4	Aortic valve	
	Autograft failure	46	No valve procedure	136
	False	2	Repair	10
	Takayasu arteriitis	1	Mechanical prosthesis	68
	Other	42	Bioprosthesis	26
	Idiopathic	4	Allograft	67
	Marfan/CTD	1	Valved conduit	283
	Infectious	5	T.David/Yacoub	32
	Traumatic	2	Pulmonary autograft	4
	Allograft failure	27		
	Iatrogenic	2		
	Aortic arch stenosis	1		
Group 3. Descending aorta (N=175)	Acute/urgent dissection	34	ECC method	
	Aneurysm	115	No ECC	49
	Idiopathic	75	Passive shunt	53
	Marfan/CTD	1	Left heart bypass	27
	Post-dissection	20	Full bypass with DHCA	46
	Infectious	6	Descending aorta	
	Traumatic	10	Prosthesis	156
	False aneurysm	2	With (partial) arch	12
	Leiomyosarcoma	1	Patch repair	14
	Traumatic aortic rupture	34	With (partial) arch	2
			No descending aortic procedure	5[b]

			Re-implantation	
			Left subclavian artery	13
			Intercostal arteries	7
Group 4. Thoraco-abdominal aorta (N=97)	Aneurysm	97	ECC method	
	Idiopathic	71	No ECC	13
	Marfan/CTD	7	Left heart bypass	37
	Post-dissection	17	Full bypass with DHCA	47
	Infectious	1	Thoraco-abdominal aorta	
	Traumatic	1	Prosthesis, distal anastomosis supra-renal	12
			Prosthesis, distal anastomosis infra-renal	67
			Prosthesis, including bifurcation	17
			No aortic procedure[c]	1
			Re-implantation	
			Left subclavian artery	2
			Intercostal arteries	62
			Visceral/renal arteries	82

CTD: connective tissue disease, CABG: coronary artery bypass grafting, AVR: aortic valve replacement, PCI: percutaneous catheter intervention, ECC: extra-corporeal circulation.

[a]: 2 patients were operated by a lateral thoracotomy approach and 2 patients could not be stabilized on extra-corporeal circulation.

[b] 5 patients could not be stabilized after thoracotomy.

[c] 1 patient could not be stabilized after thoraco-laparotomy.

Operation

Over time the operations were performed by 17 attending staff surgeons. Over the years anesthetic and extra-corporeal circulation management and preferred surgical procedures evolved, as detailed below.

Patients with ascending aortic or aortic arch pathology were operated by median sternotomy, using cardiopulmonary bypass. Routine arterial canulation was in the ascending aorta. Alternative arterial canulation sites (femoral artery or subclavian artery) were used for acute aortic dissections or when otherwise indicated. Venous canulation was routinely in the right atrium. Deep hypothermia and circulatory arrest was used when indicated. Additional retrograde or antegrade cerebral perfusion was introduced in 1997 and used in selected cases. In patients who required multiple periods of cardio-pulmonary bypass, aortic cross-clamping or circulatory arrest the total times were calculated by adding up these periods. Cold crystalloid cardioplegia was used for cardiac protection. For aortic replacement we used various types of vascular prosthesis. In the present era we use impregnated vascular grafts (Gelsoft or Gelseal, Vascutek Ltd., *Renfrewshire*, Scotland, UK). For aortic arch replacement a branched prosthesis (Plexus 4, Vascutek Ltd., *Renfrewshire*, Scotland, UK) with separate revascularization of arch vessels was used, or the arch vessels were implanted using an island technique.[5]

Table 2 . Pre-operative patient characteristics.

Characteristic	Total N=1159	Group 1 Acute type A N=261	Group 2 Asc. An/Chron. Type A diss. N=626	Group 3 Descending N=175	Group 4 Thor.-abd. N=97	P
Mean age (years (SD; range))	56 (16; 9-83)	58 (13; 19-83)	53 (17; 9-83)	57 (16; 15-79)	64 (9; 34-75)	<0.001
Male/female ratio (%/%)	794/365 (68/32)	166/95 (64/36)	435/191 (70/30)	134/41 (77/23)	59/38 (61/39)	0.011
Creatinin (µmol/L,N=1109,(SD; range))	97 (54; 25-861)	115 (84;25-861)	88 (31; 27-367)	103 (58; 41-613)	98 (45; 39-385)	<0.001
Prior cardiac surgery/ PCI	19.5% (N=226)	12.3% (N=32)	27.2% (N=170)	5.7% (N=10)	14.4% (N=14)	<0.001
Prior aortic surgery	16.7% (N=193)	5.0% (N=13)	18.7% (N=116)	18.3% (N=32)	33.0% (N=32)	<0.001
Hypertension	43.5% (N=504)	52.9% (N=138)	34.5% (N=216)	47.4% (N=83)	69.1% (N=67)	<0.001
COPD	8.6% (N=100)	6.9% (N=18)	7.3% (N=46)	10.9% (N=19)	17.5% (N=17)	0.004
Prior CVA	3.4% (N=39)	1.5% (N=4)	4.3% (N=27)	1.7% (N=3)	5.2% (N=5)	0.077
Diabetes mellitus	2.7% (N=31)	1.5% (N=4)	2.9% (N=18)	2.9% (N=5)	4.1% (N=4)	0.631
Prior myocardial infarction	5.2% (N=60)	5.4% (N=14)	5.4% (N=34)	3.4% (N=6)	6.2% (N=6)	0.707
Systolic LVF (N=631)						
Good	75.4% (N=476)	88.5% (N=100)	71.2% (N=326)	85.7% (N=18)	82.1% (N=32)	0.009
Impaired	15.2% (N=96)	5.3% (N=6)	18.6% (N=85)	-	12.8% (N=5)	
Moderate/Bad	9.4% (N=59)	6.2% (N=7)	10.2% (N=47)	14.3% (N=3)	5.1% (N=2)	
Logistic Euroscore (mean (SD; range)	14.6 (11.2;5-88)	21.1 (14.4;5-79)	12.6 (9.5;5-88)	12.3 (8.6;5-62)	13.8 (8.2;5-5-40)	<0.001
Urgency operation						
Acute (<24 hours)	29.0% (N=336)	93.1% (N=243)	4.3% (N=27)	34.9% (N=61)	5.2% (N=5)	<0.001
Urgent (<14 days)	15.8% (N=183)	6.9% (N=18)	15.8% (N=99)	25.1 (N=44)	22.7% (N=22)	
Elective	55.2% (N=640)	-	79.9% (N=500)	40.0% (N=70)	72.2% (N=70)	

SD: standard deviation, PCI: percutaneous catheter intervention, COPD: chronic obstructive pulmonary disease, CVA: cerebro vascular accident, CTD: connective tissue disease, LVF: left ventricular function

Patients with descending aortic pathology were operated by lateral thoracotomy, patients with thoraco-abdominal pathology by thoraco-laparotomy with splitting of the diaphragm. In patients with descending aortic aneurysms we preferably used a passive shunt until 1983. Thereafter we used left heart bypass or full bypass with deep hypothermic circulatory arrest. For thoraco-abdominal aneurysms we used the clamp and sew technique described by Crawford until 1988.[6] From 1989-1999 exclusively a full bypass with deep hypothermic circulatory arrest was used. From 1999 we preferably used a left heart bypass. Selective perfusion of renal arteries and visceral arteries was used in combination with left heart

bypass. Spinal cord fluid drainage was introduced in 2002. Intercostal, renal and visceral arteries were implanted in the vascular prosthesis used when indicated and feasible.

Follow-up

All patients were followed at our institution or by their referring cardiologist. From hospital records and referring cardiologist documentation we collected information on vital status, reoperations and complications. In addition we consulted the municipal civil registries to ascertain vital status of all patients. Valve-related complications were defined according to the 2008 guidelines for reporting morbidity and mortality after cardiac valvular operations.[7] Early mortality was defined as mortality in hospital or within 30 days of surgery

The study database was frozen for analysis on December 31 2011. Follow-up was 99% complete: 11 patients were lost to follow-up. The mean follow-up duration was 6.0 years (range 0-35.3 years), with a total follow-up of 6888 patient years.

Statistical methods

Continuous data are presented as means (standard deviation (SD); range). Categorical data are presented as proportions. Differences between groups were analyzed using a Student T test or ANOVA testing with Bonferroni correction for continuous data and Chi-square test for categorical data. Cumulative survival was analyzed using the Kaplan-Meier method. The survival of a patient started at the time of operation and ended at the time of death (event) or at the last follow-up or reoperation (censoring). Comparison of Kaplan-Meier estimates was done using the Tarone-Ware test.

Univariable and multivariable logistic regression analysis (stepwise backward; inclusion criteria $p \leq 0.10$, exclusion criteria $p \geq 0.10$) was used to study determinants of early mortality. The Cox proportional hazards model was used for univariable and multivariable analysis of time-related events. Variables that were tested as potential risk factors for early and mortality are presented in Appendix A.

A p-value of ≤ 0.05 was considered statistically significant. All testing was performed 2-sided.

For all analyses SPSS 17.0 for Windows statistical software (SPSS, Chicago, Ill) was used.

RESULTS

During the study period 1159 consecutive operations for thoracic aortic pathology were performed in 1075 patients. Fifty-nine patients were operated upon twice, 7 patients 3 times and 3 patients 4 times. Fourteen of 56 (25%) patients with Marfan disease or other connective tissue disease underwent multiple operations, compared to 54 out of 1019

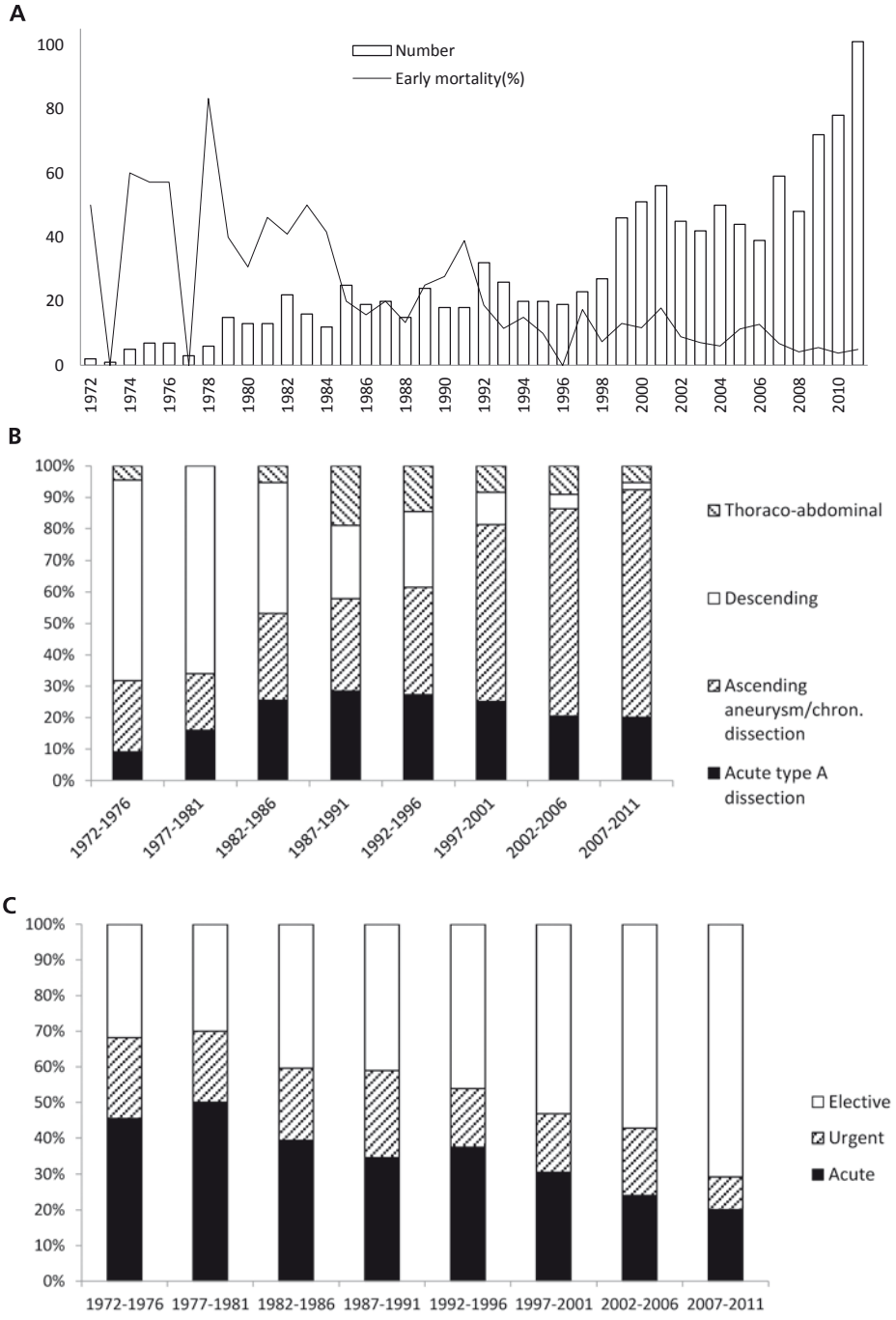


Figure 1. Overview of number of operations and early mortality per year (A), distibution over 4 patients groups per 5 years time period (B) and distibution over 3 urgency classes per 5 year time period (C)

(5.3%) patients without known genetic diseases (Odds ratio (OR) 5.8 (95% Confidence Interval (CI) 3.0-11.3; p<0.001).

Figure 1A presents the number of operations per year, showing a steady increase of the annual number of procedures over time. Figure 1B presents the distribution of the 4 patient groups over time, showing an increase of ascending aortic aneurysm operations from 23% to 72% over time. Figure 1C presents the distribution of procedures by urgency of operation over time, showing a shift from 68% acute or urgent operations to 71% elective operations in the most recent era.

The perioperative data for all operations are shown in Table 1. In Group1 deep hypothermia with circulatory arrest was used in 220 (84%) patients (mean duration 49 minutes (SD 35), and in Group 2 in 346 (55%) patients (mean duration 30 minutes (SD 36). In Group1 antegrade cerebral perfusion was used in 48 (18%) patients (mean duration 77 minutes (SD 44), and in Group 2 in 62 (10%) patients (mean duration 83 minutes (SD 73).

In 46 (26%) patients in Group 3 deep hypothermia with circulatory arrest was used with a mean duration of 44 minutes (SD 15), in 47 (48%) patients in Group 4 deep hypothermia with circulatory arrest was used with a mean duration of 51 minutes (SD 16).

Early mortality and morbidity

Early mortality occurred in 167 patients (14.4%), 146 patients (12.6%) died within 30 days postoperative. Over time the early mortality risk decreased from over 50% to 5% in recent years (Figure 1A). Causes of early mortality were bleeding (n=45), cardiac failure (n=49), sepsis/multiple organ failure (n=30), aortic rupture (n=13), neurological (n=17) and other causes (n=13). Mortality within 60 days was 14.2% (164 patients); mortality within 90 days was 15.6% (180 patients). Figure 2A shows the early mortality per patient group and per 5-years' time period. In all 4 patient groups the mortality risk decreased significantly over time. Early mortality in the most recent time period 2007-2011 was 15.3% in Group 1, 1.9% in Group 2, 0% in Group 3 and 10.5% in Group 4. In Group 1 independent risk factors for early mortality were: earlier year of operation (OR 0.961 (95% CI 0.924-0.999); p=0.044), collapse as the main presenting symptom (OR 3.3 (95% CI 1.3-8.6); p=0.013)) and pre-operative resuscitation (OR 4.7 (95% CI 1.0-20.9); p=0.044). In Group 2 independent predictors for early mortality were earlier year of operation (OR 0.852 (95% CI 0.812-0.895); p<0.001), older patient age (OR 1.032 (95% CI 1.008-1.056); p= 0.008), higher Euroscore (OR 1.047 (95% CI 1.017-1.077); p=0.002), longer cardiopulmonary bypass time (OR 1.006 (95% CI 1.003-1.009)); p<0.001) and the use of circulatory arrest (OR 3.4 (95% CI 1.1-10.4); p=0.029). In Group 3 independent predictors for early mortality included earlier year of operation (OR 0.944 (95% CI 0.898-0.995); p=0.026), older patient age (OR 1.053 (95% CI 1.011-1.085); p= 0.001), emergency operation (OR 0.2 (95% CI 0.1-0.6); p=0.001) and post-operative renal dialysis (OR 8.4 (95% CI 1.7-41.6); p=0.009). Prior aortic surgery (OR 0.1 (95% CI 0.0-0.9); p=0.038) was associated with a reduced

Table 3. Post-operative complications

	Era 1972-2006 (N=801)				Era 2007-2011 (N=358)			
	Group 1 N=189	Group 2 N=367	Group 3 N=167	Group 4 N=78	Group 1 N=72	Group 2 N=259	Group 3 N=8	Group 4 N=19
Early mortality	40 (21.2%)	31 (8.4%)	47 (26.6%)	31 (39.7%)	11 (15.3%)	5 (1.9%)*	0*	2 (10.5%)*
ICU stay								
Mean (days, (SD))	8.2 (10.4)	3.4 (5.7)	5.8 (9.5)	15.0 (28.2)	8.2 (12.0)	2.3 (5.6)	3.1 (3.9)	12.7 (12.7)
> 2 days	136 (72.0%)	114 (31.1%)	79(46.1%)	61 (78.2%)	54 (75.0%)	33 (12.7%)*	2 (25.0%)	18 (94.7%)
Ventilation								
Mean (days, (SD))	6.2 (9.3)	2.1 (4.8)	4.4 (8.6)	12.2 (31.2)	6.1 (11.9)	1.8 (5.2)	2.0 (2.8)	9.3 (12.2)
>1 day	153 (81.0%)	136 (37.1%)	121 (74.9%)	64 (82.1%	42 (58.3%)*	21 (8.1%)*	1 (12.5%)*	16 (84.2%)
Tracheostomy	13 (6.9%)	7 (1.9%)	19 (11.4%)	13 (16.7%)	5 (6.9%)	2 (0.8%)	0	1 (5.3%)
Myocardial infarction	12 (6.3%)	10 (2.7%)	2 (1.2%)	4 (5.1%)	1(1.4%)	4 (1.5%)	0	0
Renal dysfunction (creat >150 µmol/l)	56 (29.6%)	34 (9.3%)	48 (28.7%)	43 (55.1%)	25 (34.7%)	22 (8.5%)	2 (25.0%)	9 (47.4%)
dialysis	20 (10.6%)	8 (2.2%)	12 (7.2%)	11 (14.1%)	9 (12.5%)	5 (1.9%)	0	5 (26.3%)
Atrial fibrillation	56 (29.6%)	114 (31.1%)	12 (7.2%)	14 (17.9%)	20 (27.8%)	71 (27.4%)	0	2 (10.5%)
CVA	25 (13.2%)	15 (4.1%)	12 (7.2%)	6 (7.7%)	6 (8.3%)	5 (1.9%)	2 (25.0%)	0
Paraplegia	6 (2.2%)	0	11 (6.3%)	16 (20.5%)	1 (1.4%)	0	0	3 (15.8%)
Recurrent nerve paralysis	8 (3.1%)	10 (1.6%)	24 (13.7%)	10 (10.3%)	0	5 (1.9%)	3 (37.5%)	3 (15.8%)
Delirium	46 (17.6%)	28 (4.5%)	7 (4.0%)	18 (18.6%)	21 (29.2%)	17 (6.6%)	0	3 (15.8%)

*=P<0.05 comparing era 2007-2011 to era 1972-2006.
ICU= intensive care unit, SD=standard deviation, CVA=cerebro-vascular accident

early mortality. In Group 4 the use of left heart bypass was associated with reduced early mortality (OR 0.1 (95% CI 0.0-0.5); p=0.005) while post-operative renal dialysis (OR 8.8 (95% CI 2.2-35.2); p=0.002) was an independent predictor of early mortality. More details of the univariable and multivariable analysis of risk factors for early mortality are presented in Appendix B.

Table 3 presents post-operative complications by patient group for the era 1972-2006 compared to the present era. Early mortality in Group 2, 3 and 4, ICU stay more than 2 days in group 2 and ventilatory support more than 1 day in Group 1, 2 and 3 were lower in the present era compared to the era 1972-2006. In Group 1 and 2 the overall stroke rate was 11.9% and 3.2% respectively, with no difference whether or not circulatory arrest was used (p=0.552 and p=0.185).The duration of circulatory arrest or the use of antegrade cerebral perfusion did not influence the post-operative stroke rate. The paraplegia rates in Group 3 and 4 were 6.2% and 19.6% respectively.

Late survival

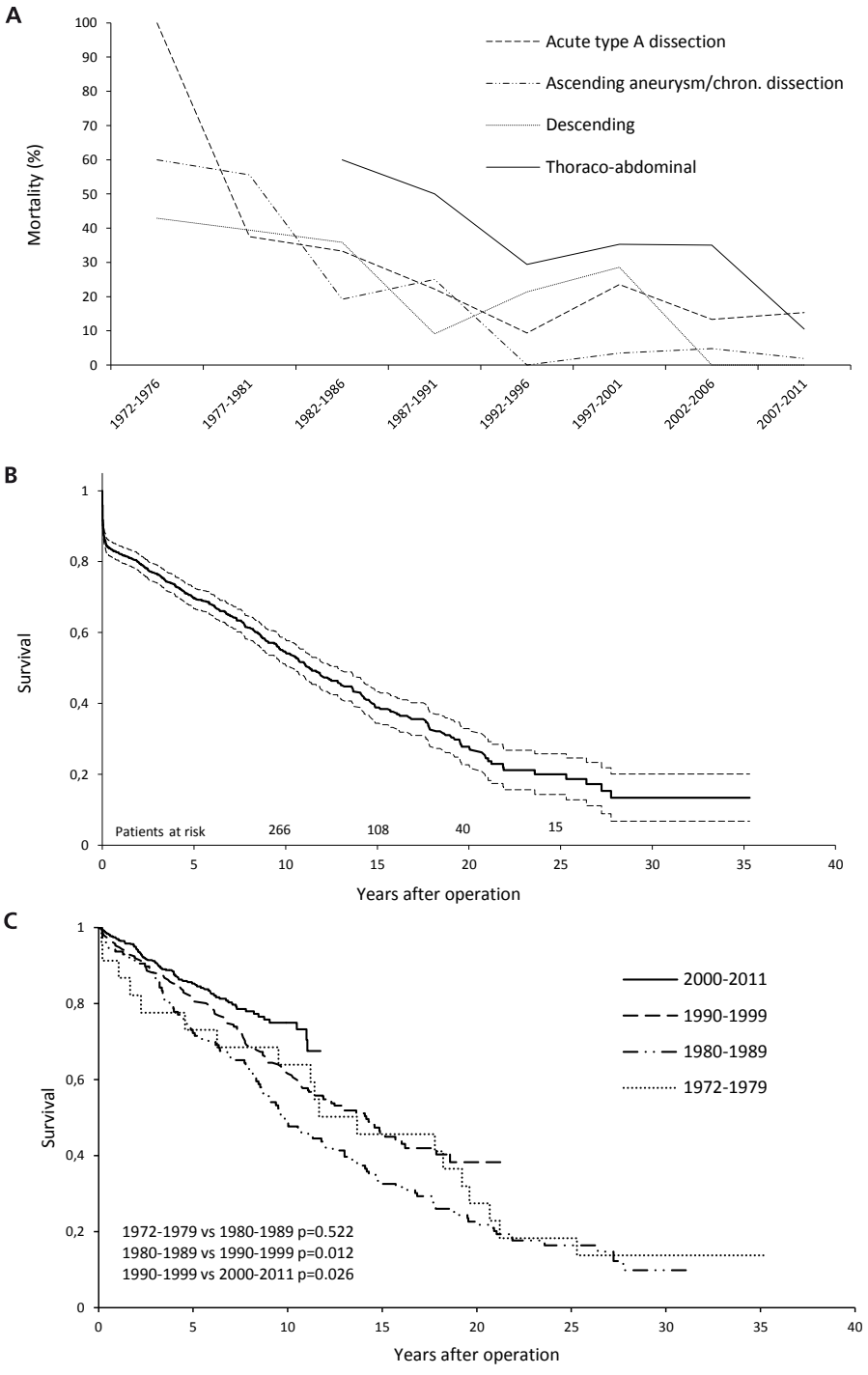
During follow-up an additional 330 patients died. Causes of late death were cardiac in 45 patients, aortic or vascular related in 20 patients, malignancy in 24 patients, neurological in 6 patients and other or unknown causes in 235 patients.

Overall cumulative survival (including early mortality) was 54.3% (95% CI 50.7%-57.9%) after 10 years and 27.8% (95% CI 22.6%-32.9%) after 20 years (Figure 2B). Figure 2C depicts late survival by decade, showing an evident improvement of late survival over time except in the first 2 decades. For the 996 hospital survivors, late survival was 63.2% (95% CI 59.3%-67.1%) after 10 years and 32.3% (95% CI 26.4%-38.3%) after 20 years. This was clearly impaired compared with the age matched Dutch population (Figure 2D). Figure 2E depicts the late survival of hospital survivors per group. Survival of patients with ascending aortic/aortic arch aneurysms operated after 2000 was 75.8% at 10 years, which is still reduced in comparison to the 88.0% of an age matched Dutch male in the general population (Figure 2F).

In Group 1 independent risk factors for late mortality were: earlier year of operation (Hazard Ratio (HR) 0.960 (95% CI 0.922-0.998); p=0.041), older patient age (HR 1.046 (95% CI 1.023-1.069); p<0.001), pre-operative obstructive pulmonary disease (HR 4.2 (95% CI 1.9-9.3); p<0.001), higher pre-operative creatinin (HR 1.003 (95% CI 1.002-1.005); p<0.001), aortic arch replacement (HR 2.9 (95% CI 1.2-6.9); p=0.015) and reduced left ventricular function (HR 6.2 (1.9-20.2);p=0.002). In group 2 independent predictors for late mortality were earlier year of operation (OR 0.937 (95% CI 0.913-0.962); p<0.001), older patient age (HR 1.051 (95% CI 1.036-1.066); p<0.001), higher pre-operative creatinine (OR 1.005 (95% CI 1.000-1.010); p=0.031), higher Euroscore (OR 1.024 (95% CI 1.004-1.045); p=0.021), aortic arch replacement (HR 1.9 (95% CI 1.1-3.5); p=0.026) and post-operative myocardial infarction (HR 5.6 (95% CI 2.3-13.2); p,0.001). In Group 3 independent predictors for late mortality included older patient age (HR 1.060 (95% CI 1.041-1.080); p<0.001) and pre-operative obstructive pulmonary disease (HR 1.9 (95% CI 1.0-3.5); p=0.041) and in Group 4 older patient age (OR 1.097 (95% CI 1.041-1.135); p=0.001) was an independent predictor of late mortality. More details of the univariable and multivariable analysis of risk factors for late mortality are presented in Appendix C.

Reoperations

Eighty patients underwent 111 reoperations. Appendix D presents an overview of these reoperations per patient group. In Group 1 (acute type A dissection) most reoperations were for aortic valve incompetence in repaired or preserved native aortic valves at the primary operation (n=14) or structural valve deterioration after allograft implantation (n=5). The rate of aortic valve reoperation was increased in patients with pre-operative severe aortic valve insufficiency who had their aortic valves preserved (Hazard ratio 2.9 (95% CI 1.1-8.2); p=0.049). Reoperations for distal aortic pathology, related to the chronic rest-dissection after


A
Mortality (%)
Acute type A dissection
Ascending aneurysm/chron. dissection
Descending
Thoraco-abdominal
1972-1976
1977-1981
1982-1986
1987-1991
1992-1996
1997-2001
2002-2006
2007-2011
B
Survival
Patients at risk
266
108
40
15
Years after operation
C
Survival
2000-2011
1990-1999
1980-1989
1972-1979
1972-1979 vs 1980-1989 p=0.522
1980-1989 vs 1990-1999 p=0.012
1990-1999 vs 2000-2011 p=0.026
Years after operation

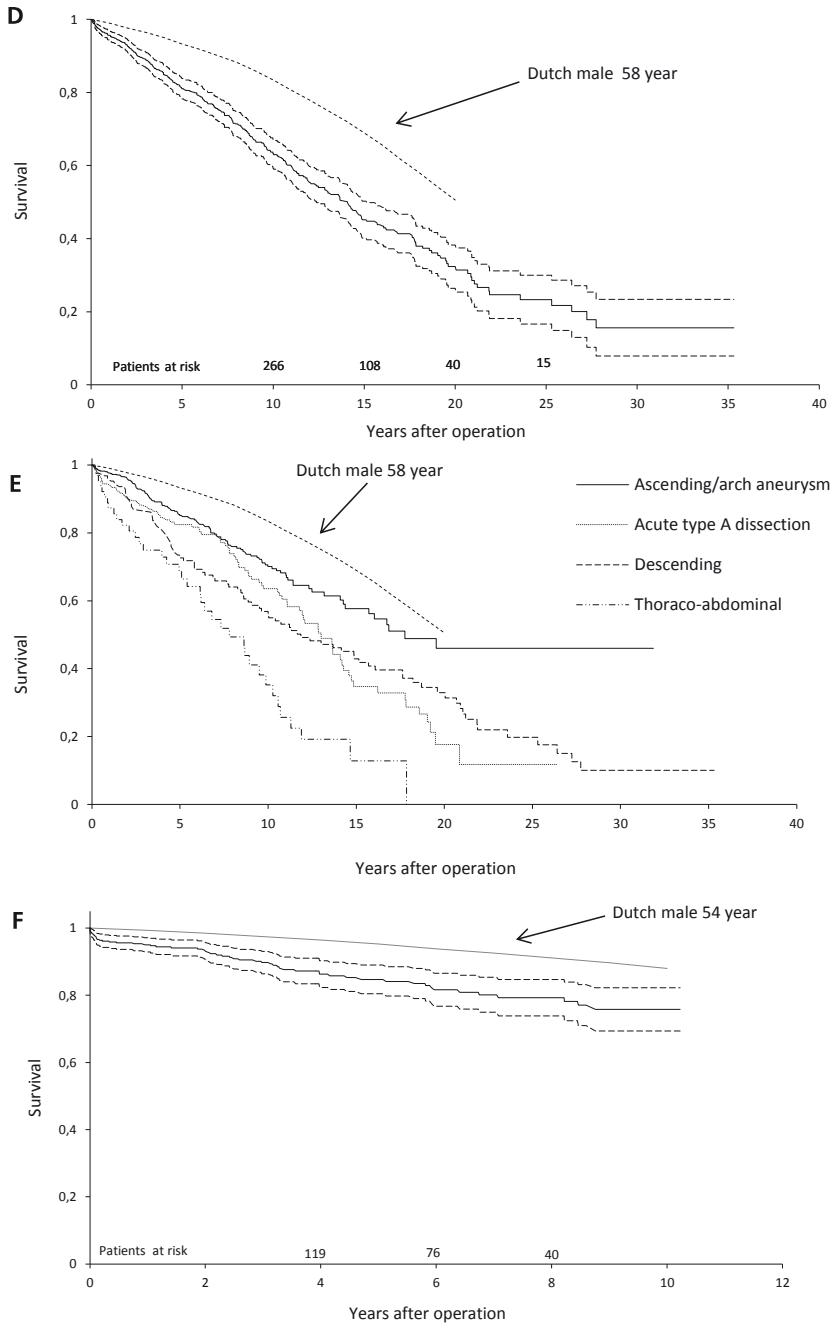


Figure 2. Early mortality per patient group and per 5 year time period. (A), overall survival of 1159 patients after thoracic aortic surgery between 1972-2011 (B), overall survival after thoracic aortic surgery per decade (C), survival of 996 hospital survivors after thoracic aortic surgery compared to the survival of a 58-years old Dutch male (D), survival of hospital survivors per group (E), Survival of 417 patients operated for ascending aortic or aortic arch aneurysms between 2000-2011, compared to a 54 year old Dutch male (E).

repaired type A dissection were more frequent in patients with a connective tissue disease or with type 1 dissection versus type 2 dissection, although not significant. The freedom from proximal reoperation was 84.6% at 10 years and 71.4% at 15 years. The freedom from distal aortic reoperations was 90.2% after 10 years and 83.7% after 15 years. In the other patient groups reoperations on the aorta were less frequent. In Group 2 (chronic aortic aneurysm/ dissection) reoperations were more frequent in patients with Marfan's disease or other known connective tissue diseases with a HR for proximal reoperation of 3.5 (95% CI 1.5-8.5; p=0.005) and HR for distal reoperation 6.2 (95% CI 2.7-14.5; p<0.001). Furthermore distal reoperations were more frequent after elephant trunk aortic arch replacement.In Group 3 (descending aorta) most reoperations were for abdominal aortic pathology.

COMMENT

In this report we provide an overview of all thoracic aortic operations performed in our centre between 1972 and 2011. We observed a substantial increase in the annual number of operations in this 40 year time period to about 10% of the annual case-load in our department. We demonstrate a shift from 70% emergent or urgent operations to 70% elective surgery. Furthermore we observed a shift from predominantly descending aortic operations to 70% ascending aortic or aortic arch operations, confirming observations by Achneck et al.[8] Olssen and colleagues also demonstrated an increase in prevalence of thoracic aortic disease and number of operations performed between 1987 and 2002 in Sweden.[9] The increased knowledge of inherited conditions has led to further recommendations for early intervention at only slightly abnormal aortic diameters in patients with specific gene mutations[10,11] and might play an additional role in the increase of the number of operations performed.

We observed a decrease in descending aortic surgery. Thoracic endovascular aortic replacement (TEVAR) is increasingly used as the first choice therapy for descending aortic aneurysms[4] and traumatic aortic rupture with equal or even lower early mortality and complications.[12,13] However, long term results of TEVAR therapy are still unknown and randomised trials comparing open surgery and TEVAR are lacking, making definitive conclusions on the merits of TEVAR impossible.[14]

In our series we observed an impressive decrease in early mortality from over 50% early in the series in all 4 patients groups analysed to15% for acute type A dissections, 1.9% for ascending aortic and arch pathology, other than acute type A dissections, 0% for the limited number of descending aortic aneurysms and 10.5% for thoraco-abdominal aneurysms in the most recent era 2007-2011. These recent early mortality rates are in line with other published series and outline the safety of thoracic aortic surgery in the present era. For acute type A dissections the International Registry of Acute Aortic Dissections (IRAD) reports an overall in hospital mortality of 23.9% for patients operated upon between 1996

and 2003.[15] Achneck and colleagues report a mortality of 3.0% in elective ascending aorta or arch surgery, a mortality of 2.9% for elective descending aortic surgery and a mortality of 11.9% for elective thoraco-abdominal aortic surgery.[8,16] Estrera and colleagues report a 30 day mortality of 7.3% and an incidence of 2.3% neurological deficit in 300 patients operated for descending aortic aneurysms.[17]

In a previous study on acute type A dissection, excluding patients with traumatic or iatrogenic dissections we found the reduction in 30 day mortality to be related to technical improvement in the conduct of the operation.[18]

In descending aortic surgery the reduction in operative mortality might be associated to major changes in operative indications. Acute surgery for traumatic aortic rupture or complicated dissection is nowadays replaced by endovascular procedures. On the other hand open surgery is presently reserved for patients with a chronic dissection or unfavourable anatomy, not amenable for TEVAR procedures. In our patient group with predominantly chronic dissections or otherwise contra-indications for TEVAR we found no mortality or paraplegia in the last 10 years. Prior aortic surgery was associated with a lower early mortality and emergency operations were associated with a higher early mortality.

In thoraco-abdominal aneurysms we found the improvement in early mortality to be related to changes in operative technique. The currently preferred technique, using left heart bypass, visceral perfusion and cerebro-spinal fluid drainage resulted in significantly lower mortality as is described by others.[19]

Information on late survival after thoracic aortic surgery is rare. Kouchoukos and colleagues found 10 year survival rates of 40-65% after acute ascending aortic dissection, 57-75% after other ascending aortic or arch operations and 32-37% after thoraco-abdominal aortic operations.[20] Olssen and colleagues found an overall survival of hospital survivors of 57% at 10 years and 43% at 15 years in 2455 patients operated upon for various types of thoracic aortic disease between 1987-2002.[9] In our series we demonstrate an overall long-term survival of 54% at 10 years and 28% at 20 years. The late survival for hospital survivors was 63% at 10 years and 32% at 15 years, and improved over time. This late survival was reduced, when compared to survival in the normal population. Late survival was reduced after thoraco-abdominal aortic surgery predominantly related to general risk factors for reduced survival. We found the survival of contemporary patients, operated since 2000, with ascending aortic or aortic arch aneurysms to be 76% at 10 years. This survival is reduced to the 88% survival at 10 years of the age matched general population. This reduction in 10 year survival has to be weighed against the risk of a fatal outcome in untreated aortic aneurysms. Davies and colleagues estimate the yearly rate of rupture, dissection or death to be 6% for aneurysms of 5.0-5.9cm and 15% for aneurysms lager than 6cm.[21] They found the 5 year survival of unoperated patients to be 54%, which is clearly inferior than the survival of operated patients. This information can be used in advising patients with asymptomatic aneurysms and may be used to lower the threshold for elective aortic replacement.

Aortic disease may be present in multiple segments of the aorta, especially in patients with Marfan's disease or other genetic aortic diseases. In our series 61 out of 1075 individual patients (5.6%) underwent multiple operations. In patients with genetic diseases multiple operations were a 5 fold more frequent. Multiple operations in patient after acute type A dissection are reported in 10-15% of patients, with a freedom from reoperation of 71-79% after 10 years.[22,23] We recently found an increased rate of aortic valve reoperations in patients presenting with severe aortic insufficiency pre-operatively who had their valves preserved or after allograft implantation.[18] In the present series we found 48 reoperations on the aortic valve or the proximal aorta, with a freedom from proximal reoperation of 85% at 10 years and 72% at 15 years. Freedom of distal reoperation after acute type A aortic dissection was 90% at 10 years and 84% at 15 years. Reoperations after descending aortic replacement were most frequently for abdominal aortic aneurysms. Reoperations after ascending aortic surgery, other than for acute dissections or thoraco-abdominal aortic surgery were less frequent.

LIMITATIONS

Our study presents a retrospective single center experience in a 40 year time period. Operations have been performed by 17 different surgeons. In this time period changes in patient population, operative indications, diagnostics, operative and anesthesiologic management and conduct of cardio-pulmonary bypass have occurred, that can only partly be evaluated. Although follow-up information on the vital status of patients is nearly complete, exact information on the causes of death is not available.

CONCLUSIONS

Thoracic aortic surgery is increasing in numbers of operations performed in a 40 year time period. There has been a shift from predominantly emergency or urgent operations to elective procedures and from descending aortic to ascending aortic operations. Early mortality decreased significantly over time for all patients groups. Long term-survival improved significantly over time, although still being reduced compared to the general population. A significant proportion of patients required multiple operations, especially patients with Marfan's disease or other connective tissue diseases and patients operated for acute ascending aortic dissection.

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APPENDIX B

Univariable and multivariable analysis on factors for early mortality.

	Group 1		Group 2		Group 3		Group 4	
Factor	Univariable OR (95% CI); p value	Multivariable OR (95% CI); p value	Univariable OR (95% CI); p value	Multivariable OR (95% CI); p value	Univariable OR (95% CI); p value	Multivariable OR (95% CI); p value	Univariable OR (95% CI); p value	Multivariable OR (95% CI); p value
Year of operation	0.962 (0.932-0.993); 0.018	0.961 (0.924-0.999); 0.044	0.887 (0.856-0.919); <0.001	0.852 (0.812-0.895); <0.001	0.928 (0.888-0.969); 0.001	0.944 (0.898-0.993); 0.026	0.932 (0.882-0.986); 0.014	
Age			1.032 (1.008-1.056); 0.008	1.039 (1.004-1.075); 0.029	1.033 (1.008-1.059); 0.011	1.053 (1.022-1.085); 0.001		
Prior CVA			3.0 (1.0-9.4); 0.049					
Prior myocardial infarction							4.3 (0.7-24.7); 0.104	
Collaps main presenting symptome	4.1 (1.8-9.3); 0.001	3.3 (1.3-8.6); 0.013						
Prior aortic surgery					0.1 (0.0-0.6); 0.010	0.1 (0.0-0.9); 0.038		
Pre-operative shock			10.6 (2.4-46.4); 0.002					
Pre-operative malperfusion	2.6 (1.3-5.2); 0.005							
Pre-operative ventilatory support	6.2 (2.2-17.6); 0.001							
Pre-operative resuscitation	6.9 (1.9-25.6); 0.004	4.7 (1.0-20.9); 0.044						
Pre-operative pericardial drainage	5.6 (1.4-21.8); 0.012							
Pre-operative creatinin			1.014 (1.006-1.021); <0.001					
Euroscore	1.020 (1.001-1.040); 0.043	1.024 (0.999-1.050); 0.060	1.057 (1.032-1.083); <0.001	1.047 (1.017-1.077); 0.002	1.043 (1.004-1.083); 0.032			
Urgency 1 vs 2-3			0.1 (0.0-0.2); <0.001		0.3 (0.2-0.6); 0.001	0.2 (0.1-0.6); 0.001		

Use of CPB							
None				ref		ref	ref
Passive shunt				2.0 (0.9-4.5); 0.114		-	-
Left heart bypass				0.8 (0.3-2.4); 0.678		0.121 (0.0-0.5); 0.004	0.103 (0.0-0.5); 0.005
Full bypass/DHCA				0.4 (0.1-1.2); 0.107		0.424 (0.1-1.5); 0.182	0.567 (0.1—2.2); 0.413
CPB time	1.005 (1.003-1.008); <0.001	1.006 (1.004-1.009); <0.001	1.006 (1.003-1.009); <0.001	1.006 (1.001-1.011); <0.012		1.006 (1.001-1.011); <0.012	
AoX time	1.006 (1.002-1.011); <0.001	1.006 (1.002-1.010); 0.004					
Use of circ arrest	0.5 (0.2-1.1); 0.091	1.9 (0.9-3.9); 0.083	3.4 (1.1-10.4); 0.029				
Glue use	0.5 (0.3-1.0); 0.039						
post-operative myocardial infarction		7.3 (2.2-24.4); 0.001					
post-operative CVA	3.1 (1.4-6.9); 0.006	8.2 (3.0-22.9); <0.001					
Post-operative dialysis	3.5 (1.5-7.9); 0.003	8.1 (2.4-27.6); 0.001		6.4 (1.8-22.3); 0.004	8.4 (1.7-41.6); 0.009	5.9 (1.8-18.9); 0.003	8.8 (2.2-35.2); 0.002

OR:odds ratio, CVA: cerebro-vascular accident, CPB: cardiopulmonary bypass, DHCA: deep hypothermia with circulatory arrest, AoX: aortic cross-clamp time

APPENDIX C.

Univariable and multivariable analysis on factors for late mortality.

	Group 1		Group 2		Group 3		Group 4	
Factor	Univariable HR (95% CI); p value	Multivariable HR (95% CI); p value	Univariable HR (95% CI); p value	Multivariable HR (95% CI); p value	Univariable HR (95% CI); p value	Multivariable HR (95% CI); p value	Univariable HR (95% CI); p value	Multivariable HR (95% CI); p value
Year of operation	0.977 (0.947-1.008); 0.142	0.960 (0.922-0.998); 0.041	0.957 (0.935-0.980); <0.001	0.937 (0.913-0.962); <0.001				
Age	1.039 (1.019-1.060); <0.001	1.046 (1.023-1.069); <0.001	1.051 (1.036-1066);<0.001	1.048 (1.032-1.065); <0.001	1.060 (1.041-1.080); <0.001	1.060 (1.041-1.080); <0.001	1.097 (1.041-1.155); 0.001	1.097 (1.041-1.155); 0.001
Gender (female vs male)			1.6 (1.1-2.2); 0.019					
TAR vs other					0.2 (0.1-0.5); <0.001			
Dissection type (1 vs 2)	1.5 (0.9-2.3); 0.094							
Acute CVA	2.7-(1.1-6.8); 0.031							
Prior myocardial infarction	2.1 (1.1-4.0); 0.024		2.5 (1.5-4.3); 0.001					
Hypertension	1.6 (1.0-2.5); 0.030		1.8 (1.2-2.5); 0.002		2.2 (1.4-3.4); 0.001			
Diabetes mellitus			4.3 (2.1-8.9); <0.001					
COPD	3.6 (1.7-7.7); 0.001	4.2 (1.9-9.3); <0.001	3.1 (1.9-5.2); <0.001		2.6 (1.4-4.7); 0.002	1.9 (1.0-3.5); 0.041		
Pre-operative creatinin	1.003 (1.002-1.005); <0.001	1.003 (1.002-1.005); <0.001	1.008 (1.003-1.012); 0.001	1.005 (1.000-1.010); 0.031				
Reduced LVF	3.9 (1.4-10.8); 0.011	6.2 (1.9-20.2); 0.002						
Pre-operative severe AI	0.6 (0.3-1.0); 0.045							
Euroscore	1.016 (1.000-1.032); 0.046		1.043 (1.025-1.060); <0.001	1.024 (1.004-1.045); 0.021	1.055 (1.028-1.083); <0.001			
Coronary artery disease			2.2 (1.4-3.3); 0.001					
Urgency 1 vs 2-3			2.2 (1.1-4.3); 0.026		2.2 (1.3-3.7); 0.003			
Use of circulatory arrest			1.7-(1.2-2.5); 0.005					

Aortic arch replacement						
None			ref			
Hemi-arch			1.5 (1.0-2.2); 0.059			
Full arch		2.9 (1.2-6.9); 0.015	3.0 (1.8-5.2); <0.001	1.9 (1.1-3.5); 0.026		
Post-operative myocardial infarction			7.9 (3.5-18.2); <0.001	5.6 (2.3-13.2); <0.001		
Post-operative CVA					2.3 (1.1-5.2); 0.003	
Post-operative renal dysfunction	2.5 (1.4-3.9); 0.001		2.2 (1.3-3.7); 0.003		2.1 (1.3-3.3); 0.002	

HR:Hazard ratio, TAR: traumatic aortic rupture, CVA: cerebro-vascular accident, COPD: chronic obstructive pulmonary disease, LVF: left ventricular function, AI: aortic insufficiency, CPB: cardiopulmonary bypass, DHCA: deep hypothermia with circulatory arrest, AoX: aortic cross-clamp time

APPENDIX D.

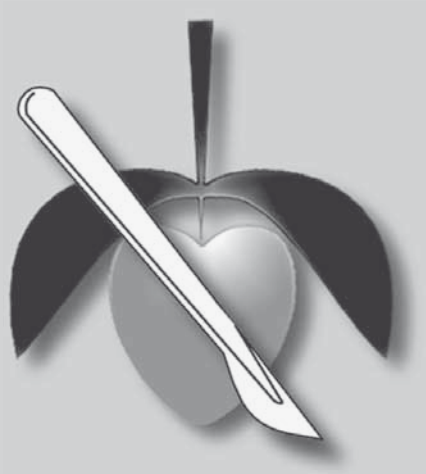
Reoperations

	Reoperations (%)	Type of reoperation	N
Group 1 (N=261)	48		
Aortic valve	19 (7.3)	replacement	8
		valved conduit	10
		allograft	1
Ascending aorta/arch	11 (4.2)	valved conduit	2
		ascending/arch replacement	9
Descending/THAA/ Abdominal	18 (6.9)	aortic replacement	17
		TEVAR	1
Group 2 (N=626)	43		
Aortic valve	9 (1.4)	AVR	9
Ascending aorta/arch	9 (1.4)	closure false aneurysm	5
		root replacement (mechanical/allograft) ± arch replacement	2
		arch replacement	2
Descending/THAA/ Abdominal	25 (4.0)	aortic replacement	23
		TEVAR	2
Group 3 (N=175)	18		
Ascending aorta/arch	7 (4.0)	Acute type 1 dissection	1
		Valved conduit	1
		ascending/arch replacement	5
THAA/abdominal	10 (5.7)	abdominal aortic replacement	8
		THAA	2
Other	1 (0.6)	CABG	1
Group 4 (N=97)	2		
Ascending aorta/arch	1 (1.0)	ascending/arch replacement	1
Descending	1 (1.0)	TEVAR	1

THAA= thoraco-abdominal aneurysm, TEVAR= thoracic endovascular aortic replacement, AVR= aortic valve replacement, CABG= coronairy bypass operation

Chapter 14

General discussion and future perspectives



INTRODUCTION

This thesis explored several aspects of thoracic aortic surgery, with an emphasis on aortic root surgery and on long-term results.

The results presented in this thesis will be discussed in the following paragraphs, focusing on aortic root replacement with human tissue valves and reoperations after these procedures, surgery for aortic dissection, aortic root dilatation surgery in patients with a recently discovered genetic syndrome and the overview of our 40 year experience with thoracic aortic surgery.

THE USE OF ALLOGRAFTS AND AUTOGRAFTS

Both a cryopreserved allograft and a pulmonary autograft have proven to be valuable methods for aortic valve replacement or aortic root replacement, not only for complex aortic root pathology, but also for isolated aortic valve pathology.[1,2] In our institution we started using allografts and autografts in 1987 for aortic valve or aortic root replacement, expecting these valve substitutes to provide excellent hemodynamic properties combined with a superior durability compared to biological valve prostheses and without the need for anti-coagulant treatment. In subsequent years we prospectively studied the results of these operations. In the initial years both a subcoronary implantation and full root replacement techniques for allografts were employed. The full root replacement showed to provide superior results compared to a subcoronary implantation, due to a reduced technical failure rate and subsequently became the preferred surgical method. For patients after aortic allograft implantation life expectancy is very acceptable, although reduced compared with the age- and gender-matched general population. This observation is a well-known phenomenon for patients after aortic valve replacement.[3] Further studies, especially on the association between pre-operative patient characteristics at the time of the primary operation and survival, will be necessary to elucidate this observation. For pulmonary autografts, on the other hand, patient survival is excellent. Long-term survival studies demonstrate survival to be equivalent to survival in the age- and gender-matched population. There is an ongoing debate whether this superior patient survival is caused by selection bias or by the superior hemodynamic performance of pulmonary autografts. A recent randomized controlled trial suggests that the latter is true[4], although observational studies suggest that patient selection is a major driver of the observed survival differences.[3,5,6]

In both allograft and pulmonary autograft patients the durability of the valve substitute is limited. In our allograft series we demonstrated an age-dependent hazard of structural valve deterioration, with a life-time risk of 70% for a 35 year old patient and 15% for a 65 year old patient. These hazards of valve deterioration were comparable with the hazards

reported in stented porcine or pericardial bioprostheses. In our autograft series we found increased reoperation rates in adults, compared to children less than 16 years.

In allograft recipients, the mode of allograft failure is degeneration and calcification, causing stenosis, regurgitation or a combination of the two. The median time to allograft deterioration necessitating a reoperation was 15 years. In pulmonary autograft patients the failure mode after operation is completely different: autograft root dilatation, often in combination with aortic valve insufficiency. The median time to autograft failure was 15 years.

Because allografts and pulmonary autograft carry an increasing hazard for valve deterioration, lifelong careful follow-up is indicated. In our prospective institutional clinical follow-up, combined with biennial echocardiography, possible valve failure can be detected in an early phase, with the possibility of a well-planned elective reoperation.

These findings have had significant implications in our preferences for certain types of valve substitutes. The aortic allograft lost a part of its popularity due to its limited durability and significant need for reoperations, in particular in younger patients. For isolated aortic valve replacement other alternatives are preferred, unless anticoagulant therapy is contra-indicated or the patient has a strong preference for a biological valve substitute. For patients with complex aortic root pathology or destructive endocarditis, however, the use of an aortic allograft may still be the preferred valve substitute because aortic allografts provide superior possibilities for reconstruction of the aortic root and are relatively resistant to endocarditis. The pulmonary autograft is still seen as the only attractive option for aortic valve replacement in young, growing, patients. Its use combines the advantages of a viable valve substitute, able to accommodate to the increasing body size, with excellent hemodynamic properties and no negative effect on life expectancy. For most patients a reoperation will be necessary at an adult age, allowing for a definitive type of valve replacement at reoperation or, in selected cases, a valve-sparing aortic root replacement.

REOPERATION AFTER AORTIC ALLOGRAFT OR PULMONARY AUTOGRAFT IMPLANTATION

For patients after allograft or autograft implantation in the aortic root, longer follow up is associated with an increase in re-interventions due to valve failure of autograft dilatation in the second decade after operation.

Although reoperations after previous heart surgery and in particular, aortic root replacement are complex and technically demanding, the results in this thesis show that these can be performed with very satisfactory results. One of the principal requirements for a successful operation is a safe reopening of the chest. In patients with a dilated pulmonary autograft, the autograft or the aorta may be adherent to the posterior aspect of the

sternum. Aortic allografts have no tendency to dilate, but may form severe calcification of the allograft aortic wall with severe adhesions to the posterior sternum. Pre-operative CT-scanning provides valuable information on the anatomic relations in the chest when preparing these patient for a reoperation. In patients in whom difficulties in reopening the chest are anticipated, elective institution of cardiopulmonary bypass with femoral vessel canulation might prevent extra risks in reopening the chest. This prevents emergency institution of cardiopulmonary bypass due to accidental injury of the aorta or the pulmonary artery.

In reoperations after allograft root replacement, implantation of a new valve prosthesis within the allograft may be possible, but the severe aortic wall calcifications will usually make a new root replacement inevitable. Usually it is possible to resect all allograft material and use the original aortic valve annulus to implant an as large as possible valved conduit.

In pulmonary autograft reoperations it is worthwhile to attempt to salvage the autograft valve leaflets, provided that autograft root dilatation and not structural valve dysfunction is the cause of autograft valve insufficiency. Valve sparing techniques may be used in these patients. Alternatively, implantation of a valved conduit may be the technique of choice.

In reoperative aortic root replacement, the preparation of the previously reimplanted coronary buttons requires special attention. Due to scarring, preparation and mobilization of the coronary buttons may be troublesome, leading to coronary artery injury, necessitating local repair or revascularization using coronary bypasses.

Although reoperations after previous aortic valve, aortic root or ascending aortic surgery are complex and technically demanding, these reoperations can be performed relatively safely. Although most authors consider reoperations on the aortic root high risk operations with high reported mortality rates [7-9], we were able to perform these operations with a very low and acceptable mortality. Moreover, in both the series of reoperations after allograft implantation and pulmonary autograft implantation we found the early mortality (3.9% and 0% respectively) to be less than after the initial operations.

AORTIC DISSECTION

Aortic dissection is a vascular emergency with a very high mortality if left untreated. Emergency operation is the only available therapy to save a patient's life. We found an important decline in early mortality in our total 40 year experience. The 30 day mortality after surgery for acute ascending aortic dissection decreased from over 30% before 1985 to 12.5% in the most recent era 2007-2011.

The risk of early mortality is partly related to the pre-operative condition of the patients. Increased understanding of the underlying pathology of acute aortic syndromes, improvements in diagnostic tools, using echocardiography and rapid CT scanning techniques and

adequate stabilization of patient, followed by an emergency operation were significant evolutions in time. Furthermore, the improvement in early mortality over time is related to advances in operative techniques used. The use of deep hypothermic circulatory arrest and an open distal anastomosis technique and the use of biological glue to reconstruct the dissected aortic wall layers are associated with a lower early mortality. In operating a patient with an acute ascending aortic dissection, the essential element in the operation is the reconstruction and replacement of the ascending aorta, but additional replacement of the aortic valve or aortic root may be required. In our series we were able to preserve the patients' aortic valve in two-thirds of the patients. We prefer to preserve the aortic valve in order to prevent the inherent risk of a valve replacement, although we found an increased risk for late reoperations in patient presenting with severe aortic insufficiency preoperatively.

Survival of patients after a successful operation is satisfactory, although reduced in comparison with the general population. On the other hand, we found a comparable reduction in survival in patients who underwent other types of heart surgery. Pre-operative patient characteristics and risk factors, reducing late survival, are probably of influence on this observed reduced late survival.

Patients after successful operation for acute aortic dissection are not "cured" from their disease. After DeBakey type 1 dissection, residual dissection of the descending or thoraco-abdominal aorta may require a reintervention in a substantial proportion of patients.

TRENDS AND DEVELOPMENTS IN THORACIC AORTIC SURGERY

The last part of this thesis provides a complete overview of our institutional experience with thoracic aortic surgery. We analyzed 1159 operation on the thoracic aorta in 1075 patients in four decades, beginning in 1972. In this time period we found a significant increase in the number of operations performed annually. At present the number of thoracic aortic operations constitutes approximately 10% of the total workload of our department of cardio-thoracic surgery. Over time we found important changes in pathology and patient profiles. Early in our series predominantly symptomatic patients were operated emergently or acutely on the descending aorta. Gradually this patient profile shifted toward asymptomatic patients who underwent elective ascending aortic surgery. A greater awareness of the risks of asymptomatic aortic aneurysms, combined with advancement of diagnostic tools has led to earlier referral of patients with often only limited dilatation of the aorta, for elective surgery. Knowledge of inherited diseases, both syndromic and non-syndromic, causing aortic dilatations has increased over time, in combination with the introduction of genetic diagnostic tools. In some of these familial syndromes very aggressive forms of aortic dilatations, with acute dissections occurring at only slightly enlarged aortas have been

described. As an example, the recently discovered Aneurysms-Osteoarthritis Syndrome, caused by a mutation in the SMAD3 gene, is an autosomal dominant disease with an impressive number of family members with fatal aortic dissections at only minimally dilated aortas. Screening of family members and early prophylactic surgery when the SMAD3 mutation is present is strongly advised in these families. Nine patients with a SMAD3 mutation and a dilated aortic root underwent a successful valve sparing aortic root replacement.

Other factors influential in the changes in the patient population that require surgery for aortic aneurysms are new catheter based techniques for aortic replacement, thoracic endovascular aortic replacement (TEVAR). The introduction and development of these elegant techniques have enormously expanded possibilities for the treatment of descending aortic pathology. Traumatic aortic ruptures, constituting 20% of patients operated on the descending aorta, are at present preferably treated endovascularly. Since 2002 no conventional surgery for traumatic aortic ruptures has been performed in our institution. For descending aortic aneurysms, the possibilities for TEVAR are increasing, leading to a shift away from open surgery. For chronic descending aortic dissections and the more extensive thoraco-abdominal aneurysms, conventional surgery still is the most appropriate treatment option.

In analyzing our series of thoracic aortic surgery we found an impressive decline in early mortality from over 50% in the early 1970's to less than 5% in the present era 2007-2011. We analyzed four patients groups: acute ascending aortic dissection, ascending aortic or arch pathology other than acute dissection, descending aortic surgery and thoraco-abdominal surgery. In all four patient groups we observed a significant decrease in early mortality over time. The mortality in the most recent era 2007-2011 was 15% for acute dissections, 2% for other ascending aortic/arch pathology, 0% for descending aortic surgery and 10% for thoraco-abdominal aortic surgery. These results are very comparable to other reported series of various types of aortic surgery,[10-13] and may serve as a reference in advising patients and referring specialists on the indications for aortic surgery.

Data on long-term survival after thoracic aortic surgery are rare. In our overview study on thoracic aortic surgery we analyzed long-term survival after various operations on the thoracic aorta. Similarly to the early mortality, late survival improved in the more recent years for all 4 patients groups. Late survival was best after surgery for ascending aortic/arch surgery and worst after thoraco-abdominal surgery. Differences in patient characteristics, but also the more extensive nature of the aortic pathology determine these differences in late survival. Late survival was reduced, in comparison with the general population. In further analyzing late survival of the most contemporary patient group operated for elective ascending aortic or aortic arch aneurysms, we found a relatively small reduction in 10 years survival compared with the age- and sex-matched general population. For this group of patients this information on life expectancy after operation are relevant in in weighing the risks of surgery and a further conservative treatment in the presence of an aortic aneurysm.

FUTURE PERSPECTIVES

Based on the studies in this thesis, we gained further knowledge on the durability of aortic allografts and pulmonary allografts and techniques for reoperations, the surgery for acute aortic dissections and general trends and results in thoracic aortic surgery, which will serve as a guide for further studies and new technological developments.

For patients with aortic valve or aortic root diseases, the explicit knowledge on long-term performance and failure modes of aortic allografts and pulmonary autografts is helpful in choosing the optimal valve substitute for patients who require aortic root replacement. Patients can be advised more precisely about the expectations after different types of operation and be more involved in the choice of their preferred type of heart valve replacement. Especially in pulmonary autograft implantation modifications in surgical technique are explored in order to prevent early autograft failure and prevent or delay reoperations.[14-16]

For patients with asymptomatic aortic aneurysms, especially those with genetic aortic disease, more thorough insights of the natural behavior and risks of complications will be helpful in offering tailor made advise on the optimal timing of prophylactic surgery. Microsimulation models have previously been used to compare long-term outcome after different types of aortic valve replacement.[17-19] The availability of long-term survival data after surgery, combined with data on long-term risks of death or complications of an aortic aneurysm, will enable the development of risk models to help advising patients in the choice of the optimal strategy once the diagnosis of an aortic aneurysm has been made.

In patients with acute aortic dissection there is little doubt, that an emergency operation is the only viable option to save a patient's life. A greater awareness of the possibility of an acute aortic dissection in patients with acute chest pain, rapid diagnostics, including the use of biomarkers[20] and advanced imaging may prevent delay in referral of patients for acute surgery and bring them to the operation room in a better condition, with a better chance of a favorable outcome after surgery. In the conduct of the operations, the primary goal will be to save a patient's life, but surgeons must have the long-term outcome after the operation in mind. We found a considerable proportion of patients requiring additional procedures after initial successful operation, both on the proximal aorta and the distal aorta. Catheter based stent-grafts to obliterate the false lumen in the descending aorta at the primary operation are attractive new techniques in the treatment of acute aortic dissections.[21] Further experience with these techniques will have to prove, whether these new options are advantageous in improving late outcome after operation, without compromising the early results.

Catheter based interventions on the thoracic aorta are emerging after successful introduction in the abdominal aorta. In this rapidly evolving field the present limitations in the applicability of thoracic endovascular aortic replacement (TEVAR) are the need for

sufficient length landing zones for successful and durable stent-graft placement and the need for revascularization of side branches of the aortic arch and the abdominal aorta. A possible solution to overcome the need for direct revascularization of these arteries is the use of a hybrid procedure in which extra-anatomic revascularization of the involved vessels is followed by stent-graft placement in the aorta. These procedures have been described for aortic arch[22] and abdominal aortic[23] pathology. It is further expected that future technological developments will expand the applicability of endovascular techniques for the more complex pathology. Stent-grafts with side branches may be applicable for descending aortic pathology involving the aortic arch and possibly provide alternatives in thoraco-abdominal aneurysms.

Future studies, both on the conventional approach of aortic disease with open surgery as well as on the new endovascular treatment options, not only on early surgical results but also on procedural durability and late patient outcome will delineate the merits of both types of procedures. Close cooperation of surgeons trained in open, conventional surgery and those involved in modern catheter techniques will be required and is essential in selecting the optimal treatment for each individual patient.

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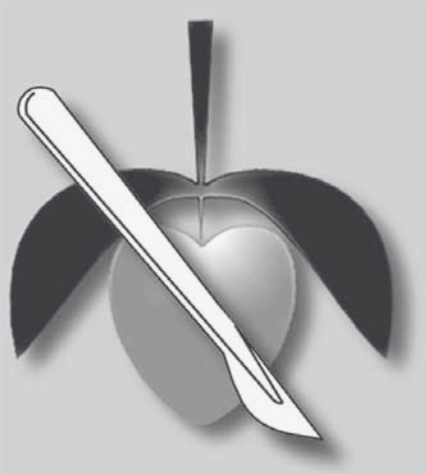
Chapter 15

Summary, samenvatting



SUMMARY

In this thesis we have studied several aspects of thoracic aortic surgery during a time period of four decades.

Chapter 1 is the general introduction. An overview of basic anatomy, pathology and surgery of the aorta is provided and the aim of the thesis outlined.

Chapter 2 describes the results of 275 aortic allograft implantations with a follow-up duration of 13 years. Patient survival (73% at 9 years) was found to be satisfactory, but the durability of the allografts is limited (freedom of reoperation of 77% at 9 years), despite improvements in operative technique.

Chapter 3 further updates the allograft series to a total follow-up duration of 18 years. In a microsimulation model patients receiving allografts were compared with patients receiving stented bioprosthesis. The incidence of valve related complications is low in allograft patients compared with bioprosthesis patients, but the durability of aortic allografts (freedom of structural valve deterioration 77% at 12 years) is comparable to the durability of conventional aortic bioprosthesis.

Chapter 4 describes the use of aortic allografts and pulmonary autografts in young adult patients with congenital aortic valve disease. Early and long-term survival of the patients was comparable to the general population, but we found a high incidence of valve deterioration requiring reoperation. The freedom of reoperation was 63% after 13 years after autograft procedure and 69% at 13 years after allograft operation).

Chapter 5 Describes long term results of the pulmonary autograft operation. The survival of the patients and quality of live proves to be excellent, although the durability of the autograft is limited and reoperations in the second decade after implantation are frequently required with a freedom from reoperation of 69% at 13 years.

Chapter 6 summarizes the total experience of reoperations after previous aortic valve replacement or ascending aortic or aortic root replacement with various types of conduits. Overall operative mortality was acceptable (9 %), but higher for patients after previous prosthetic valve replacement (14%) or allograft implantation (13%), than for patients with their native valve in situ (6%) or after pulmonary autograft implantation (0%).

Chapter 7 provides further information on the durability of aortic allograft root replacement and detailed information on reoperations. The freedom reoperation is 56% after 14 years. Reoperations are technically demanding for the surgeon, but can be performed with a low mortality (4%) and complication rate.

Chapter 8 describes the long-term experience with pulmonary autografts. Long-term durability and the need for reoperations (48% at 15 years) and technical details of the reoperations are further analyzed.

Chapter 9 is the symposium discussion on the presentation on aortic root reoperations after pulmonary autograft implantation.

Chapter 10 provides a general overview on acute aortic dissection, describing the pathology, presentation and basic principles of the operative treatment.

Chapter 11 further describes the experience with acute ascending aortic dissections. The early mortality declined over time from over 50% in the early experience to 12% at present, and was mainly determined by preoperative patient factors and improvements in surgical technique.

Long-term survival after successful operation was 68% at 10 years and 37% at 15 years. Reoperations on the aortic valve or the aorta were necessary in 43 of 185 hospital survivors. Furthermore we determine the risk factors for these reoperations.

Chapter 12 describes the early clinical findings and results of surgery in the recently discovered Aneurysms-Osteoarthritis-Syndrome, caused by a mutation in the SMAD3 gene.

Chapter 13 presents the complete 40 years' experience with thoracic aortic surgery in the Erasmus University Medical Center. The annual number of operations increased significantly over time from less than 10 per year in the early experience to 100 per year at present and we found major changes in patient profiles. The early results after these operations in four patients groups analyzed improved greatly over time from 50% mortality in the early experience to 5% at present. Long-term survival in these four patient groups was 54% after 10 years and 28% after 20 years, reduced compared to the general population. Late survival improved over time. Multiple operations were required in 80 patients.

Chapter 14 provides a general discussion on the subject.

SAMENVATTING

In dit proefschrift hebben wij diverse aspecten van thoracale aorta chirurgie gedurende een periode van 40 jaar bestudeerd.

Hoofdstuk 1 is de algemene introductie. Een overzicht over anatomie, pathologie en chirurgie van de aorta wordt gegeven en het doel van de studies beschreven.

Hoofdstuk 2 beschrijft het resultaat van 275 implantaties van menselijke donorkleppen met een follow-up duur van 13 jaar. De overleving van patienten is goed (73% na 9 jaar), maar de duurzaamheid van de donorkleppen is beperkt (vrijheid van reoperatie 77% na 9 jaar), ondanks verbeteringen in de gebruikte operatietechniek.

Hoofdstuk 3 geeft aanvullende informatie over de donorklepserie tot een follow-up duur van 18 jaar. Met een microsimulatiemodel worden patienten die een donorklep implantatie ondergingen vergeleken met patienten de een gestente bioprothese kregen. In de donorkleppatienten is de incidentie van klep-gerelateerde complicaties laag in vergelijking met bioprothese-patienten, maar de duurzaamheid van de donorkleppen (vrijheid van structureel klepfalen 77% na 12 jaar) is vergelijkbaar met die van conventionele aortale bioprothesen.

Hoofdstuk 4 beschrijft het gebruik van aorta donorkleppen en pulmonalis autografts in jonge volwassenen met een aangeboren aortaklep vernauwing. Vroege en late overleving van de patienten waren vergelijkbaar met de algemene bevolking, maar wij vonden een hoge incidentie van hartklepslijtage, waarvoor een nieuwe operatie noodzakelijk was. De vrijheid van reoperatie was 63% na 13 jaar na autograft implantatie en 69% na 13 jaar na donorklep implantatie.

Hoofdstuk 5 beschrijft de lange termijn resultaten van de pulmonalis autograft operatie. De overleving van de patienten en de kwaliteit van leven zijn uitstekend, maar de levensduur van de kleppen is beperkt en heroperaties in de 2^{e} decade na implantatie zijn vaak noodzakelijk met een vrijheid van reoperatie van 69% na 13 jaar.

Hoofdstuk 6 geeft een samenvatting van de totale ervaring met heroperaties na eerdere aortaklep vervanging, aorta ascendens vervanging of aortawortel vervangingen met verschillende typen klepprothesen. De operatiesterfte in de totale groep was acceptabel (9%), maar hoger na eerdere aortaklepvervanging (14%) of donorklepimplantatie (13%) en lager in patienten met hun eigen aortaklep (6%) of na pulmonalis autograft implantatie (0%).

Hoofdtuk 7 geeft nadere informatie over de duurzaamheid na aortawortelvervanging met een donorklep en verdere details over de heroperaties. De vrijheid van reoperatie is 56% na 14 jaar. De heroperaties zijn een technische uitdaging voor de chirurg, maar kunnen met een lage sterfte (4%) en lage kans op complicaties worden uitgevoerd.

Hoofdstuk 8 beschrijft de lange termijn ervaring met pulmonalis autograft implantaties. De duurzaamheid na implantatie, frequentie van heroperaties (48% na 15 jaar) en technische details van de heroperaties worden verder geanalyseerd,

Hoofdstuk 9 is de symposium discussie na de voordracht over aortawortel reoperaties na pulmonalis autograft implantatie.

Hoofdstuk 10 geeft een algemeen overzicht van de totale ervaring met acute aorta dissecties met een beschrijving van pathologie, presentatie van de patienten en de algemene pricipes van de operatieve behandeling.

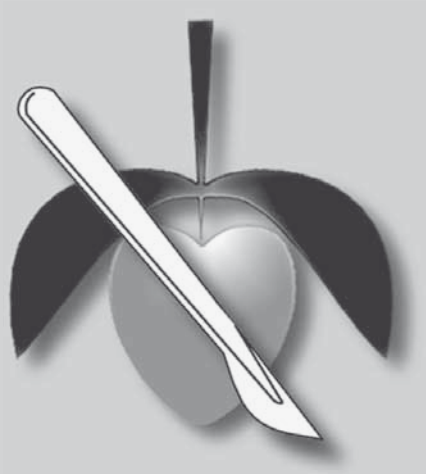
Hoofdstuk 11 geeft nadere informatie over acute aorta dissecties. De vroege sterfte na operatie nam in de loop van de tijd af van meer dan 50% tot 12% in de meest recente jaren en werd voornamelijk bepaald door pre-operatieve patienten kenmerken en verbeteringen in operatie techniek. De late overleving na een geslaagde operaties was 68% na 10 jaar en 37% na 15 jaar. Bij 43 van de 185 patienten die na operatie overleefden waren heroperaties aan de aortaklep of de aorta noodzakelijk. Risico factoren voor deze reoperaties worden verder geanalyseerd.

Hoodfstuk 12 beschrijft de eerste klinische gegevens en resultaten van operaties bij het recent ontdekte "Aneurysma-Osteoarthritis-Syndroom", veroorzaakt door een mutatie in het SMAD3 gen.

Hoofdstuk 13 presenteeert de totale ervaring met operaties aan de thoracale aorta in het Erasmus MC gedurende 40 jaar. Het aantal operaties per jaar is belangrijk toegenomen van minder dan 10 operaties in de beginjaren tot 100 operaties per jaar in de huidige tijd. Er waren belangrijke verschuivingen in patienten profielen. De vroege resultaten na de operaties werden in geanalyseerd in 4 patienten groepen en verbeterde sterk van meer dan 50% vroege sterfte in de eerste jaar van de serie tot 5% in de meest recente periode. De late overleving in deze 4 patienten groepen was 54% na 10 jaar en 28% na 20 jaar, hetgeen lager is dan in de algemene bevolking. Deze late overleving verbeterde in de loop van de tijd. In 80 patienten werden meerdere operaties verricht.

Hoodfstuk 14 is de algemene discussie en bespreekt toekomstige ontwikkelingen en mogelijkheden voor nader onderzoek.

Curriculum Vitae



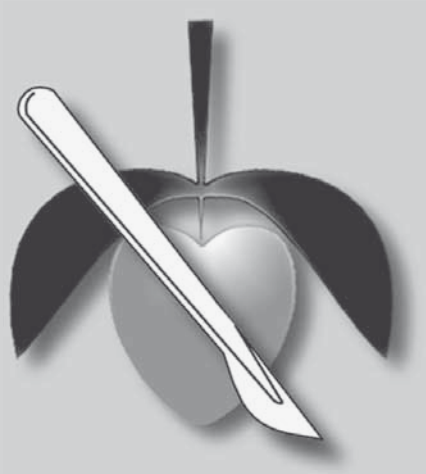
Jos Bekkers werd op 3 maart 1959 geboren in Haarlem. De middelbare school werd gevolgd op het Mendel College te Haarlem, waar het Gymnasium B diploma werd behaald in 1977. Hij studeerde Geneeskunde aan de Universiteit van Amsterdam en behaalde het doktoraalexamen op 5 juli 1983 en het artsexamen op 19 juni 1985.

Na een korte periode als assistent chirurgie in het Diaconessen ziekenhuis te Heemstede werkte hij ruim 1 jaar als assistent op de afdeling Thoraxchirurgie van het toenmalige Dijkzigt ziekenhuis, thans opgegaan in het Erasmus MC.

Van 1 oktober 1986 tot 31 september 1988 werd de opleiding algemene Heelkunde gevolgd in de Mariastichting te Haarlem (opleider B. Lether). Hierna volgde de speciele opleiding Cardio-thoracale Chirurgie in het Erasmus MC (opleider Prof.dr. E. Bos). De registratie als Cardio-thoracaal Chirurg vond plaats op 1 oktober 1992.

De auteur bleef als staflid werkzaam op de afdeling Thoraxchirurgie van het Erasmus MC. Naast de algemene hart- en longchirurgie heeft hij zich verder toegelegd op de thoracale aortachirurgie, de transplantaties van hart en longen en implantaties van kunstharten.

Publications



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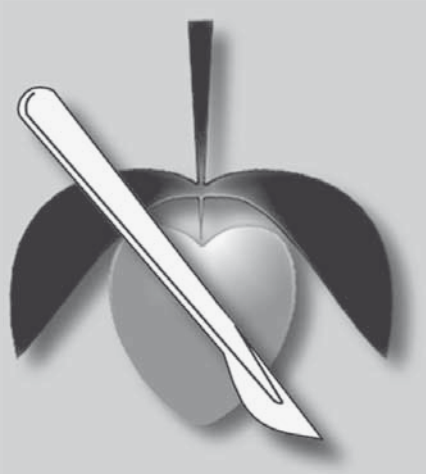
Dankwoord



Het voltooien van je proefschrift is een mooi moment om even in gedachten stil te staan. Aangezien de promotie beschouwd kan worden als de uiteindelijke voltooiing van de academische opleiding is het goed terug te gaan naar de aanvang daarvan.

Als eerste wil ik mijn ouders bedanken. Zij hebben voor het juiste genetische pakket in mij gezorgd en, minstens zo belangrijk, voor de juiste opvoeding en stimulans. Jullie hebben mij altijd aangespoord en gesteund op school, tijdens studie en later in het werk en daarmee ervoor gezorgd dat dit boekje er is gekomen. Helaas in mijn vader al lang geleden overleden, maar ik weet zeker dat hij dit werk met gepaste trots zou bekijken. Daarom is dit proefschrift aan hem opgedragen. Lieve moeder, jij hebt lang in je eentje het gezin gerund en bent altijd zeer betrokken en geïnteresseerd. Ik ben erg trots op je.

Dan wil ik de vele mensen die betrokken zijn geweest bij opleiding, werk en het onderzoek dat zich gedurende vele jaren heeft afgespeeld bedanken:

Hooggeleerde Bogers, promotor. Beste Ad, jij bent de aanvoerder van de troepen op onze geweldige afdeling Thoraxchirurgie van het Erasmus MC. Als hoofd van de afdeling ben jij onze manager, maar dat is niet wat jij het leukste werk vindt. De klinische praktijk en anderen om jou heen stimuleren in hun werk en onderzoek geeft jou het meeste plezier en je bent daar ontzettend goed in. Het is een voorrecht onder jouw leiding te werken en uiteindelijk te promoveren

Zeergeleerde vrouwe Takkenberg, co-promotor. Beste Hanneke, jij vormt de wetenschappelijke spil van onze afdeling. Het is een unicum dat een klinische afdeling een zo excellente onderzoeker aan zich verbonden weet die ook kans ziet vele anderen te enthousiasmeren en mee te slepen in de wereld van nadenken over resultaten van het werk, opzetten van onderzoek, bewerking van de gegevens en uiteindelijk opschrijven en publiceren. Het moment dat ook jij een toga en baret mag uitzoeken is zeer nabij en uitermate verdiend.

Hooggeleerde Bos, emeritus hoogleraar Cardio-thoracale Chirurgie. Beste Egbert. Het is een voorrecht geweest door jou in ons mooie vak opgeleid te zijn. Natuurlijk is het belangrijk een chirurg de benodigde technische vaardigheden aan te leren, maar voor jou was al lang voor het competentie gerichte onderwijs vanzelfsprekend, dat voor goede patiënten zorg veel meer kwaliteiten noodzakelijk zijn. Een ogenschijnlijk terloopse opmerking over nazorg voor patiënten die aan de aorta geopereerd waren heeft tot het opzetten van onze aortapoli geleid en mijn belangstelling voor de aortachirurgie gewekt.

Hooggeleerde Zijlstra. Beste Felix, jouw terugkeer naar het Erasmus MC heeft de afdeling Cardiologie een nieuw elan gegeven. Met jouw duidelijke stellingnames en heldere formuleringen kunnen onze beider afdelingen naar een mooie toekomst vooruit zien. Ik bedank

je zeer, dat je het manuscript hebt willen beoordelen als lid van de promotiecommissie en bereid me nu al voor op een kritische bevraging.

Hooggeleerde Mochtar. Beste Bas, jij was reeds een ervaren staflid op onze afdeling, toen ik als beginnend assistent naar Rotterdam kwam. Veel heb ik van je geleerd, vooral om operaties niet nodeloos ingewikkeld te maken. Tijdens het schrijven van dit proefschrift, dacht ik af en toe aan het door jou soms voor een operatie gebezigde: "ik wou dat het al klaar was". Het is een eer dat jij in mijn promotiecommissie wil zitten.

Hooggeleerde Verhagen. Beste Hence, jouw komst naar het Erasmus MC heeft de afdeling vaatchirurgie veel goeds gebracht. Het vaardig werken met catheters en stent-grafts in plaats van brute operaties is voor velen een uitkomst. Maar jij houdt zeker een open oog voor de kwaliteiten van de ouderwetse open benadering. Regelmatig bespreken wij wat voor een ingewikkeld probleem de beste oplossing zou kunnen zijn en voeren dat dan ook nog in goed teamverband uit. Stelling 7 is onze vaste praktijk.

Hooggeleerde van Herwerden. Beste Lex, ook jij was zeer vormend voor mij in ons vak. Jouw kritische blik naar onderzoek en vasthoudendheid bij de moeilijkste operaties zijn altijd een voorbeeld geweest. Mijn eerste serieuze kennismaking met onderzoek was samen met jou en heeft geleid tot de microsimulatiemodellen die nog steeds van grote waarde zijn. Samen in het bestuur van de NVT en nu in de dataregistratie commissie werken wij aan goede analyse en verslaglegging van ons werk.

Hooggeleerde vrouwe Roos. Beste Jolien, jouw werk op gebied van aangeboren hartafwijkingen, aortaklepziekten en vooral de aortapathologie brengt uiteindelijk vele patiënten naar onze operatietafel. De ontwikkelingen op dit gebied de laatste jaren zijn enorm en de samenwerking tussen onze afdelingen zeer intensief. We kunnen hier nog jarenlang veel plezier aan beleven.

Zeergeleerde Hofland, beste Jan. Samenwerken met een cardio-anaesthesioloog is een noodzakelijk goed in ons vak. Het is een eer voor mij, dat jij als uiting daarvan in de promotiecommissie hebt willen plaatsnemen.

Mijn collega stafleden van de afdeling Thoraxchirurgie ben ik zeer dankbaar voor hun enorme steun en vriendschap. Wij werken al vele jaren in een hecht team, waarbij vooral ook de zorg voor elkaar essentieel is. Als het in werk of privé even moeilijk is, zie je meteen wie er voor je klaar staan en dan zijn jullie er altijd.

Lex Maat ken ik sinds onze gedenkwaardige eerste dienst in 1985. Jij als co-assistent en ik als trillende assistent. Daarna zijn we samen opgetrokken in de opleiding en als jonge

stafleden en inmiddels hebben we iedere onze eigen terreinen verder ontwikkeld. Jij hebt zoveel kennis over kunstharten en longchirurgie dat het onvermijdelijk ook ooit tot een schriftelijk verslag moet leiden.

John Bol-Raap bleek als co-assistent reeds een fijn gevoel voor de aorta te hebben, toen hij bij het krachtig knopen van een draad plotseling een half bloedvat in zijn handen had. Het is allemaal goed gekomen en jij bent alweer jaren mijn "partner in crime" in de aortachirurgie. Daarom ben ik ook erg blij dat jij mijn paranimf wil zijn.

Charles Kik is ons voorbeeld in creatieve oplossingen bedenken. Voor elk probleem weet hij iets in elkaar te knutselen, al is het thuis in de schuur. Jij weet ons altijd weer te verrassen en hebt altijd weer iets moois gemaakt, soms nog om te eten ook.

Peter de Jong is ook al een oude bekende uit onze opleidingstijd. Jij bent een voorbeeld van structuur en precisie. Een plan wordt goed uitgedacht en daarna nauwkeurig uitgevoerd. Dit keer geen gevaarlijke sporten gaan doen en afbellen voor het feest!

Arie-Pieter Kappetein is onze reizende ambassadeur die kans ziet 48 uur werk in 24 uur te verzetten en dan ook nog tijd te houden voor plezier en vriendschappen te onderhouden. Jouw internationale activiteiten zijn voor ons allen van groot belang te je vergeet zeker niet je collega's mee te slepen in de vaart der volkeren. Als jij ooit stopt met werken, zal dat desastreuze gevolgen voor de financiële positie van de KLM hebben.

Frans Oei is de angry young man in onze groep, die alles wil en alles kan. Een groot talent in het vak en daarnaast een aimabele persoonlijkheid. Met jouw lef en blik vooruit gaan we nog veel mooie ontwikkelingen tegemoet zien.

Pieter van de Woestijne is de langste van de groep, maar schuwt het kleine werk niet. Jouw rust en overzicht zijn bewonderenswaardig. Wij zullen nog regelmatig samen iets moois van een lastige aortawortel gaan maken.

Ozcan Birim is onze jongste aanwinst. Als student al zeer gedreven, inmiddels als chirurg iemand met een scherpe eigen visie. Jij weet je razendsnel in iets nieuws in te werken en wil dan meteen vol gas verder gaan.

Han Spierenburg, mijn andere paranimf, ken ik al sinds onze ontmoeting in het Zeeweg Ziekenhuis in Velsen. Jij als assistent interne Geneeskunde, ik als co-assistent Chirurgie. Wij werden allebei opgesteld in het hockeyteam van het ziekenhuis. Daarna bleven onze paden zich kruisen, totdat jij in Schiedam terecht kwam en ik in Rotterdam. Naast de goede professionele contacten zijn de recidiverende skivakanties met onze beide families en de educatieve duikreizen altijd een genoegen. Het is mij een eer, dat jij op deze bijzondere dag naast mij staat.

Meindert Taams, thans cardioloog in Leeuwarden, staat aan de basis van de huidige aortapoli. Door vele patiënten samen te bekijken heb ik geleerd vooral praktisch en concreet te zijn bij ingewikkelde keuzes. Nog steeds vragen patiënten op de poli naar Dr. Taams.

Vele studenten en onderzoekers hebben bijgedragen aan de onderzoeken in dit proefschrift, waarvan ik er 2 met name wil noemen:

Elmer Naaktgeboren was de eerste student die verder onderzoek naar aortaoperaties wilde doen. Hij heeft in 1999 de aortadatabase gemaakt, die nu nog steeds gebruikt wordt en waaruit de gegevens van alle aortaoperaties vanaf het begin van ons centrum geanalyseerd kunnen worden.

Loes Klieverik was als onderzoekster op onze afdeling onze kamergenoot en toen wij samen een artikel bekeken over reoperaties aan de aortawortel bedachten wij: "dat kunnen wij veel beter". Of dat helemaal waar is weet ik niet, maar het was wel de aanzet voor een serie artikelen over dit thema en het echte begin van het werk aan dit proefschrift.

Onze afdeling mag zich gelukkig prijzen met een geweldige ondersteuning door ons secretariaat, planningsbureau, onderzoekssecretariaat en datamanagement. Annet Damhuis, Rianne Kalkman, Caroline van der Burg, Jos Pieters, Maureen Lioe-A-Tjam, Marijke van de Vijver, Ria Hussaarts, Sylvia van der Velde, Marja Boks, Usha Jadoenath, Liesbeth Duininck, Liz van der Velden, Angeliek Venema, Els Berenschot, Solita Troost en Marjon de Groot zijn betrokken geweest bij vele aspecten van dit werk. De planning van operaties en regelen van polibezoeken, opvragen van statussen, verzamelen van data en het compleet krijgen van de laatste ontbrekende stukjes, aanvragen van METC toestemmingen, achterhalen van GBA gegevens en overlijdensoorzaken, analyse van vele getallen en alles wat ik nog vergeten ben. Ik wil jullie hier heel hartelijk voor bedanken.

Zonder toegewijde cardio-anaesthesiologen is ons vak onmogelijk. Ik wil Dries van der Woerd, Christian Luthen, Carsten Preis, Jenny Kissler, Annewil van Saet, Inge de Liefde, Anke de Bruijn, Thierry Scohy, Xavier Orellana Ramos, Kris Vermeylen en ook Rene Hagenouw bedanken voor hun kennis, kunde, zorg en ook geduld en vasthoudendheid waarmee we vele uren samen hebben doorgebracht

De vele (oud) assistenten Thoraxchirurgie wil ik bedanken voor jullie hulp bij operaties, maar vooral ook de toewijding in het werk en gezelligheid in de loop van de jaren. Velen van jullie zijn inmiddels uitgevlogen, maar zeker niet vergeten en zorgen altijd weer voor een gezellig weerzien, soms op verafgelegen plaatsen.

Een operatieteam kent vele teamspelers: alle operatie-assistenten, anaesthesie-medewerkers en perfusionisten wil ik heel hartelijk bedanken voor jullie kunde, enthousiasme, steun, en vrolijkheid in vele jaren samenwerking. Wat jullie doen is echt niet gemakkelijk en jullie zijn er erg goed in.

Na een mooie operatie wordt de verdere zorg toevertrouwd aan de artsen en verpleegkundigen van de Intensive Care en Medium Care afdelingen. Met groot respect en dank kijk ik naar het werk dat jullie voor onze patiënten verzetten. Soms zijn ze lang te gast op jullie afdelingen, maar juist dan zullen jullie er alles aan doen om te zorgen voor een uiteindelijk goed herstel.

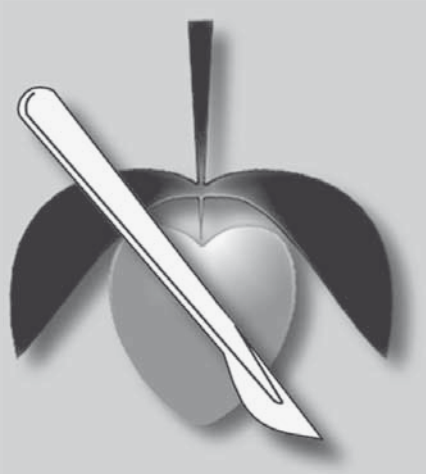
Alle (kinder)cardiologen in ons ziekenhuis wil ik bedanken voor de goede samenwerking, onontbeerlijk voor de top patiëntenzorg die wij nastreven. Hierbij wil ik ook alle cardiologen uit de regio en daarbuiten bedanken voor de soepele samenwerking en plezierige contacten.

Mijn zussen Loes en Marieke en mijn helaas te vroeg overleden broer Wouter dank ik voor de hechtheid van onze familie. Iedereen heeft het druk en is altijd in de weer, maar we houden elkaar goed in de gaten en vinden altijd een manier om met onze kinderen iets te organiseren of te vieren. Sinterklaas vieren in ons ouderlijk huis is een traditie die we in stand moeten houden.

Lieve Carien, jij bent in vele opzichten mijn tegenpool, maar gelukkig ook in heel veel dingen niet. Het is soms moeilijk met een drukbezet man samen iets op te bouwen en vooral onverwachte afwijkingen van een zorgvuldig opgebouwd schema vallen soms zwaar, maar met jouw enthousiasme, ideeën en energie ben jij een enorme steun en komt uiteindelijk alles dik in orde. Ik ben heel blij met je.

En dan tenslotte. Ik begon met het doorgeven van genetisch materiaal en opvoeding en stimulans en kom dan vanzelf uit bij Eline, Thijs en Michiel. In ieder van jullie zie ik stukjes van mijzelf terug, maar ik zie vooral hoe jullie jezelf ontwikkelen tot je eigen persoon met je eigen talenten. Ik ben enorm trots op jullie en wens jullie toe, dat je, zoals het mij ook gelukt is, in studie, werk en je persoonlijke leven gaat doen waar je goed in bent en waar je iedere dag weer veel plezier aan beleeft.

PhD Portfolio Summary



SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD student: Jos Bekkers	PhD period:2007-2012
Erasmus MC Department: Cardiothoracic Surgery	Promotor(s):Prof. dr. A.J.J.C. Bogers
Research School: COEUR	Supervisor: Dr. J.J.M. Takkenberg

1. PhD training

	Year	**Workload (Hours/ECTS)**
General academic skills		
Incompany course:financieel management Erasmus MC	2008	24
HR Module Veiligheid en Kwaliteit	2010	8
Leiderschapsprogramma Koers 013	2011	40
Presentations		
6th European congress of trauma and emergency surgery	2004	5
Society for Heart Valve disease (poster)	2007	5
Nederlandse Transplantatie Stichting	2007	5
TRIP symposium weefsel vigilantie	2007	5
Aortic Symposium 2008 New York (poster)	2008	5
Aortic Symposium 2010, New York	2010	5
European Association for Cardio-thoracic Surgery 2010, Geneva	2010	5
Aortasymposium, Rotterdam	2011	5
TRIP symposium weefselvigilantie	2011	5
Aortic Symposium 2012 (video on demand)	2012	5
International conferences		
American Association of Thoracic Surgery	2012	24
Society of Thoracic Surgery	2009,2011	48
European Association for Cardio-thoracic Surgery	2007, 2010, 2012	72
Society of Heart Valve Disease	2007,2011	48
World Conference on Lung Cancer	2007	24
International Society of Heart and Lung Transplantation	2008	24
Eurotransplant Meeting	2008,2009	8
World Society of Cardio-thoracic Surgeons	2009	16

Seminars and workshops		
Surgery of the Thoracic Aorta, Bologna	2007, 2009, 2011	48
Get Rhytm, Utrecht	2009	6
Over hartkleppen en pompen	2009	3
Master of Valve Repair, Bad Neustad	2010	16
Mini AVR en MPL, Nieuwegein	2010	8
Mitral Valve repair, Milaan	2010	8
National Conferences		
Wetenschappelijke vergadering Nederlandse Vereniging voor Thoraxchirurgie	2005-2012	72
TRIP symposium weefselvigilantie	2007,2011	8
Lustrum congres NVVC	2008	4
Other		
Locale refereeravonden	2007-2012	20
Regionale refereeravonden Rijnmond Cardiologen Club	2007-2012	20

2. Teaching activities

	Year	**Workload (Hours/ECTS)**
Lecturing		
Minor onderwijs cardiologie	2007-2012	15
Minor onderwijs congenitale hartziekten	2007-2012	15
Minor onderwijs transplantaties	2007-2012	15
Onderwijs assistenten cardiologie	2007-2012	15
Onderwijs assistenten Cardio-thoracale Chirurgie	2012	3
Other		
Onderwijs Intensive care opleiding	2007-2012	30
Onderwijs opleiding operatie-assistenten	2007-2012	60

Total Workload (hours)	753