SURGERY FOR ADULT CARDIOVASCULAR DISEASE

PRIMARY AORTIC VALVE REPLACEMENT WITH ALLOGRAFTS OVER TWENTY-FIVE YEARS: VALVE-RELATED AND PROCEDURE-RELATED DETERMINANTS OF OUTCOME

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Objectives: Allografts offer many advantages over prosthetic valves, but allograft durability varies considerably. **Methods:** From 1969 through 1993, 618 patients aged 15 to 84 years underwent their first aortic valve replacement with an aortic allograft. Concomitant surgery included aortic root tailoring (n = 58), replacement or tailoring of the ascending aorta (n = 56), and coronary artery bypass grafting (n = 87). Allograft implantation was done by means of a "freehand" subcoronary technique (n = 551) or total root replacement (n = 67). The allografts were antibiotic sterilized (n = 479), cryopreserved (n = 12), or viable (unprocessed, harvested from brain-dead multiorgan donors or heart transplant recipients, n = 127). Maximum follow-up was 27.1 years. **Results:** Thirty-day mortality was 5.0%, and crude survival was 67% and 35% at 10 and 20 years. Ten- and 20-year rates of freedom from complications were as follows: endocarditis, 93% and 89%; primary tissue failure, 62% and 18%; and redo aortic valve replacement, 81% and 35%. Multivariable Cox analyses identified several valve- and procedure-related determinants: rising allograft donor age and antibiotic-sterilized allograft for mortality; donor more than 10 years older than patient for endocarditis; rising donor age minus patient age, rising implantation time (from harvest to aortic valve replacement), and donor age more than 65 years for tissue failure; and rising donor age minus patient age, young patient age, rising implantation time, and subcoronary implantation preceded by aortic root tailoring for redo aortic valve replacement. Estimated 10- and 20-year rates of freedom from tissue failure for a 70-year-old patient with a viable valve from a 30-year-old donor and no other risk factors were 91% and 64%; the figures were 71% and 20% if the donor age was 65 years. The rates of freedom from tissue failure for a 30-year-old patient with a 30-year-old donor were 82% and 39%; the figures were 49% and 3% with a 65-year-old donor. Beneficial influences of a viable valve were largely covered by short harvest time (no delay for allografts from brain dead organ donors or heart transplant recipients) and short implantation time. **Conclusions:** Primary allograft aortic valve replacement can give acceptable results for up to 25 years. The late results can be improved by the use of a viable allo-

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graft, by matching patient and donor age, and by more liberal use of free root replacement with re-implantation of the coronary arteries rather than tailoring the root to accommodate a subcoronary implantation. (J Thorac Cardiovasc Surg 1999;117:77-91)

The allograft aortic valve was the first successful replacement valve used in the aortic position,¹ and its advantages suggested in early series¹⁻³ still stand: excellent hemodynamic function, low thrombogenicity, and resistance to infection. A few centers have consistently used the allograft since the 1960s,⁴⁻⁸ and it still is the valve of choice at our center. A current growing interest in stentless xenografts in aortic valve replacement (AVR) rests to a significant degree on accumulated experience with the allograft.

The main concern regarding the allograft is its durability, which to some degree is determined by source (living or diseased donor)^{5,7,9} and methods of sterilization and preservation.¹⁰ Furthermore, as with any other biologic valve, primary (degenerative) tissue failure of the allograft accelerates more than 10 years after the operation, indicating that follow-up well beyond 15 years is needed to judge the true freedom from failure at 10 and 15 years.

The aim of the present study was to judge the true behavior of the allograft after first-time AVR in a large homogeneous patient series with a follow-up exceeding 25 years, that is, beyond the high hazard phase for failure between 10 and 20 years after the operation. Furthermore, we wanted to identify independent determinants of outcome related to the allograft and the surgical procedure.

Patients and methods

During the 25-year period 1969 through 1993, 618 patients aged 15 to 84 (mean 51 years), who underwent their first AVR at Harefield Hospital, had an aortic allograft implanted. Patients with concomitant surgical procedures on the aortic root or the ascending aorta, as well as coronary artery bypass grafting, were included; any other surgical procedure and age of 14 years or younger served as exclusion criteria. The allograft was chosen irrespective of age, poor left ventricular function, and emergency operation, subject only to availability. The present 618 patients constitute 74% of all (with similar inclusion/exclusion criteria) who had a primary AVR performed by or under the service of one senior surgeon. The primary indication for surgery included aortic stenosis (n = 285), aortic regurgitation (n = 146), combined stenosis and regurgitation (n = 100), active endocarditis (n = 52), and aortic aneurysm or dissection with aortic regurgitation (n = 33) or stenosis (n = 2). Heart catheterization was performed before the operation in the majority of patients, combined

Table I. Preoperative patient profile

Demographic data	
Age (y)	51 ± 16 (15-84)
≤49	39% (242)
50-69	54% (333)
≥70	7% (43)
Male sex	70% (430)
Non-UK residency	9% (55)
Nonwhite race	11% (70)
Clinical/paraclinical data	
Etiology	
Degenerative	17% (108)
Bicuspid	36% (222)
Rheumatic	13% (82)
Congenital	11% (67)
Previous endocarditis	4% (24)
Active endocarditis	8% (52)
Marfan syndrome	3% (17)
IMN/syphilis/CTD	6% (33)
Other	2% (13)
NYHA class	
I	3% (29)
II	19% (117)
III	62% (383)
IV	16% (98)
Limiting symptom	
Dyspnea	67% (416)
Angina	20% (122)
Syncope	4% (27)
Other	6% (33)
Clinical left ventricular failure	32% (198)
Valve disease	
Stenosis	47% (291)
Regurgitation	36% (224)
Combination	17% (103)
Cardiothoracic index	0.54 ± 0.06 (0.39-0.78)
Kidney failure	5% (31)
Hypertension	9% (56)
Previous myocardial infarction	9% (56)
Diabetes mellitus	3% (18)
Arrhythmia*	4% (27)
Bundle branch block	8% (48)
Atrioventricular block, grade 1-3	6% (36)
Ventricular ectopia†	3% (18)

Data are mean ± SD (range) or percent (number). IMN, Idiopathic medial necrosis; NYHA, New York Heart Association; CTD, connective tissue disease.

*Atrial fibrillation or paced rhythm.

†More than 10% of beats in the electrocardiogram.

with echocardiography in 177, while 43 had an echocardiogram exclusively. Coronary angiography was performed in 292 patients, of whom 87 had significant coronary artery disease (luminal diameter narrowing ≥50% of at least one major

Table II. *Allograft profile*

	Viable (n = 127)	Antibiotic sterilized (n = 491)*	P value
Donor			
Cadaver	0	98% (483)	
Transplant recipient	88% (112)	2% (8)	<.0001
BD multiorgan donor	12% (15)	0	
Donor age (y)	44 ± 11 (14-65)	52 ± 12 (14-77)	<.0001
Donor minus patient age (y)	-5 ± 19 (-47 to 37)	1 ± 18 (-61 to 57)	.002
Gender			
Patient-donor match	69% (87)	72% (353)	.45
Patient-donor mismatch	31% (40)	28% (138)	
Harvest time (h)†	0	40 ± 22 (0-102)	.0001
Implantation time (h)‡	48 (2-720)	168 (12-1080)	.002
≤48	49% (62)	22% (110)	
49-96	31% (31)	19% (92)	
≥97	20% (25)	59% (289)	
Year of operation	1990 (1980-1993)	1974 (1969-1993)	<.0001
1969-1979	0	85% (419)	
1980-1989	46% (59)	6% (29)	
1990-1993	54% (68)	9% (43)	

Data are percent of patients (number), mean ± SD (range), or median (range). AB, Antibiotic solution, see text; BD, brain dead.

*Includes 12 cryopreserved valves, see text.

†From death of donor to harvest of valve; 0 when harvest from living donor (transplant recipient and brain dead multiorgan donor).

‡From harvest to operation.

epicardial artery or a first branch). Clinical left ventricular failure was recorded in case of pulmonary edema or vascular congestion within a year before the operation,¹¹ kidney failure if the S-creatinine concentration was elevated above the reference level for our laboratory in at least two preoperative blood samples, systemic hypertension in case of current or previous medical treatment, and diabetes mellitus in case of treatment with oral antidiabetic drugs or insulin. The preoperative patient profile is given in Table I.

Allograft data. A total of 483 aortic allografts were obtained during routine autopsies. The valves were dissected under sterile conditions, sterilized in antibiotic solutions,^{9,12} and either cryopreserved (n = 10)¹² or kept at 4°C in tissue culture medium with antibiotics (n = 473)⁹ until insertion. The remaining 135 allografts were harvested from brain dead multiorgan donors (n = 15) or heart transplant recipients (n = 120). Eight of these valves were antibiotic sterilized (n = 6) or cryopreserved (n = 2), and 127 were unprocessed viable allografts⁵: they were kept at 4°C in tissue culture medium (Medium 199 with Earle's salts, ICN Biomedicals, High Wycombe, Bucks, United Kingdom) containing extremely small doses of penicillin and inserted at the earliest opportunity. A detailed allograft profile is given in Table II. The viable allografts were first used in 1980; the 127 viable allografts constituted 64% of the 199 allografts used from 1980 to 1993, the limiting factor being availability of a living donor. Viable valves and antibiotic-sterilized allografts differed in terms of harvest time, but also as regards donor age, donor and patient age difference, and implantation time (Table II). Before 1980, 20 (4.8%) of 419 patients had a full root replacement compared with 47 (23.6%) of 199 patients operated on in the period 1980 to 1993 ($P < .0001$). As many as 38 (57%) of the 67 root

replacements but only 89 (16%) of the 551 subcoronary allograft implantations were done with a viable valve ($P < .0001$).

Surgical technique. Standard total cardiopulmonary bypass with either continuous or intermittent coronary perfusion (n = 486) or crystalloid (standard St Thomas Hospital solution) cardioplegic cardiac arrest (n = 132) was used. In case of a subcoronary implantation, the allograft was scalloped according to the anatomy of the aortic root and inserted with a "2-line freehand" technique as previously described³ (n = 551). In 58 patients, an aortic root tailoring or widening with a gusset of autologous pericardium was necessary to accommodate a subcoronary implantation. A full root replacement with reimplantation of the coronary ostia was performed in the remaining 67 patients as previously described.¹³ The latter technique was preferred especially in patients with mismatch in size or shape between the patient's aortic root and the allograft and in patients with aortic root disease.^{14,15} Surgical procedures on the ascending aorta included partial replacement with the allograft aorta in case of proximal disease (n = 23), complete replacement with a preclotted Dacron prosthesis (n = 26), or tailoring (n = 7). Coronary bypass was performed in 87 patients (1-4 grafts, mean 1.7). A total of 188 patients (30.4%) had at least 1 of these associated surgical procedures (n = 136) or were operated on because of active endocarditis (n = 52). A summary of the surgical procedures is given in Table III. A total of 53 patients received life-long anticoagulant therapy (or antiplatelet treatment) with warfarin (n = 22) or acetylsalicylic acid and dipyridamole (n = 31) because of chronic atrial fibrillation, previous stroke, or coronary disease.

Follow-up. All patients attended an outpatient clinic appointment 4 to 7 weeks after the operation, and those liv-

Table III. Surgical profile and early* mortality

	Surgical profile (all 618 patients)	Early* mortality (clean procedure or combination†‡§)	P value
Allograft valve procedure			
Subcoronary implantation	80% (493)	4.1% (17/415†)	.99
Subcoronary with root tailoring	9% (58)	4.0% (2/50†)	
Root replacement	11% (67)	4.1% (2/49†)	
Coronary artery bypass			
No	86% (531)	3.9% (17/436†)	.60
Yes	14% (87)	5.1% (4/78†)	
Ascending aorta procedure			
No	91% (562)	4.1% (21/514‡)	.002
Replacement with allograft	4% (23)	0% (0/22‡)	
Replacement with Dacron prosthesis	4% (26)	20.0% (5/25‡)	
Tailoring	1% (7)	0% (0/5‡)	
Operation for active endocarditis			
No	92% (566)	4.1% (21/514§)	.06
Yes	8% (52)	9.6% (5/52)	
Crossclamp time (min)	83 ± 21 (34-200)		
≤90 min	67% (413)	3.1% (13/413)	.003
>90 min	33% (205)	8.8% (18/205)	
ECC time (min)	102 ± 35 (46-288)		
≤150 min	91% (560)	4.1% (23/560)	.001
>150 min	9% (58)	13.8% (8/58)	
Myocardial preservation			
Coronary perfusion¶	79% (486)	5.6% (27/486)	.25
Crystalloid cardioplegia	21% (132)	3.0% (4/132)	

Data are mean ± SD (range) or percent (number). ECC, extracorporeal circulation.

*Death within 30 days after the operation.

†Early death/No. of patients excluding those operated on for active endocarditis or with ascending aorta procedure.

‡Early deaths/No. of patients excluding those operated on for active endocarditis.

§Early death/No. of patients excluding those with ascending aorta procedure.

||Of mortality comparison.

¶Intermittent or continuous.

ing in England additionally attended annual outpatient clinic appointments at our hospital. Since 1978 the outpatient clinic investigation has included an echocardiogram. From August 1995 through April 1997, we interviewed (mailed questionnaire and telephone) all patients who were still alive, and we contacted the general practitioner (mailed questionnaire and telephone) of all patients (living as well as deceased). All hospital contacts were checked. At termination of the study, 31 patients had died within 30 days after the operation (early mortality), 263 patients had died later, 294 patients were still alive, and 30 (4.9%) could not be traced. A total of 6229 patient-years (mean 10.1, maximum 27.1 years; maximum 17.1 years for the viable allografts) had been accumulated. Follow-up with an allograft in place (first or redo) totaled 5719 patient-years, which was used in the analyses of valve-related complications; that is, a patient was censored at the time of a redo AVR if the replacement valve was a xenograft or mechanical prosthesis.

Valve-related complications. Registration of valve-related complications followed internationally accepted guidelines¹⁶ as previously detailed.^{5,17,18} Embolism was recorded if a systemic arterial vascular event could not be proved to be throm-

botic or hemorrhagic. Bleeding was recorded if the patient received anticoagulant (or antiplatelet) treatment. Embolic and hemorrhagic events were recorded as minor if symptoms subsided within 48 hours (eg, transitory cerebral ischemia) or as major if they did not. In addition, we recorded non-valve-related strokes, that is, major cerebral events proven to be thrombotic or proven to be hemorrhagic in patients who did not receive anticoagulant treatment. Primary tissue failure (n = 258) of the allograft was recorded in case of significant regurgitation (at least grade 3/4) or stenosis (gradient ≥ 35 mm Hg) at aortic root angiography (n = 60) or Doppler echocardiography (n = 99), discovered during redo AVR (n = 52) or postmortem examination (n = 21), or when the following clinical criteria were fulfilled: the presence of a diastolic murmur, a wide pulse pressure (>50 mm Hg), increased cardiothoracic index (>0.50), and increasing left ventricular hypertrophy and strain pattern in the electrocardiogram,⁴ all in the absence of infectious endocarditis.

Statistical analysis. All analyses were computerized by means of the BMDP Dynamic version 7.0 software package (BMDP Software, Los Angeles, Calif).¹⁹ Simple comparisons were done with the use of a nonpaired *t* test, a 1-way analy-

Fig 1. Cumulative survival of all 618 patients. Cumulative survivals ± 1 SE are given at 5-year intervals. Numbers of patients at risk are given at 5-year intervals above the *abscissa*.

Table IV. Causes of death

	Early* (n = 31)	Late (n = 263)
Cardiac	74% (23)	55% (144)
Low cardiac output/ congestive heart failure	(15)	(84)
Myocardial infarction	(4)	(44)
Arrhythmia	(4)	(8)
Sudden unexpected	(0)	(8)
Valve related†	3% (1)	15% (39)
Postoperative bleeding	3% (1)	0%
Other	20% (6)	30% (80)

Data are percent (number).

*Death within 30 days after the operation.

†See Table VII.

Table V. Independent determinants for early mortality

Risk factor	b (SE)	OR	P value
Kidney failure	2.37 (0.50)	10.7	.0001
Replacement of ascending aorta with prosthesis	1.77 (0.59)	5.9	.007
Bundle branch block	1.44 (0.48)	4.2	.006
Patient age ≥ 70 y	1.38 (0.52)	4.0	.01
Crossclamp time ≥ 90 min	0.96 (0.41)	2.6	.02

b, Regression coefficient; SE, standard error; OR, odds ratio (see text).

and event freedom, as well as linearized incidences, are given with ± 1 standard error (SE); 95% confidence limits (95% CL) were identified by the " ± 2 SE" cutoff points.²⁰ Quantitative data are given as mean $\pm$ standard deviation (SD).

Results

Early and late mortality. The causes of deaths are given in Table IV; cardiac causes dominated and only 15% of late deaths could be related to the allograft.

Early mortality. By univariate analysis, early mortality (5.0%) was unrelated to allograft procedure and associated coronary bypass grafting. It was higher for patients who had the ascending aorta replaced with a Dacron prosthesis, and it tended to be higher for those operated on because of active endocarditis (Table III). The independent risk factors for early mortality are shown in Table V.

Long-term survival. Crude survival of all 618 patients is shown in Fig 1. Patients with a viable allograft had a better overall survival than those with an antibiotic-sterilized allograft (Fig 2). Allograft proce-

sis of variance, or a Pearson χ^2 test as appropriate. Cumulative survival and event-freedom curves were made by means of the Kaplan-Meier product-limit method, and differences between curves were tested with a log-rank and a Gehan test. Multivariable analysis of early mortality was done with a stepwise logistic regression analysis, whereas late mortality and valve-related complications were tested with a Cox proportional hazards regression analysis. All variables of Tables I to III were tested in the analyses. The multivariable tests were done by means of a comprehensive formalized analysis sequence, which has been previously described.^{11,18} The odds ratio was calculated¹⁸ for each independent risk factor to indicate the increase of risk associated with the risk level of a dichotomous risk factor or the risk increase relative to 1 unit increase of a quantitative risk factor. Estimated event-freedom curves for subgroups of patients were made by means of the Cox model; this method re-uses the common underlying event-freedom function of all 618 patients for each subgroup estimate.^{18,19} Cumulative survival

Fig 2. Cumulative survival in relation to type of allograft (see text). AB, Antibiotic sterilized (the group includes 12 patients who received a cryopreserved allograft). Cumulative survivals $\pm$ 1 SE (number of patients at risk) are given at 5-year intervals.

Fig 3. Cumulative survival in relation to allograft procedure: Full root replacement with reimplantation of the coronary ostia; subcoronary implantation of a scalloped allograft with 2-line suturing technique; and subcoronary implantation preceded by tailoring of the aortic root in patients operated on for chronic valve disease (aortic stenosis, regurgitation, or a combination), excluding patients operated on primarily because of endocarditis or ascending aortic aneurysm or dissection. Cumulative survivals $\pm$ 1 SE (number of patients at risk) are given at 5-year intervals.

dures also influenced survival, with the most favorable results related to root replacement (Fig. 3). The final Cox model for late mortality is given in Table VI. Donor age and patient age were both directly related to mortality independently of one another and with different strength. A viable allograft independently reduced the late death rate. The beneficial influence of residency outside the United Kingdom probably was related to the fact that our foreign patients were a highly selected

group who were self-funding and who represented a fairly high socioeconomic status.

Valve-related complications. The complications observed during follow-up are summarized in Table VII, and the cumulative event-free curves are depicted in Fig. 4. There were no paravalvular leakages or other complications.

Bleeding and embolism. The incidence of anticoagulant-related bleeding episodes was negligible, whereas

Fig. 4. Cumulative freedom from valve-related complications in all 618 patients; see Table VII and text. AC, Anticoagulant (warfarin, 22 patients; acetylsalicylic acid and dipyridamole, 31 patients; the remaining 565 patients did not receive any anticoagulant treatment). Cumulative freedoms $\pm$ 1 SE are given at 10, 15, 20, and 25 years. Numbers of patients at risk are given in parentheses for thromboembolism and tissue failure.

Table VI. Independent determinants for late mortality

	<i>b</i> (SE)	OR	P value
Patient age*	0.03 (0.005)	1.36†	<.0001
Male sex	0.63 (0.15)	1.87	<.0001
Cardiothoracic index*	3.08 (1.06)	1.36‡	.004
Crossclamp time*	0.008 (0.003)	1.27§	.004
Donor age*	0.015 (0.006)	1.16†	.009
Viable allograft	-0.66 (0.27)	0.52	.01
Non-UK residency	-0.78 (0.37)	0.45	.03
NYHA class III-IV	0.35 (0.17)	1.42	.04
Marfan syndrome	0.40 (0.19)	1.49	.04

b, Regression coefficient; SE, standard error; OR, odds ratio (see text); NYHA, New York Heart Association.

*Entered with continuous value.

†For an age increase of 10 years.

‡For a cardiothoracic index increase of 0.1.

§For a crossclamp time increase of 30 minutes.

there were 82 embolic episodes (vascular events that could not be proven to be hemorrhagic or thrombotic) in 66 patients; 76% ($n = 62$) of the events were cerebral and 67% ($n = 55$) were classified as minor (Table VII). The independent determinants for embolism (Table VIII) included long harvest time (for a cadaver valve; see Table II).

Background incidence of stroke. Using tabulated age- and sex-stratified incidences of a United Kingdom population study,²¹ we estimated the background incidence of first stroke as previously described.²² The incidence of a background population with a sex and age composition like those of the present 618 patients was

Table VII. Valve related complications

	Major (fatal) /minor*	Rate $\pm$ SE (%/pt-y)
Anticoagulant-related bleeding	4 (2)/1	0.09 $\pm$ 0.03
Embolism	27 (4)/55	1.43 $\pm$ 0.16
Endocarditis	34 (7)†	0.59 $\pm$ 0.10
Tissue failure	258 (13)†	4.51 $\pm$ 0.28
Redo valve replacement		
For endocarditis	15 (0)	
For tissue failure	136 (14)	
Total	151 (14)	2.64 $\pm$ 0.21

SE, Standard error.

*Number of events.

†Excluding death after redo valve replacement.

Table VIII. Independent determinants for embolism

	<i>b</i> (SE)	OR	P value
Patient age $\geq$ 50 y	0.99 (0.30)	2.69	.0008
Aortic regurgitation	0.71 (0.27)	2.03	.009
Hypertension	0.81 (0.34)	2.25	.02
Harvest time $\geq$ 96 h	1.11 (0.40)	3.03	.03

b, Regression coefficient; SE, standard error; OR, odds ratio (see text).

0.25%/pt-y. Twenty of the present patients had a stroke (anticoagulant-related bleeding, $n = 2$; embolic stroke, $n = 13$ [Table VII]; non-valve-related stroke, $n = 5$), giving a patient incidence of 0.35%/pt-y (95% CL: 0.19%-0.51%/pt-y). With or without the age risk factor, 415 patients of the present group with none of the other

Table IX. Independent determinants for endocarditis

	<i>b</i> (SE)	OR	P value
Limiting symptom "other"	1.44 (0.42)	4.22	.008
Male sex	1.20 (0.53)	3.32	.02
Donor $\geq$ 10 y older than patient	0.86 (0.34)	2.36	.01

b, Regression coefficient; SE, standard error; OR, odds ratio (see text).

Table X. Independent determinants for tissue failure

	<i>b</i> (SE)	OR	P value
Donor minus patient age*	0.020 (0.004)	1.22†	<.0001
Implantation time*	0.001 (0.0003)	1.11‡	.002
Donor age > 65 years	0.56 (0.20)	1.75	.006
Cardiothoracic index >0.55	0.33 (0.13)	1.39	.01
Diabetes mellitus	0.96 (0.46)	2.61	.04
Previous myocardial infarction	0.65 (0.31)	1.92	.04

b, Regression coefficient; SE, standard error; OR, odds ratio (see text).

*Entered with continuous value.

†For a donor minus patient age increase of 10 years.

‡For an implantation time increase of 100 hours.

3 risk factors (aortic regurgitation, hypertension, harvest time $\geq$ 96 hours) of Table VIII had an incidence of first stroke ($n = 9$) of 0.23%/pt-y (95% CL: 0.08%-0.38%/pt-y); 203 patients with 1 or 2 (no one had all 3) of the other 3 risk factors had a rate of 0.62%/pt-y (95% CL: 0.25%-0.99%/pt-y).

Endocarditis. Twenty-year freedom from allograft endocarditis (Table VII) was nearly 90% (Fig 4). The independent risk factors are shown in Table IX. An allograft donor who was 10 years or more older than the patient was a risk factor and was related to a 20-year freedom from endocarditis of $83\% \pm 4\%$ ($n = 173$) compared with $93\% \pm 1\%$ for a lesser age difference ($n = 445$; $P < .01$). "Other" as a limiting symptom (see Table I) was more prevalent (29%) among the 52 patients primarily operated on for active endocarditis than in the remaining 566 patients (3%; $P < .0001$).

Primary tissue failure. The 10- and 20-year freedoms from failure were $62\% \pm 3\%$ and $18\% \pm 3\%$, respectively (Fig 4). The hazard (instantaneous failure rate) was 2.4%/y during the first 5 years after the operation, 6.5%/y for the next 5 years, 11.1%/y for the eleventh through fifteenth years, 14.0%/y for the sixteenth through twentieth years, and 3.3%/y for the twenty-first through twenty-fifth years, with mean and median failure times of 13.1 and 12.5 years, respectively. At end-of-study, 30 patients (5%) with a failing allograft had no related symptoms, 79 (31%) had medically treated congestive heart failure, 13 (5%) had died, and 136

Table XI. Independent determinants for redo valve replacement

	<i>b</i> (SE)	OR	P value
Donor minus patient age*	0.023 (0.001)	1.26†	.001
Patient age*	-0.026 (0.008)	0.77†	.002
Implantation time*	0.0014 (0.0004)	1.15‡	.002
Marfan syndrome	1.46 (0.48)	4.31	.002
Diabetes mellitus	1.91 (0.60)	6.75	.002
Root replacement	-1.03 (0.42)	0.36	.01
AV block grade 1-3	0.89 (0.36)	2.44	.01
Aortic root tailoring§	0.46 (0.22)	1.58	.03

b, Regression coefficient; SE, standard error; OR, odds ratio (see text).

*Entered with continuous value.

†For a donor minus patient age increase or patient age increase of 10 years.

‡For an implantation time increase of 100 hours.

§Before subcoronary implantation of allograft.

(53%) had undergone a first redo AVR, of whom 14 died during the first 30 postoperative days.

The 10- and 15-year freedoms from failure for the viable versus the antibiotic-sterilized allografts (patients operated on for endocarditis or ascending aortic aneurysm/dissection excluded) were $71\% \pm 7\%$ and $71\% \pm 7\%$ ($n = 115$) versus $61\% \pm 3\%$ and $32\% \pm 3\%$ ($n = 416$; $P < .05$). Failure was less common in patients who had an allograft root replacement than in those with pure subcoronary implantation, whereas failure was more common in those with a root tailoring (Fig 5). The independent risk factors for primary tissue failure are shown in Table X. The difference between donor and patient age was the most significant risk factor, as illustrated in Fig. 6. Donor age above 65 years was a determinant in its own right, almost doubling the risk of failure (Table X); increasing implantation time (from harvest to AVR; Table II) also had a strong influence. The freedom from failure estimated by the Cox model for a "best" to a "worst" risk subset for a patient aged 70 years and one aged 30 years are depicted in Fig 7. The 70-year-old patient (*A curves*) had a considerably better freedom from failure for each risk subset than the 30-year-old patient (*B curves*). The difference from the *A1* to *A2 curves* (and corresponding *B1* to *B2 curves*) indicates the influence of viable versus antibiotic-sterilized allograft; the difference from *A2* to *A3 curves* (and the corresponding *B2* and *B3 curves*) illustrates the impact of increasing donor age from 30 to 67 years; and the *A4* and *B4 curves* include the remaining risk factors of Table X. A 70-year-old patient with a viable allograft from a 65-year-old donor (oldest viable valve donor) and no other risk factors would have 10- and 20-year freedoms from failure of 71% and 20%, respectively; the figures would be 49% and 3%, respec-

Fig 5. Cumulative freedom from tissue failure in relation to allograft procedure; see legends to Fig 3 for identification of procedure groups. Cumulative freedoms ± 1 SE (number of patients at risk) are given at 10, 15, and 20 years.

Fig 6. Cumulative freedom from tissue failure in relation to age difference between allograft donor and patient. D-P Age, Donor minus patient age. Cumulative freedoms ± 1 SE (number of patients at risk) are given at 10 and 20 years.

tively, for a 30-year-old patient (see *A1* and *B1* curves of Fig 7).

Redo valve replacement. Table VII summarizes data of the first reoperation, and the cumulative freedoms are depicted in Fig. 4. The independent risk factors are given in Table XI. Donor minus patient age again was a strong risk factor, but “decreasing” patient age was also influential. The latter was related to the increasing failure rate of young patients but also to a certain reluctance to reoperate on a very old patient with a failing allograft. Root replacement independently reduced the

risk of reoperation, whereas root tailoring to accommodate a subcoronary implantation increased the risk (Table XI, Fig 8).

The valve substitute of the 151 first redo AVRs (Table VII) included allografts in 50%, mechanical valves in 46%, and xenografts in 4%. The 10-year survival after first redo was $72\% \pm 6\%$ in the 75 patients who received a second allograft and $56\% \pm 6\%$ in the 76 who received a mechanical or xenograft valve ($P < .05$). Their ages at first redo operation were 50 ± 14 and 55 ± 14 years, respectively ($P < .05$). A total of 136

Fig 7. Estimated freedoms from tissue failure using a Cox regression model; see text and Table X. A1, A2, A3, and A4 curves, A 70-year-old patient, and A1, donor age of 30 years, viable allograft with implantation time of 48 hours, and no other risk factors (Table X); A2, similar to the preceding but with an antibiotic-sterilized allograft and an implantation time of 120 hours; A3, similar to the preceding but with a donor age of 67 years; and A4, similar to the preceding but with all other risk factors of Table X. B1, B2, B3, and B4 dotted curves, like A1, A2, A3, and A4 curves, but with a 30-year old patient. Estimated freedoms are given at 10 and 20 years.

patient had only 1 redo AVR, 14 had 2 such operations, and 1 patient had 3.

Discussion

This study has served to document the “true” long-term pattern of performance of aortic valve allografts over a period of up to 27 years and has identified several patient-, allograft-, and procedure-related factors that could influence patient outcome parameters. Several previous reports from our center^{4,5,13,15} and others^{6,7} were based on maximum follow-up periods varying around 10 to 15 years for current models of allografts. We believe that this underestimates the incidence of complications and that the true results are better represented by longer follow-up times.

A major advantage of the allograft as an aortic valve substitute is the restoration of blood flow in the aortic root, sinuses, and coronary ostia to normal or near normal. The normal aortic valve is a highly complex and sophisticated structure that starts opening and closure preceding hemodynamic events.²³ The hemodynamic advantage translates into pressure gradients across allografts, which are usually negligible and significantly lower than the gradients across stented xenografts and modern disc valves.^{24,25} The impact may be a more complete regression of left ventricular hypertrophy after a successful AVR with an allograft.²⁴ Complete regression of hypertrophy is a main factor in keeping the left ventricle well functioning in the long term,²⁶

which may be an important determinant of long-term survival.¹⁸ The current interest in unstented xenografts in general and in patients with a small aortic root in particular is understandable, particularly given the limited availability of allografts.

The hemodynamic advantage of the allograft can be exploited only if other allograft-related factors do not impair long-term survival. The present method of antibiotic sterilization^{4,12} has significantly improved results compared with earlier methods of sterilization and preservation.¹⁰ The present viable allograft⁵ and the viable cryopreserved allograft,⁷ both harvested from live donors, may have improved results further.

A first concern regarding allograft AVR is the more complex implantation technique compared with those needed for stented xenografts or mechanical valves. However, the present early mortality compares favorably with results of numerous published AVR series, both those spanning the same time period as the present series and more recent studies. Furthermore, we identified widely known risk factors for early mortality, in terms of both associated surgical procedures and patient-related factors. Notably, a full root replacement with reimplantation of the coronary arteries did not entail increased risk.

During a more than 25-year follow-up with an average starting age of 51 years, normal epidemiologic risk factors and death rates are in effect.¹⁸ Age as an independent risk factor needs no explanation, whereas the

Fig 8. Cumulative freedom from redo valve replacement in relation to allograft procedure; see legend to Fig 3 for identification of procedure groups. Cumulative freedoms $\pm$ 1 SE are given at 10 and 20 years.

influence of male sex may be related to a generally shorter life span of men compared with women. Other independent risk factors for late mortality of the present study underscored the influence of advanced heart disease before the operation, in agreement with other long-term studies spanning the same time period.^{11,27} The present long-term survival was comparable with the survivals of a predominantly biologic²⁷ and a predominantly mechanical AVR series,¹⁸ both with more than 20 years of follow-up.

In the current series, valve characteristics including method of preparation and insertion appeared to have an important influence on survival. The viable allograft and root replacement were associated with better long-term survival than the antibiotic-sterilized allograft and subcoronary implantation. The frequency of root replacement increased during the 25 years of surgery. As a result, more than half were done with a viable valve, indicating that the 2 determinants were complementary in their beneficial influence on survival. Our results regarding root replacement confirmed previous findings.^{5,14} The beneficial influence of a viable allograft on long-term survival was probably explained by its lesser tendency to failure (as was the case for root replacement) than the antibiotic-sterilized allograft. Equally important was the finding that donor age was related to late mortality; this was obviously a reflection of increased risk of both endocarditis and primary tissue failure of an allograft from elderly donors.

Allografts and other biologic valves are generally considered nonthrombogenic. However, in this series we have observed a definite incidence of thromboembolic complications. It should be recognized that there

are normal rates of thromboembolic phenomena such as stroke in the general background population.^{21,22} The internationally accepted guidelines for reporting thromboembolism after heart valve replacement¹⁶ state, in essence, that a systemic vascular event should be recorded as embolic unless there is proof of thrombosis (or hemorrhage), indicating that the rate of valve-related embolism will be overestimated. During the present very long follow-up, the rate of embolism was 1.4%/pt-y, which is lower than the average for mechanical valves, despite the absence of anticoagulant treatment in the vast majority of the present patients. In a recently published paper, a current stented pericardial xenograft aortic valve was associated with an embolic rate of 1.6%/pt-y.²⁸ However, using published tabulated age- and sex-specific rates of stroke of a general United Kingdom population,²¹ we were able to calculate²² the stroke incidence of a background population with the same sex and age composition as the present patients: the background incidence did not differ from the observed (embolic, hemorrhagic, thrombotic) stroke rate of our patients. Furthermore, systemic hypertension and age, being the predominant risk factors for stroke in the general population,²² were also independent determinants of embolism in the present patients. Our data thus confirm that the allograft in general is not thrombogenic. The exception may be the cadaver valve that is harvested too long after death of the donor.

The present 25-year freedom from endocarditis of 89% indicates that the allograft is resistant to infection. A 10-year freedom of 97% after allograft AVR in prosthetic valve endocarditis²⁹ strongly supports that

notion. The allograft, especially used as a full root replacement, is recommended in complex aortic valve endocarditis, especially with destruction of the aortic root.²⁹ The present incidence of endocarditis was comparable with the average of reported figures for mechanical valves and somewhat lower than the incidence associated with stented xenograft aortic valves. The latter was directly confirmed by Agnihotri, McGiffin, Galbraith, and O'Brien.³⁰ Interestingly, we observed that donor-patient age mismatch of 10 years or more independently increased the risk of endocarditis. This finding needs to be confirmed in future studies, and similarly the underlying mechanisms require further research.

The main drawback of allografts and of any other biologic valves is their limited durability. It is important to emphasize that length of follow-up may have a profound influence on estimated freedoms from primary tissue failure. In the present more than 25-year follow-up series, with a significant number of patients at risk in the long term, the hazard of failure seemed to be especially high during 16 to 20 years after the operation before it seemed to return to a phase of low and constant risk. In a previous publication from the present center with a maximum follow-up of just above 15 years, the 10- and 15-year freedoms from failure of the antibiotic-sterilized allograft were 77% and 48%, respectively⁴; in the present series the figures were 61% and 32%, respectively. Similarly, with 14 years of follow-up we previously reported an 89% 10-year freedom from failure for the viable allograft⁵; in the present study, with 17 years of follow-up, the 10-year freedom was 71%. The present article may thus give a picture close to the real failure characteristics of allograft aortic valves, at least as regards the antibiotic-sterilized valve.

Primary tissue failure is not a trivial complication, and any measure that can reduce the incidence is directly warranted. The technical surgical procedure seemed to influence the risk of failure. A full root replacement was associated with a low incidence of failure, whereas aortic root tailoring to accommodate a subcoronary implantation seemed to be associated with a very high failure rate between 5 and 10 years after the operation. Root replacement and root tailoring had direct beneficial and adverse influences, respectively, in the multivariable model for redo AVR that was undertaken primarily because of failure. These findings could be explained by the fact that the essential feature of root replacement is that the anatomic integrity of the valve is perfectly maintained from root to sinotubular junction. At the other extreme stands the attempt of the surgeon to recreate the anatomy by first shaping and tailoring the native

root and then stitching the scalloped allograft in place in the subcoronary position with a 2-line freehand technique. Others have also observed the increased failure tendency associated with root tailoring,⁸ as well as the favorable influence of root replacement.^{5,31,32}

Young patient age is a time-proven widely known risk factor for degenerative failure of porcine³³ and pericardial²⁸ xenografts, as well as of allografts.^{5,8,34} In the present study, patient age played a significant role but donor age was an even stronger determinant of failure. The 2 variables were interrelated: the donor-patient age match or mismatch appeared to be the dominant factor. Furthermore, the very old allograft (donor age > 65 years) in its own right significantly increased the risk of failure. It has previously been reported from the present institution that donor age of more than 65 years was related to early allograft failure.³⁵ Time from allograft harvest to implantation was also directly related to risk of failure. Donor age, donor minus patient age, and implantation time were all significantly higher for the antibiotic-sterilized allograft than for the viable valve. The former factors may thus in part explain the better freedom from failure of the viable valves.

The risk factors for redo AVR reflected the multivariable models for endocarditis and primary tissue failure. Interestingly, diabetes mellitus adversely influenced primary tissue failure and consequently also redo AVR. With a relation to "general tissue weakness" of diabetes mellitus, this finding may pinpoint factors of the tissue in which the allograft rests. The remaining risk factors, high cardiothoracic index, previous myocardial infarction, and atrioventricular block, indicate a deleterious influence of preoperatively impaired heart status. It has previously been shown that impaired left ventricular function was related to increased intravascular hemolysis in patients with aortic ball valves³⁶ and with a modern bileaflet disc valve.²⁵ A regionally or globally malfunctioning pump may give rise to higher turbulent shear forces in the flow profiles of mechanical valves, which may traumatize erythrocytes^{18,25,36} as well as the leaflet edges of an allograft. A dilated left ventricle (and root) may also add to difficulties of restoring the anatomic integrity of the valve and left ventricular outflow tract, especially in a subcoronary implantation.

In conclusion, our study has defined the long-term behavior of the allograft both in terms of survival and complications, and it has identified several factors that could influence these parameters and therefore be of clinical relevance. During the very long follow-up of the present study, the hazard of primary tissue failure "re-entered" a phase of low and constant risk first after

20 years. The failure characteristics of the present allograft series may thus indicate the true behavior of the allograft, inasmuch as studies with a shorter follow-up significantly underestimated the failure rate. Our data suggest that allograft AVR can give acceptable results for up to 25 years. Furthermore, the late results can be improved by the use of a viable allograft, by matching patient and donor age, by avoiding the old donor, and by more liberal use of free root replacement with reimplantation of the coronary ostia rather than tailoring the root to accommodate a subcoronary implantation. It is hoped that our findings will help to optimize the long-term results of allograft AVR.

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Discussion

Dr Mark F. O'Brien (*Brisbane, Australia*). Dr Lund, I congratulate you and your colleagues, specifically Sir Magdi Yacoub, for the valuable analysis of your allograft experience. You highlight the importance of donor age, reasonably short donor death-to-implantation time (although you talk of harvest-to-implantation time), and a better valve matching with the technical implantation of the root replacement.

Eleven years ago in 1987 at this very meeting we presented and published from our Brisbane experience, which is now over 1000 allografts, the incremental risk factors of reoperation for degeneration—younger age of patient at AVR and older age of donor. You have gone further, to focus on the additional factors that influence the quality of the valve, factors that affect viability and preservation of the tissue matrix. We have been saying for some decades now that a valve should be implanted early or cryopreserved as early as possible. Our mean time to preservation is 15 hours from donor death. We have shown clinically a marked difference in the durability between early cryopreserved valves and the antibiotic-sterilized valves that stayed in the refrigerator for days or weeks. The freedom from structural deterioration and reoperation at 20 years in our experience is 60%.

I read your manuscript as carefully as I could. You would be surprised to know that we would not use 51% of your homovital valves and 78%, at least, of your antibiotic-sterilized valves because the time from death to implantation is too long. This may explain why our freedom from primary tissue failure in the whole cohort, without subdivision of the cohort, was 60% at 20 years, whereas your very best results are in the 70-year-old patient with a 30-year-old donor, giving 10- and 20-year freedoms from tissue failure of 91% and 64%.

I have a number of questions. A homograft is an excellent valve at 10 years, it is a very good valve at 15 years, but it is far from optimal at 20 years. Yet you make the statement that the homograft AVR can give acceptable results for up to 25 years. I would not accept those results out to 25 years. We do not accept our own results, which really are better than yours.

There are many avenues for improvement, on some of which you have focused.

My first question is this: Do you think the homograft is an acceptable device to 25 years?

What was the time from donor death to cryopreservation?

Could you expand on the influence of patient age on reoperation, particularly in that younger age group? We are beginning to learn of the poor results in infants and teenagers, but what are your thoughts on the reasons why the results are not as good in these younger recipients?

Why do you think endocarditis was more prevalent with the older donor valve? Is it because degeneration occurs more quickly?

What modifications have you made for your collection and harvesting protocol, particularly in regard to the cutoff age of the donor?

Last, what happens if you cannot implant the valve within that magic homovital time period of 72 hours? Do you cryopreserve it, which we would regard as late cryopreservation?

Mr Lund. Thank you, Dr O'Brien. With regard to the comparison with your own results, I think there are two important things that should be said. First, I noticed from a previous publication from your center that less than 30% of your patients receive a homograft valve, so yours is a selected series whereas ours is not. The homograft was the valve of choice at Harefield Hospital, and that may significantly influence results.

Second, as your follow-up has just passed 20 years, at least with the results you have published, we might suspect that with a follow-up closer to 30 years, your 20-year results may not look as good as they do today. We have noticed with previous publications from Harefield, with the antibiotic-sterilized homograft, that the estimated 15-year freedom reported in 1985 and in 1990 has been successively dropping down to current figures with an almost 30-year follow-up. Selection of patients most certainly will influence long-term results and so will length of follow-up.

I do not know the answer to your question about the time from harvest to cryopreservation of the 12 valves.

You asked about the possible mechanism of an increased tendency for endocarditis for the old donor valve. In our analyses, the donor-patient age match or mismatch was the important factor. The worst subset seemed to be old donor in young patient. We can only speculate about the mechanism. Further research certainly is needed. Maybe the donor valve from an elderly patient is more prone to degeneration and weakness of tissues and therefore more susceptible to endocarditis, but that is only speculative.

Regarding implantation of homovital valves, if the valve is still in the refrigerator after 72 hours, we will use it. Obviously we prefer to implant the valve as soon as possible after harvest from the viable donor, and preferably within 48 hours, but that is something that needs to be tightened up in our center.

Matching of patient and donor age is going to be relevant in the future, but we have not done it so far. However, this analysis is quite new.

Dr Charles A. Yankah (*Berlin, Germany*). I rise to congratulate Dr Lund and Sir Magdi Yacoub for this excellent clinical study. Twenty-five years of homograft valve function is impressive, and it also provides important information for us surgeons with regard to how to speak to the relatives and patients.

We have implanted more than 250 homografts in the aortic position, subcoronary and also root replacement. We define our homovital valves as those homografts harvested during our transplant program and preserved within 24 hours, maximum 35 hours. We made prostacyclin studies, which indicated cellular viability in about 20% of these valves at the time of implantation. The rest of them, however, possessed no endothelial cells. The viability of the homografts was defined in relation to structural viability, that is, those without endothelial cells but with some living fibroblasts that will not survive long after implantation.

My question is this: What is the cellular viability definition in your homovital valves? Can you derive your experience from the results whether the antibiotic treatment in the homovital group had an impact on the results of the implantation technique such as sizing, root replacement, and the subcoronary technique?

Mr Lund. Regarding viability of the valve: Will viability influence long-term results? In this respect, we would all think in terms of major histocompatibility antigens. Results on research in that field are conflicting. Results from Harefield and also from Holland seem to indicate that major antigenicity is not a factor in the viable homograft, whereas results from Dr O'Brien's group tend to indicate the opposite.

With regard to technical procedure, we do not distinguish between a homovital or an antibiotic-sterilized homograft.

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