CHAPTER IV

REPORT OF THE DUTCH EXPERIENCE WITH THE ROSS PROCEDURE IN 343 PATIENTS

Report of the Dutch Experience with the Ross Procedure in 343 Patients.
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Abstract

Objective: Limited information is available on outcome after autograft aortic valve replacement, in particular with respect to the durability of the autograft and of the allograft used to reconstruct the right ventricular outflow tract. A retrospective follow-up study of all patients who underwent a Ross procedure in the Netherlands since 1988 was done to obtain an overview of the Dutch experience with this procedure.

Methods: Since 1988 until January 2000 348 Ross procedures were performed in 9 centers in the Netherlands. Preoperative, peri-operative and follow-up data from 343 patients in 7 centers (99% of all Dutch autograft patients) were collected and analyzed.

Results: Mean patient age was 26 years (SD 14, range 0-58), male/female ratio 2.1. Bicuspid valve or other congenital heart valve disease was the most common indication for operation. The root replacement technique was used in 95% of patients, concomitant procedures were done in 12%. Hospital mortality was 2.6% (N=9). Mean follow-up was 4 years (median 3.8, SD 2.8, range 0-12.5). Overall cumulative survival was 96% at 1 year (95% CI 94-98%) and 94% at 5 and 7 years postoperative (95% CI 91-97%). At last follow-up 87% of the surviving patients was in NYHA class I. Independent predictors of overall mortality were pre-operative NYHA class IV/V and longer perfusion time. Autograft reoperation had to be performed in 14 patients, reintervention on the pulmonary allograft in 10 patients. Freedom from any valve-related reintervention was 88% at 7 years (95% CI 81-94%).

Conclusions: The Dutch experience with the Ross procedure is favorable, with low operative mortality and good mid-term results. Although both the autograft in aortic position and the allograft in the right ventricular outflow tract have a limited durability, this has not yet resulted in considerable reoperation rates and associated morbidity and mortality.

Key words: Ross procedure, autograft, allograft, multicenter study, clinical outcome

Introduction

Autograft aortic valve replacement, the Ross procedure, is performed worldwide since 1967, particularly in young patients. Potential advantages are the use of the patient's own valve with favorable hemodynamic characteristics, low endocarditis risk, low thrombogenicity, avoidance of anticoagulant therapy, and the alleged growth potential of the autograft valve in children[1-4]. On the other hand, the Ross procedure is a complicated operation that requires replacement of both the aortic and the pulmonary valve. Also, little clinical information is available on the durability of the autograft in aortic position and the durability of the valve substitute in the right ventricular outflow tract.

The Ross procedure was introduced in the Netherlands by Dr Donald Ross himself in 1988 in Rotterdam, but to date the outcome of the Ross procedures that were performed in the Netherlands is unknown. In the light of recent concern regarding progressive dilatation of the pulmonary autograft in aortic position[5] and growing evidence on the limited durability of the allograft in the right ventricular outflow tract[6], a retrospective analysis of all patients who underwent a Ross procedure in the Netherlands was performed.

Methods

All cardio-thoracic surgery centers in the Netherlands were invited to participate in a national retrospective study concerning the Dutch experience with the Ross procedure. Of the 13 centers, 4 replied that no autograft procedures were performed. In the other 9 centers a total of 348 Ross procedures were performed between 1988 and 2000. One center had a very limited experience with the Ross procedure (N=2) and did not wish to participate in the study. In one other center only 1 patient underwent a Ross procedure that was performed by a surgeon from the Rotterdam center. This patient was considered as a patient from the Rotterdam center. The 7 participating centers received a relational database (Microsoft Access) with the request to obtain pre-operative patient characteristics, peri-operative data, clinical and echocardiographic follow-up data from the patient records. If necessary, patients or their cardiologist or general practitioner were contacted to obtain their functional status. Main outcome measures were death, reoperation or reintervention on the autograft or pulmonary allograft, and valve related events defined according to Edmunds' criteria[7]. Of 2

patients no information could be obtained, resulting in a final study population of 343 patients.

The combined results of the data collection were analyzed using SPSS 10.0 for Windows. Means were compared by the unpaired t-test. The χ2-test or Fisher's exact test was used to compare categorical variables. All tests were 2-sided, with an α-level of 0.05. Univariate logistic regression was used to study potential determinants of early mortality (death during hospitalization or within 1 month after operation). The following parameters were considered: patient age (continuous variable), prior cardiac surgery (yes/no), preoperative serum creatinin (continuous variable), NYHA class IV/V (versus NYHA class I-III), extended Ross procedure (autograft aortic root replacement with additional enlargement of the left ventricular outflow tract), concomitant procedures (yes/no), perfusion time (continuous variable), preoperative left ventricular function. Cumulative survival and freedom from reoperation or reintervention were analyzed using the Kaplan-Meier method. The survival of a patient started at the time of surgery and ended at death (event) or at last follow-up (censoring). The analysis of autograft and pulmonary allograft survival started at the time of implantation and ended with reoperation or reintervention (event) or last follow-up or patient death (censoring). The differences between Kaplan-Meier curves were evaluated using the log-rank test. For overall survival the parameters that were also considered for operative mortality were analyzed. The following parameters were considered for freedom from reoperation or reintervention: patient age (continuous variable), aortic regurgitation versus stenosis, type of valve disease (bicuspid, tricuspid or prosthesis), prior cardiac surgery (yes/no), extended Ross procedure, concomitant procedures (yes/no), size donor valve (mm), type donor valve (pulmonary versus aortic), type donor (heart beating, domino or non-heart beating), preservation technique (cryopreserved versus fresh), origin (Rotterdam, London, Berlin, Barcelona, other) and quality code donor valve (ranging from 1 to 5). 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.

Table 1. Preoperative patient characteristics (N=343)

	Total N=343	**Age<16 years** N=98	**Age≥16 years** N=245
Mean age (years (SD; range))	26 (14; 0.02-58)	8 (5; 0.02-16)	33 (10; 16-58)*
Male/female ratio	232/111 (2.1)	71/27 (2.6)	161/84 (1.9)
Prior cardiac surgery	N=125 (36%)	N=57 (58%)	N=68 (28%)#
Prior balloon dilatation	N=23 (7%)	N=18 (18%)	N=5 (2%)#
Diagnosis (N=341)			
Aortic valve regurgitation (AR)	121 (36%)	25 (26%)	96 (39%)#
Aortic valve stenosis (AS)	86 (25%)	24 (24%)	62 (25%)
AR + AS	130 (38%)	45 (46%)	85 (35%)
Subvalvular aortic valve stenosis	4 (1%)	4 (4%)	0 (0%)
Etiology (N=342)			
Congenital incl. bicuspid valve	231 (68%)	91 (93%)	140 (57%)#
Degenerative	34 (10%)	0 (0%)	34 (14%)
Rheumatic	30 (9%)	3 (3%)	27 (11%)
Endocarditis	14 (4%)	3 (3%)	11 (5%)
Other (mainly prosthetic valve)	33 (10%)	1 (1%)	32 (13%)
Heigth (cm, N=338; (SD; range))	160 (31;48-200)	125 (37;48-185)	174 (11;135-200)*
Weight (kg; (SD, range))	61 (25; 3-165)	32 (21;3-105)	73 (15;46-165)*
Sinus rhythm	343 (100%)	98 (100%)	245 (100%)
Creatinin (N=322;(SD, range))	75 (33, 12-550)	54 (16;12-96)	82 (34;38-550)*
Qualitative LVF (N=330)			
Good	254 (77%)	70 (80%)	184 (76%)
Impaired/moderate	67 (20%)	15 (17%)	52 (21%)
Bad	9 (3%)	2 (2%)	7 (3%)
NYHA class (N=332)			
I	98 (30%)	46 (51%)	52 (22%)#
II	155 (47%)	30 (33%)	125 (52%)
III	71 (21%)	9 (10%)	62 (26%)
IV/V	8 (2%)	6 (7%)	2 (1%)
Ventilation support	6 (2%)	5 (5%)	1 (<1%)#

SD = standard deviation; LVF = left ventricular function; *P ≤0.05 unpaired *t*-test children versus adult group; #P ≤0.05 χ^2-test or Fisher's exact test children versus adult group

Results

Data were collected from 343 patients who underwent a Ross procedure between September 1988 and January 2000. This is 99% of the total number of patients who underwent a Ross procedure during this time period. The distribution of number of patients by center was Rotterdam N= 116, Nieuwegein N= 91, Leiden N= 71, Nijmegen N= 45, Utrecht N= 12, Groningen N= 8. Pre-operative patient characteristics are displayed in Table 1 and peri-operative data are displayed in Table 2 for all 343 patients and for patients aged ≥ 16 years (N=245) and < 16 years (N=98) separately. The right ventricular outflow tract was reconstructed with an allograft in 341 patients; a bioprosthesis was used in 2 patients (bovine pericardium mounted xenograft). Allograft characteristics are displayed in Table 3. Nine patients died during or shortly after operation (2.6% hospital mortality). Of these patients, 5 were children aged 0.02-5.1 years with complex congenital heart defects. In 8 patients death was operative and not valve related. In one patient who underwent an autograft aortic root replacement with reimplantation of the coronary arteries, intraoperative malperfusion of the reinserted right coronary artery occurred, necessitating coronary artery bypass grafting. However, the patient had already developed a major acute myocardial infarction causing massive heart failure and died shortly after operation. Therefore, this death is considered to be valve-related.

According to univariate logistic regression analysis the following parameters were associated with an increased risk of operative mortality: pre-operative NYHA class IV/V (OR 66, 95% CI 12-341), longer perfusion time (OR 1.02, 95% CI 1.01-1.03), extended Ross procedure (OR 47, 95% CI 6-387), younger patient age (OR 0.93, 95% CI 0.88-0.99), prior cardiac surgery (OR 6.4, 95% CI 1.2-31.3), and concomitant procedures (OR 4.7, 95% CI 1.2-17.9).

Follow-up was obtained for all patients until at least discharge. Long-term follow-up was complete until at least January 1 1999 for 307 patients (92% of all hospital survivors). The 27 patients whose follow-up was incomplete (last information from before 01/1999) were censored at the time of their last follow-up. Mean follow-up duration was 4.0 years (median 3.9 years, SD 2.8, range 0-12.5 years) with a total follow-up of 1387 patient years. During follow-up another 8 patients died. Cause of death was non-valve-related in 5 patients: 1 patient died 6 months postoperative of recurrent rheumatic fever, 3 patients died of cardiac causes at 1.8, 4.2 and 4.7 years postoperative, and 1 patient died of sepsis 7 weeks

Table 2. Peri-operative data (N=343)

	Total N=343	**Age<16 years** N=98	**Age≥16 years** N=245
Aortic valve			
Bicuspid	189 (55%)	63 (64%)	126 (51%)#
Tricuspid	129 (38%)	34 (35%)	95 (39%)
Prosthesis	25 (7%)	1 (1%)	24 (10%)
Type operation			
Root replacement	316 (95%)	95 (97%)	221 (90%)#
Subcoronary implantation	11 (3%)	1 (1%)	10 (4%)
Inlay/miniroot	12 (4%)	0 (0%)	12 (5%)
Extended root	4 (1%)	2 (2%)	2 (1%)
RVOT conduit			
Allograft	341 (99%)	98 (100%)	234 (99%)
Bioprosthesis	2 (1%)	0 (0%)	2 (1%)
Concomitant procedures			
None	301 (88%)	83 (85%)	218 (89%)
Closure ASD/VSD	8 (2%)	5 (5%)	3 (1%)
Mitral valve surgery	5 (2%)	1 (1%)	4 (2%)
Other	29 (8%)	9 (9%)	20 (8%)
Mean aortic cross-clamp	141 min	130 min	144 min *
time (N=342; SD, range)	(SD 36, 60-291)	(SD 45; 69-291)	(SD 31; 60-248)
Mean perfusion time	211 min	207 min	213 min
(N=341; SD, range)	(SD 70, 114-685)	(SD 79; 124-615)	(SD 66; 114-685)
Circulatory arrest	3 (1%)	1 (1%)	2 (1%)
Hospital death	9 (2.6%)	5 (5.1%)	4 (1.6%)
Re-exploration bleeding	37 (11%)	2 (2%)	35 (14%)#
CABG for lesion	2 (1%)	0 (0%)	2 (1%)
coronary artery			
Peri-operative stroke	1 (< 1%)	0 (0%)	1 (<1%)
Permanent pacemaker	8 (2%)	3 (3%)	5 (2%)

RVOT = right ventricular outflow tract, ASD = atrial septal defect, VSD = ventricular septal defect, SD = standard deviation, CABG = coronary artery bypass grafting. *P ≤0.05 unpaired *t*-test children versus adult group; #P ≤0.05 χ^2-test or Fisher's exact test children versus adult group.

Table 3. Allograft characteristics (N=341)

	N (%)
Type allograft	
Pulmonary	329 (96%)
Aortic	12 (4%)
Size allograft	
≤ 20 mm	28 (8%)
21-25 mm	125 (37%)
25-29 mm	176 (52%)
≥30 mm	12 (4%)
Donor (N=322)	
Heart beating	173 (54%)
Non heart beating	114 (35%)
Domino	35 (11%)
Preservation technique (N=325)	
Cryopreserved	322 (99%)
Fresh	3 (1%)
Origin (N=340)	
Rotterdam	247 (73%)
London	13 (4%)
Berlin	39 (11%)
Barcelona	29 (9%)
Other	13 (4%)
Quality code (N=315)	
1	104 (33%)
2	169 (54%)
3	31 (10%)
4	6 (2%)
5	5 (2%)

postoperative. Cause of death was valve-related in 3 patients. One patient died of unknown causes 6 months postoperative (valve-related by definition). One patient who underwent an autograft aortic root replacement had coronary artery bypass grafting 6 months postoperative after an acute myocardial infarction caused by stenosis of the reimplanted left coronary artery ostium, and finally died of heart failure 1 year postoperative. Finally, 1 patient died of a stroke 2.9 years after operation. Cumulative overall survival is displayed in Figure 1A, and was 97% at 1 month postoperative (95% CI 96-99%), 96% at 1 year (95% CI 94-98%) and 94% at 5 and 7 years postoperative (95% CI 91-97%).

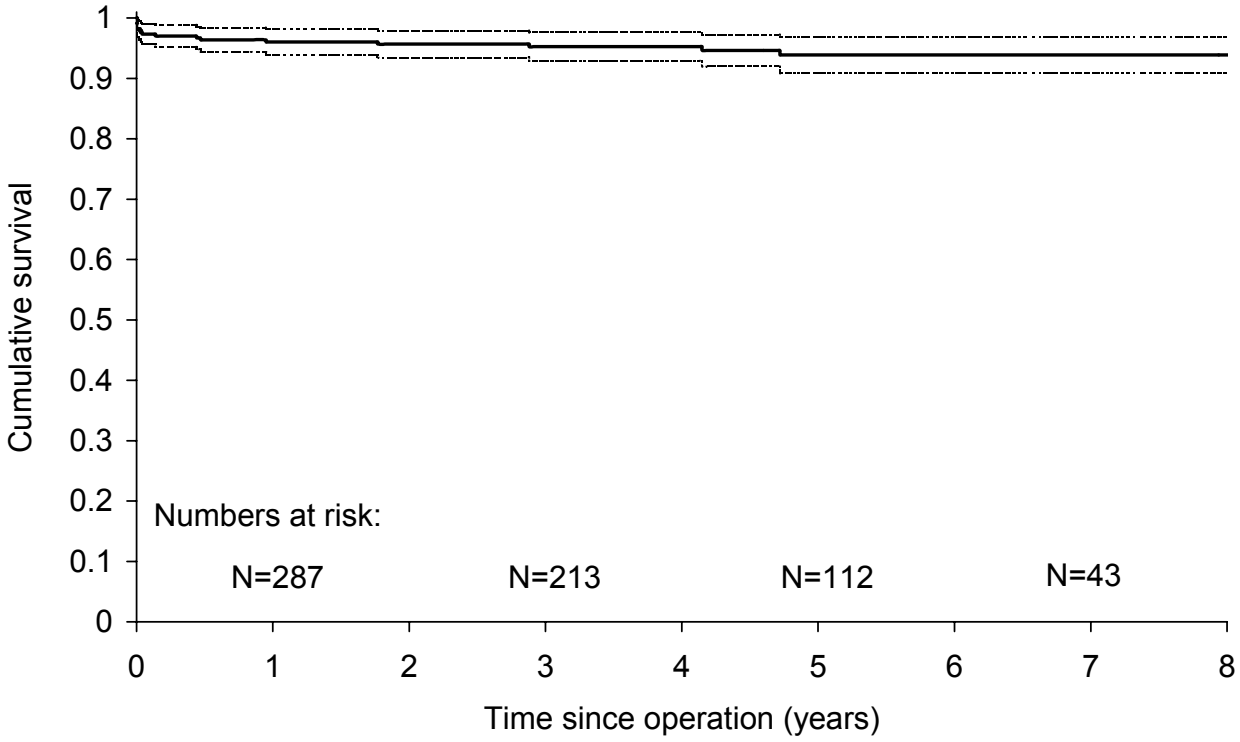

Figure 1A. Cumulative overall survival after Ross procedure.

NYHA class at last follow-up was available in 320 patients (99% of patients still alive). Two-hundred-and-seventy-eight patients (87%) were in NYHA class I, 40 (13%) in NYHA class II, and 2 (< 1%) in NYHA class III. Table 4 displays the hazard ratios for those parameters that univariately had a significant effect on overall survival, and the results of the full multivariate Cox regression model. The only two factors that independently predicted overall mortality were pre-operative NYHA class IV/V and longer perfusion time.

Table 4. Determinants of overall mortality (N=17).

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Preop NYHA class IV/V	35 (13-96)	<0.001	45 (12-170)	<0.001
Perfusion time (min)	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.02)	<0.001
Age (years)	0.95 (0.92-0.99)	0.009	0.98 (0.94-1.02)	NS
Extended Ross procedure	28 (6-134)	<0.001	1.3 (.2-10.7)	NS
Pre-operative LVF	1.8 (1.1-3.0)	0.02	1.3 (0.7-2.2)	NS
Concomitant procedures	3.1 (1.1-8.3)	0.03	0.6 (0.1-2.4)	NS

During follow-up 12 patients required a reoperation of the autograft, 8 patients required a reoperation or balloon dilatation of the allograft, and 2 patients had a reoperation of both the autograft and the allograft simultaneously. In addition, one patient developed a myocardial infarction and had coronary artery bypass grafting 6 months postoperative for ostium stenosis of the left coronary artery (considered as valve-related reoperation). This was possibly caused by dilatation of the neo-aortic root. Of the 14 patients who had a reoperation of the autograft, all had aortic regurgitation. In 13 patients the cause was autograft structural valve failure, in 1 patient paravalvular leakage. In 9 patients the autograft was replaced by a mechanical valve, in 1 patient by an allograft, in 1 patient by a bioprosthesis, and 3 patients underwent autograft valve repair. Two of the 3 patients who had autograft valve repair required replacement of the valve at a later point in time. Of the 10 patients who required reintervention on the allograft in pulmonary position, 9 had pulmonary stenosis and 1 had pulmonary regurgitation. In all patients the cause was structural allograft valve failure. Mean age of these patients was 14 years (SD 6, range 0.1-28 years), 5 were younger than 16 years at the time of Ross operation. In 5 patients the allograft was replaced by a new allograft, in 3 patients repair with a pericardial or allograft patch was done, and two patients underwent balloon dilatation.

Freedom from reoperation on the autograft (Figure 1B) was 99% at 1 year (95% CI 98-100%), 95% at 5 years (95% CI 92-98%), and 91% at 7 years (95% CI 85-97%). No risk factors for reoperation on the autograft could be identified, in particular no relation was seen with pre-operative hemodynamic diagnosis (aortic regurgitation versus stenosis) and bicuspid valve disease. Freedom from reintervention (reoperation or catheter intervention) on the

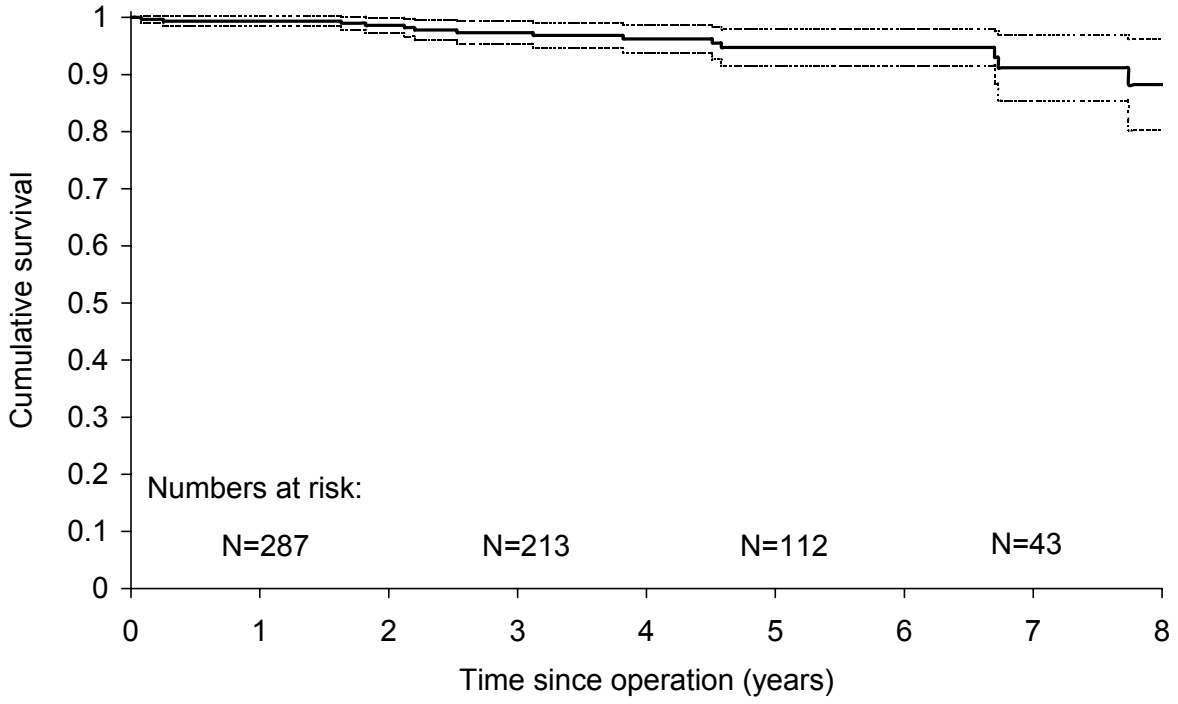

Figure 1B. Freedom from reoperation on the autograft.

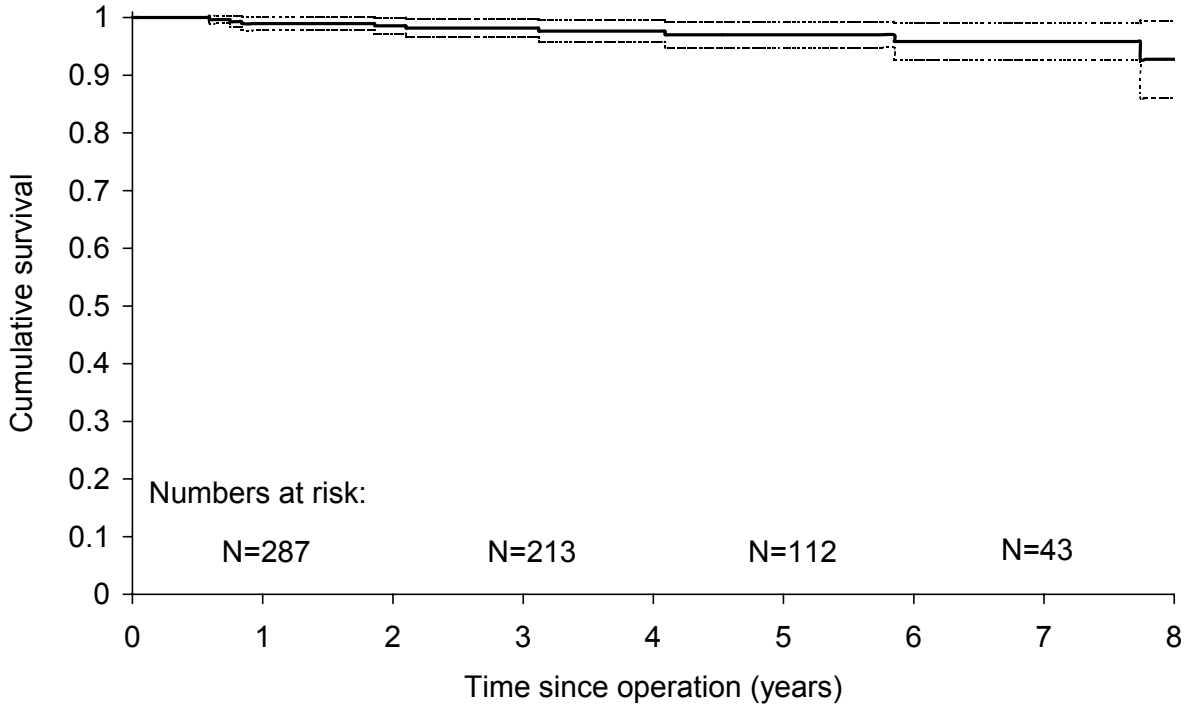

Figure 1C. Freedom from reintervention on the allograft in the right ventricular outflow tract.

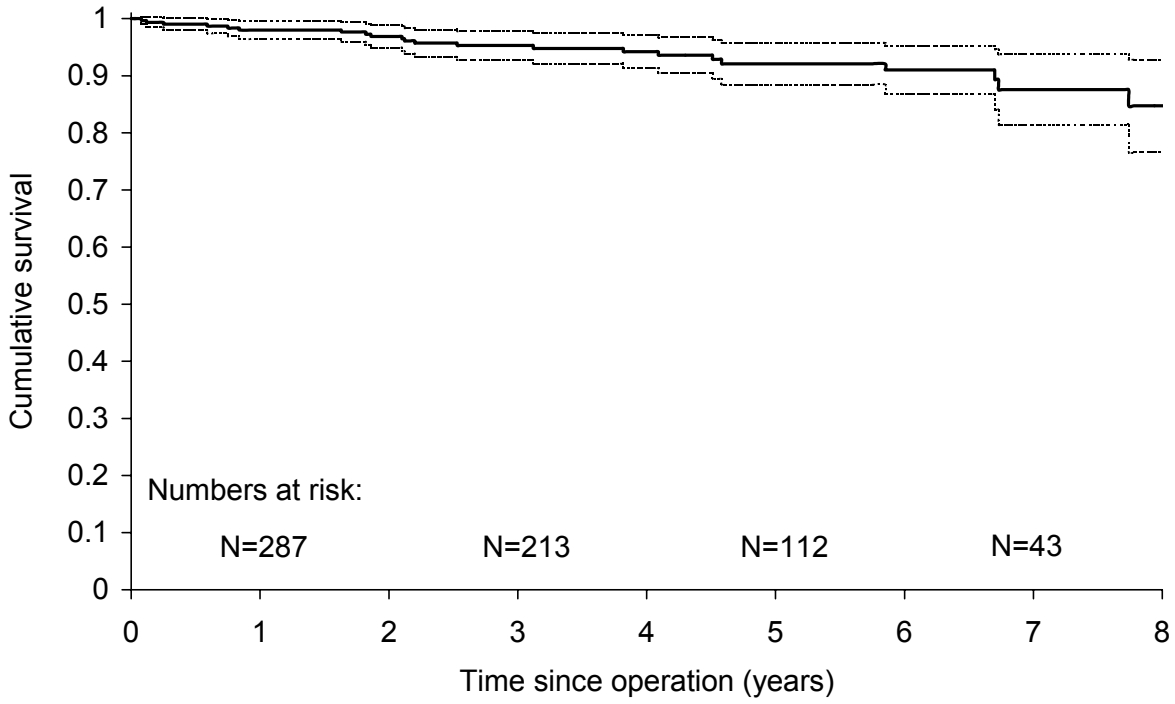

Figure 1D. Freedom from any autograft or allograft related reintervention.

allograft in the right ventricular outflow tract (Figure 1C) was 99% at 1 year (95% CI 98-100%), 97% at 5 years (95% CI 95-99%), and 96% at 7 years (95% CI 93-99%). The only 2 parameters that were univariately associated with an increased hazard for reintervention on the allograft in the right ventricular outflow tract was younger patient age (HR 0.94, 95% CI 0.88-0.99) and smaller size of donor valve (HR 0.80, 95% CI 0.69-0.93). None of the other allograft characteristics (pulmonary versus aortic allograft, type donor, preservation technique, origin and quality code of the donor valve) were associated with an increased hazard. Freedom from any autograft or allograft related reintervention (Figure 1D) was 98% at 1 year (95% CI 96-100%), 92% at 5 years (95% CI 88-96%), and 88% at 7 years (95% CI 81-94%). No risk factors for any autograft or allograft related reintervention could be identified.

Echocardiographic follow-up studies were available in 309 patients who were alive at last clinical follow-up and did not undergo a replacement of the aortic or pulmonary valve. The majority of patients (96%; N=296) had no to mild aortic regurgitation. Moderate to severe aortic regurgitation was present in 4% (N=13) of patients, reversed descending aorta

diastolic flow in 3% (N=8). Of the 281 patients with echocardiographic data on the right ventricular outflow tract, 10% (N=29) had a peak gradient over the right ventricular outflow tract >30mmHg. Ninety-nine percent of patients (N=277) had no to mild pulmonary regurgitation, while 1% (N=4) had moderate to severe pulmonary regurgitation.

Other non-fatal valve-related events occurred in 4 patients: 2 patients who received cumarin therapy for non-cardiac reasons had a major bleeding (0.14%/patient year), 1 patient had a CVA (0.07%/patient year), and 1 patient developed endocarditis of a degenerated pulmonary autograft after surgical treatment of an axillary abscess (0.07%/patient year). No other valve related events were reported.

Discussion

The Dutch experience with the Ross procedure is favorable, as evidenced by this national multicenter report. It is the first study on this subject on a national level and, although retrospective, with a good mid-term follow-up of a considerable number of patients. It highlights a number of potential advantages and disadvantages that are associated with the Ross procedure.

Both operative mortality and mid-term mortality in this series are low, and functional mid-term results are good when considering the pre-operative functional status of patients. Most operative deaths were in young patients with complicated and lengthy procedures. However, one patient died due to a perioperative myocardial infarction caused by malperfusion of a reinserted right coronary artery. This is a serious potential complication when using the root replacement technique with reimplantation of the coronary arteries. Another example of this technical problem is the patient who required coronary artery bypass grafting during the Ross procedure because of surgical damage to a coronary artery. Finally a third patient had a major myocardial infarction 6 months postoperative caused by stenosis of the ostium of the reimplanted left coronary artery possibly due to dilatation of the autograft root, required coronary artery bypass grafting and died of heart failure at 1 year postoperative. Therefore, when using the root replacement technique, reimplantation of the coronary arteries should be done carefully using sufficiently large buttons of aortic wall tissue around the coronary ostia and paying close attention to possible kinking of the coronary arteries.

Autograft failure necessitating reoperation occurred in 14 patients, of which 13 had dilatation of the autograft root causing severe aortic valve regurgitation. There was no autograft stenosis. Another 13 patients have echocardiographic evidence of moderate to

severe aortic regurgitation and will probably require replacement of the autograft relatively soon. Progressive dilatation of the neo-aortic root after autograft aortic root replacement is of great concern, and may possibly be related to bicuspid valve disease[5, 8-10]. However, it may also be related to the way the autograft root is implanted in the aortic annulus. When implanted inside of the aortic annulus instead of on top, the occurrence of dilatation may be prevented[11]. Support of a prosthetic or pericardial tissue strip is being applied in this regard as well. Unfortunately, details on annular support were not available from the Dutch experience study. No evident risk factors for autograft valve failure, including surgical technique and bicuspid valve disease, emerged from this study.

Structural valve failure of the allograft in pulmonary position required reintervention in 10 patients. Another 29 patients currently have considerable peak gradients over the right ventricular outflow tract. Unlike the autograft failure, structural valve failure of the allograft in pulmonary position is characterized by degenerative changes, calcification and stenosis. There are several possible explanations for the limited durability of allografts in the right ventricular outflow tract. First of all, young children will outgrow their allograft after a few years. This is supported by the association found between patient age and size of the allograft with freedom from allograft related reintervention. Previous reports confirm this relationship[6, 12-14]. Another explanation for limited allograft survival may be accelerated immunologic mediated degeneration. The finding that young patient age is associated with structural allograft valve failure is supportive of this hypothesis, but may also be merely a reflection of somatic outgrowth of the allograft valve in young children. Although allograft valves have been shown to be immunogenic, no clinical relevance has been proven with regard to allograft failure[15-20]. The clinical impact of structural valve failure of the allograft in the right ventricular outflow tract on valve-related mortality and morbidity is yet unclear. In our experience no major difficulties with the replacement and repair of the degenerated allograft were encountered.

Other valve-related events were rare in this retrospective study. For example there was only 1 major thrombo-embolic event during a follow-up of 1387 patient years. This reflects one of the major advantages of the Ross procedure over the use of mechanical prostheses for aortic valve replacement. Other authors report similar low incidences of thrombo-embolic events[21-25]. Also, a high-intensity transient Doppler signal (HITS) study comparing patients after Ross procedure with patients after aortic valve replacement with a mechanical prosthesis confirms that pulmonary autografts, unlike mechanical valves, rarely cause microemboli[26].

Note that this study was retrospective and follow-up was 92% complete, which may have resulted in an underestimation of the true occurrence of valve-related events.

Of note, the Ross procedure is used relatively infrequent for the replacement of the aortic valve. For example, in 1999 in the Netherlands 1995 aortic valve operations (including concomitant procedures) were registered, of which 940 isolated aortic valve replacements (source: BHN database; 84.5% complete). In contrast, according to our study only 25 Ross procedures were done in the same year. In the pediatric population the Ross procedure can be advised as a valuable surgical technique even in complex cardiac conditions. The same applies to adolescents. In adults who require aortic valve replacement other valve alternatives are usually considered first, and the use of the Ross procedure should be limited to a highly selective group of mainly young adult patients.

In conclusion, the Dutch experience with the Ross procedure is satisfactory, with low operative mortality, good functional results, good midterm survival and few complications. Although both the autograft in aortic position and the allograft in the right ventricular outflow tract have a limited durability, this has not yet resulted in considerable morbidity and mortality.

Appendix

Surgical collaborators of the Dutch Ross Study Group are as follows: *Erasmus University Medical Center Rotterdam*: J.A. Bekkers, A.J.J.C. Bogers, E. Bos, L.A. van Herwerden, B. Mochtar (present address: University Medical Center Maastricht); *St. Antonius Hospital Nieuwegein*: A. Brutel de la Rivière (present address: University Medical Center Utrecht), K.W. Dossche, W.J. Morshuis, M.A.A.M. Schepens; *University Medical Center Leiden*: M.G. Hazekamp, P.H. Schoof; *University Medical Center Nijmegen*: A. Nijveld, S.K. Singh; *Iniversity Medical Center Untrecht:* E.W.L. Jansen; *University Medical Center Groningen:* T.W. Waterbolk.

Local investigators: *University Medical Center Leiden*: C. Wientjes; *University Medical Center Nijmegen*: T. Markou; *BIS Foundation*: J.J. van den Brand.

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