

Patient Outcome and Valve Performance Following a Second Aortic Valve Homograft Replacement

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Background—Homograft valves offer many advantages; however, there is concern about their use in second aortic valve replacement because of the complexity of the procedure and the possibility of accelerated degeneration.

Methods and Results—One hundred and forty-four patients underwent a second aortic homograft replacement between 1973 and 1997 (mean follow-up 6.5 ± 5 years, range 1 to 20 years). Eighty-three were male, and 61 were female, aged 17 to 77 years, mean 49.0 years. All patients had undergone previous aortic valve replacement with a homograft. The indication for reoperation was aortic regurgitation in 75 patients (52.1%), aortic stenosis in 28 (19.4%), and mixed aortic valve disease in 41 (28.5%). Root replacement was performed in 54 patients (38%) and subcoronary in 90 (62.5%). Early mortality was 3.4%. The actuarial survival rate was 93% and 82% at 5 and 10 years, respectively. Freedom from tissue degeneration was 96% and 80% at 5 and 10 years, respectively, and freedom from reoperation was 97% and 82% at 5 and 10 years, respectively.

Conclusions—This study shows that a second aortic valve homograft replacement results in good early and long-term survival. Accelerated degeneration does not occur. Left ventricular performance is improved, and earlier surgery could further improve outcome, indicating that an aortic homograft is a safe, durable option for patients requiring a second aortic valve replacement. (*Circulation*. 1999;100[suppl II]:II-42-II-47.)

Key words: valves ■ aorta ■ regurgitation

Aortic homografts offer superior hemodynamics (with the potential to restore normal flow in the aortic root, sinuses, and coronary orifices), freedom from thromboembolism, and resistance to infection. This has resulted in a continued increase in the use of aortic homografts for aortic valve replacement. However, their use has been limited due to lack of availability, complexity of insertion, and limited durability. Many of the patients who had homograft replacement of the aortic valve will subsequently require re-replacement at some point in the future.¹⁻⁵

There is no consensus about the choice of a valve substitute at the second operation. Although homografts may offer many advantages, there is concern about their use in this setting. The concern stems from the fact that at the second operation, advanced age, deterioration of ventricular function, and complexity of operation may add to the operative risks. We and others have shown that these valves express both class I and class II major histocompatibility antigens,⁶ and a strong donor-specific humoral immune response after homograft insertion can occur, particularly in patients who receive homovital homografts⁷; thus, at least in theory, the phenomenon of sensitization may cause accelerated degeneration of the second homograft.

To clarify these issues, we investigated early and late survival, homograft valve performance, changes in left ven-

tricular function, and determinants of outcome after a second homograft aortic valve replacement.

Methods

Between January 1973 and December 1997, 144 patients underwent aortic valve reoperation with a homograft by 1 surgeon (M.H.Y.). Eighty-three patients were male, and 61 were female. They ranged in age from 17 to 77 years, mean 49.0 years. The indication for reoperation was aortic regurgitation in 75 patients (52.1%), aortic stenosis in 28 (19.4%), and mixed aortic stenosis and regurgitation in 41 (28.5%). Postendocarditis tissue valve failure occurred in 14 (9.7%). All patients had undergone previous aortic valve replacement with a homograft, and the mean interval between the first and second operation was 11.5 ± 5.2 years. Aortic valve root replacement was performed in 54 patients (38%), and the homograft was inserted freehand in the subcoronary position in 90 patients (62.5%). Homovital homografts were used in 121 patients (84%). Concomitant procedures were performed in 38 patients (26%) as shown in Table 1.

Preoperative left ventricular function was assessed by left ventricular angiography and echocardiography. In 102 patients (71%), left ventricular end-diastolic diameter (LVEDD) was >60 mm. Of these, 32 had fractional shortening (FS) of $<25\%$.

Surgical Technique

Patients were cooled to a temperature of 28°C under total cardiopulmonary bypass. Myocardial preservation was achieved by using crystalloid cardioplegia at 4°C (St. Thomas Hospital, No 1), infused through the aortic root or directly into the coronary ostia. The

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TABLE 1. Concomitant Procedures

	Patients, No. (%)
CABG	19 (13.1)
Mitral replacement	9 (6.25)
Mitral repair	5 (3.47)
Mitral valvotomy	2 (1.38)
Replacement of ascending aorta	2 (1.38)
Left ventricular out flow tract myomectomy	1 (0.69)

myocardial temperature (measured by a myocardial temperature probe placed in the ventricular septum) was reduced to $<10^{\circ}\text{C}$. Cardioplegia infusions were repeated every 20 minutes. The left ventricle was vented through the apex in all cases.

The aortic valve was exposed through a curved aortotomy beginning anteriorly and extending into the middle of the noncoronary sinus. This allowed excellent exposure of the valve and possible enlargement of the root by extending the incision across the annulus into the subaortic curtain for 2 to 3 mm. The valves were inserted either as free homografts in the subcoronary position by means of the 2-suture line technique with a lower interrupted and upper continuous suture line or as an aortic root replacement with reimplantation of the coronary arteries. The decision as to whether to perform root replacement depended on the size of the root, distortion, size of the aortic sinuses, and the need to exteriorize abscess cavities in case of endocarditis. The techniques used for freehand and root replacement have been described in detail elsewhere.^{1,4}

Homograft Details

Homograft valves were harvested under sterile conditions from heart transplant recipients in 121 cases and from brain-dead multiorgan donors in 23 cases. Donors were aged 15 to 60 years (mean 41 ± 12 years). The valves were harvested under sterile conditions from transplant recipients, categorized as homovital, stored at 4°C (Table 2), and cryopreserved if not implanted within 12 days. Antibiotic sterilized valves were obtained from a routine postmortem examination within 48 hours of death, sterilized in antibiotic solution (Table 3) for 24 hours, placed in tissue culture medium (Table 2) at 4°C , and classified as homografts. These valves were not cryopreserved and were implanted within 4 weeks of sterilization. Cryopreservation was used in 12 (8.3%) of the valves. The interval between harvesting and insertion varied from 1 hour to 65 days (mean 11 ± 13 days). All donors were HIV and hepatitis-B surface antigen seronegative.

Follow-Up

At follow-up, functional status and physical examination were assessed, and a chest roentgenogram, an ECG, and an echocardiogram obtained in 141 patients (97.9%). Three patients (2.1%) lived abroad, and follow-up information was incomplete after 1 year. Definition and mode of defining morbidity and mortality were in accordance with the guidelines recommended by the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity.⁸ Early mortality was defined as death within 30 days of

TABLE 2. Antibiotic Solution Used for Homovital Preservation

	Dose
Medium 199, mL	100
Foetal calf serum, mL	80
Sodium Bicarbonate, mL	40
Amphotericin, mg	100
Benzylpenicillin, mg	300
Streptomycin, mg	500

TABLE 3. Antibiotic Solution Used for Homograft Preservation (Gaya 5)

	Dose
Medium 199, mL	88
Sodium bicarbonate 7.4%, mL	40
Vancomycin, mg	500
Ciprofloxacin, mg	200
Gentamycin, mg	80
Cefuroxime, mg	250
Colistin, U	1,000,000
Sterile water	Make up to 980 mL in total
Amphotericin, mg	50

These quantities make up 1 Litre of nutrient antibiotic solution.

the operation and degenerative valve failure as moderate or severe valve malfunction discovered at reoperation or postmortem examination, as well as moderate or severe regurgitation or stenosis (with a peak gradient of >30 mm Hg) diagnosed by routine echocardiographic Doppler imaging in the absence of previous or current endocarditis.

Statistical Methods

The χ^2 test was used to compare frequencies of the different variables, and a P value of <0.05 was considered significant. Probability of survival, freedom from valve degeneration, and reoperation was calculated by use of the Kaplan-Meier method.⁹ The Cox proportional hazards model¹⁰ was used to analyze the time of follow-up after reoperation and time until death or a second reoperation among those patients who did not die early after the operation. According to the Cox model, the hazard function at time t for a patient with covariates x_1, x_2, \dots, x_k is given by the following equation:

$$h(t; x) = h_0(t) \exp \{ \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k \}$$

where $h_0(t)$ is the baseline hazard and the parameters β_1, \dots, β_k are coefficients measuring the degree of influence of the covariates of the hazard function. The hazard is a measure of the rate at which death occurs, so that a positive value of β_1 indicates that the increasing value of the covariate x_1 is associated with decreased survival time. Likelihood-based methods were used to fit and test models. Qualitative covariates were fitted by means of indicator variables. In the case of quantitative covariates, a linear relationship was initially assumed. In case this was significant, the possibility of curvature was explored by adding a quadratic term. Investigations were also made into the possibility of interaction between covariates. Cox regression was used to analyze factors affecting early mortality. The hazard ratio is defined as the risk of dying (or other outcome) at a given time for members of 1 risk group compared with a second group as assessed from the occurrence of deaths in those 2 groups up to that time.

Results

Mortality

There were 5 early deaths (3.4%). One patient could not be weaned off cardiopulmonary bypass and died on the operating table. One was weaned from bypass with the help of a biventricular assist device but later died of multiorgan failure. Three patients died in the intensive care unit because of persistent low cardiac output syndrome leading to multiorgan failure.

Overall actuarial survival was 93% at 5 years and 82% at 10 years (Figure 1). During a period of follow-up that ranged from 30 to 7300 days (mean 2373 days), there were 21 late

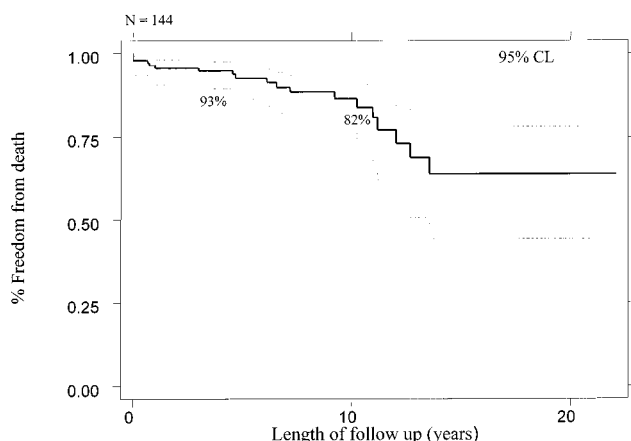


Figure 1. Kaplan-Meier estimate of probability of freedom from death. CL indicates confidence limit.

deaths. In 2 patients, aortic regurgitation resulted in left ventricular failure. In 1 patient, left ventricular function continued to deteriorate; despite a functioning homograft and maximum medical therapy, further complications of ventricular arrhythmias occurred. In another patient, left ventricular failure developed secondary to acute mitral insufficiency with a normally functioning homograft. In 3 patients, the cause of failure could not be confirmed, so it was attributed to aortic homograft failure for the purposes of analysis. One patient died after mitral-valve replacement at another institution.

The potential risk factors investigated as predictors of early death are shown in Appendix 1. Poor left ventricular function (FS <25%) and concomitant procedures, particularly coronary artery revascularization, significantly increased risk of early death.

Table 4 summarizes the causes of late deaths. The possible risk factors analyzed for late death included those used for analysis of early mortality, plus age, sex of the donor, and dissection and storage time of the homografts (Appendix 2). Multivariate analysis identified poor left ventricular function (LVEDD >6) as a significant risk factor for late death (hazard ratio 4.008, $P=0.02$).

In this series, long-term survival (93% at 5 years and 82% at 10 years) after a second homograft aortic valve replacement was similar to that after the first homograft aortic valve replacement reported from our institution,⁴ with a survival rate approaching 92% and 85% at 5 and 10 years, respectively.

Degenerative Valve Failure

With the criteria of presumed degenerative valve failure defined above, freedom from valve degeneration at 5 and 10 years was 96% and 80%, respectively (Figure 2). The linear incidence rate for the total follow-up period of 20 years was 2.88% (95% CI, 2.37% to 3.48%) per patient year. We analyzed the possible influence of all patient- and valve-related covariates (in a multivariate Cox model) in an attempt to define the factors that could affect degeneration. Although none of the factors reach statistical significance, antibiotic-sterilized homograft valves compared with homovital valves and a left ventricular end-diastolic diameter >6 cm tended to

TABLE 4. Causes of Late Death (n=139)

	Patients, No. (%)
Congestive heart failure	6 (4.3)
Cancer	3 (2.1)
Sudden death	3 (2.1)
Unknown	2 (1.43)
Mitral replacement	1 (0.71)
Myocardial infarction	1 (0.71)
Intracerebral bleed	1 (0.71)
Chronic renal failure	1 (0.71)
Chronic liver failure	1 (0.71)
Traffic accident	1 (0.71)
Fungal septicemia (IV drug abuse)	1 (0.71)
Total	21 (14.9)

increase the risk. The hazard ratios were 2.05 ($P=0.061$) and 2.01 ($P=0.093$), respectively.

To define the relative risk of degeneration after the second operation in comparison with that after the first operation, we compared reoperation rates after both operations. Freedom from reoperation after the first homograft was 90% (SE=0.024), 64% (SE=0.04), and 26% (SE=0.03) at 5, 10, and 15 years, respectively (mean=11.5 years), compared with 96% and 80% at 5 and 10 years after the second homograft.

Reoperation

Sixteen patients required further reoperation, all with another homograft. The interval between the second and third operations ranged from 6 months to 20 years (mean 8.6 ± 1.5 years). The cause of valve dysfunction was endocarditis in 5 (3.4%) and degeneration in 11 (7.6%). Freedom from reoperation from any cause was 97% at 5 years and 82% at 10 years (Figure 3). Freedom from endocarditis was 97% at 5 years (SE=0.016) and 94.5% at 10 years (SE=0.024) (Figure 4). This is comparable to freedom from endocarditis rates of 98% and 94% at 5 and 10 years, respectively, reported previously in our series of first-time aortic valve replacement with a homograft.⁴ The

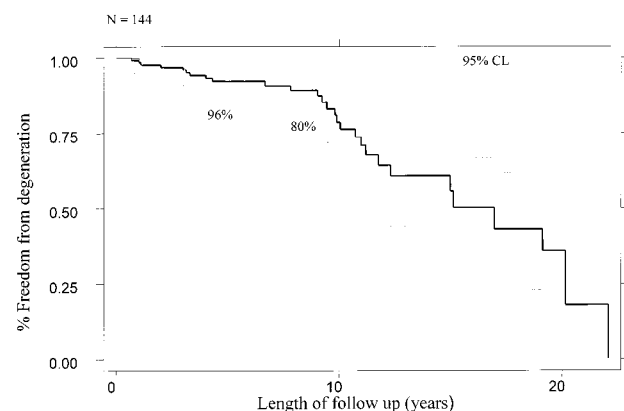


Figure 2. Kaplan-Meier estimate of probability of freedom from degeneration.

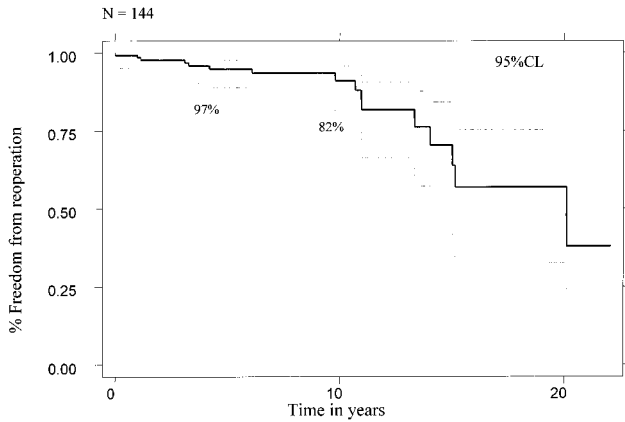


Figure 3. Kaplan-Meier estimate of probability of freedom from reoperation.

linearized incidence rate of endocarditis for the total follow-up period was 0.52% (95% CI, 0.33% to 0.82%) per patient year. Moreover, reoperation for endocarditis-related valve failure was lower after the second homograft in this series (see Methods). Multivariate analysis showed that operation for endocarditis was a risk factor for reoperation (hazard ratio 2.80, $P=0.03$).

Morbidity

Thirty-three patients had other postoperative complications as outlined in Table 5. Eight patients (5.5%) required support with intra-aortic balloon counterpulsation initially after surgery; the patients were later successfully weaned. Five patients (3.5%) required an exploratory sternotomy for bleeding. A permanent pacemaker was implanted in 1 patient who developed complete heart block due to an abscess cavity involving the interventricular septum. Three of 4 patients with neurological events recovered completely before leaving the hospital.

Echocardiography

Follow-up echocardiography was performed on 141 patients (97.9%). Patients underwent echocardiography dur-

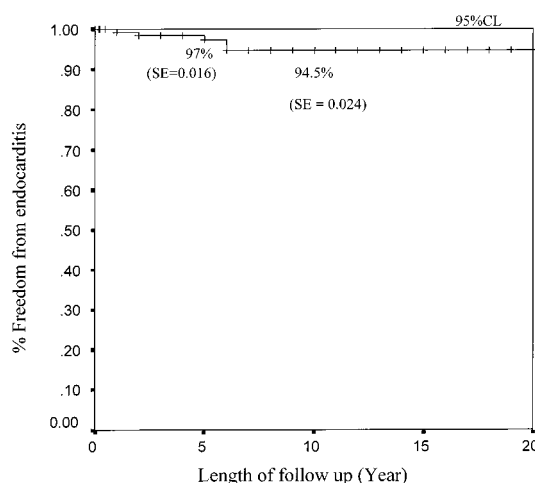


Figure 4. Kaplan-Meier estimate of probability of freedom from endocarditis after second homograft.

TABLE 5. Non fatal Postoperative Complications

Complications	Patients, No. (%)
Low cardiac output	8 (5.5)
Arrhythmias	8 (5.5)
Respiratory	6 (4.1)
Bleeding	5 (3.4)
Neurological	4 (2.7)
Complete heart block	1 (0.69)
Acute renal failure	1 (0.69)
Total	33 (22.5)

ing follow-up every 1 to 2 years. The interval between the second operation and last echocardiogram ranged from 1 to 20 years (mean 7 ± 5 years). Overall, there was no significant change in FS from the preoperative value, but in patients with a preoperative FS of $<25\%$ ($n=32$), there was an improvement in FS of $23 \pm 24\%$ (Figure 5). The left ventricular end-diastolic and end-systolic diameters significantly decreased by $12\% \pm 13\%$ and $8\% \pm 18\%$, respectively (Figures 6 and 7). Left ventricular mass index decreased by $16 \pm 31\%$ (Figure 8).

Discussion

This paper has served to define the rate of survival and valve function after a second homograft aortic valve replacement. Survival appears to be good and is similar to that of a first-time homograft,^{4,5,11} and it compares favorably with our and other series of re-replacement with tissue valves.^{12,13} It also compares favorably with re-replacement with other forms of valve substitute^{14–19} which may be due to the achievement of near-normal flow characteristics in the aortic root. We have previously shown¹³ that in aortic homograft re-replacement, patients with a homograft for the 10 years before re-replacement have a better survival after the second operation in comparison with those with a prior mechanical valve.

In the current study, multivariate analysis showed that preoperative left ventricular function strongly affected late survival, suggesting earlier surgery may give better results. In this study, multivariate analysis of other patient- and valve-related factors did not show any to affect late survival. In a large series of first-time homografts,⁵ we found that patient age, sex, donor age, and allograft viability also affected

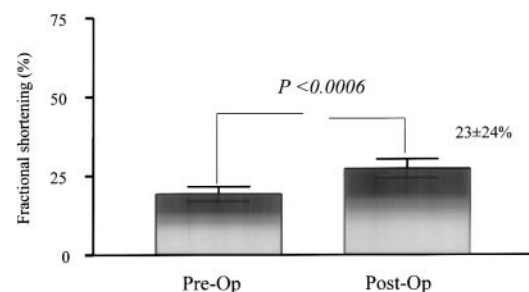


Figure 5. Echocardiographic change in the subset of patients with preoperative FS of $<25\%$. Pre-Op indicates preoperative, and Post-Op, postoperative.

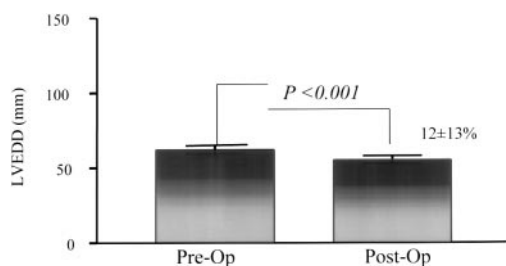


Figure 6. Echocardiographic changes in LVEDD.

survival, and it is likely that some of these factors would also affect outcome in second homograft replacement if this series were larger.

Freedom from degeneration and reoperation in this series also compared favorably with that of first-time homografts. In the absence of endocarditis, there were no early failures, suggesting no accelerated degeneration.²⁰ The interval to reoperation, even in the younger age group, did not affect degeneration after the second homograft, suggesting that previous accelerated degeneration does not predict further degeneration.

We have previously found⁴ that a recipient age of <30 increased the rate of degeneration after a first-time homograft, and it may be that by the second operation patients are older, so that degeneration is less likely. In our large series of first-time homografts, we found that other factors such as donor minus patient age, a donor age >65 years, and diabetes affected degeneration.⁵ Although the current study has a long period of follow-up, the number of degeneration events may not be great enough to predict all the factors affecting degeneration, and some of these factors may also affect degeneration. Concerns over the immunogenicity of fresh homografts that express class I and II major histocompatibility antigens, which could lead to early valve degeneration²¹ because of sensitization to the previous allograft^{20,22} were not supported by our data.

In conclusion, this study has shown that a second homograft aortic valve replacement offers good early and long-term survival, like the first operation. There is no evidence of accelerated degeneration. Left ventricular function improves postoperatively, particularly in patients with poor function before reoperation. Poor preoperative left ventricular function and associated procedures impair survival, suggesting earlier reoperation may further improve outcome.

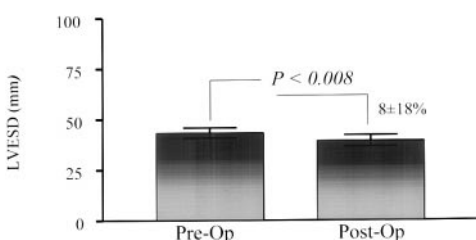


Figure 7. Echocardiographic changes in LVESD.

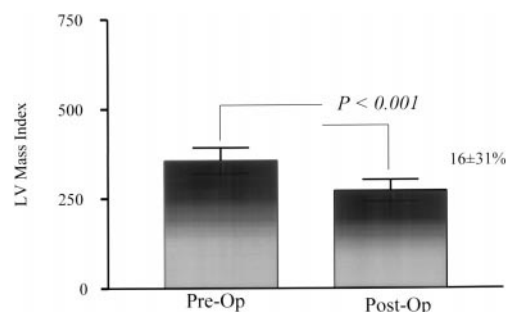


Figure 8. Echocardiographic changes in left ventricular mass index.

Appendix 1

Risk Factors Examined for Early Death

Age
Sex
Left ventricular function (LVEDD, left ventricular end-systolic diameter, FS<25%)
Indication of second operation
Associated procedures
Type of valve used (homograft/homovital)
Type of procedure (root/subcoronary)
Type of first operation
Reoperation interval

Appendix 2

Risk Factors Examined for Late Death and Valve Degeneration

Age
Sex
Left ventricular function (LVEDD, left ventricular end-systolic diameter, FS<25%)
Indication of second operation
Associated procedures
Type of valve used (homograft/homovital)
Type of procedure (root/subcoronary)
Type of first operation
Reoperation interval
Age of donor
Sex of donor
Dissection time of homograft
Storage time of homograft

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