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Homograft Implantation for Aortic Valve Replacement Since 15 Years: Results and Follow-up

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ABSTRACT

Background: The use of homografts in aortic valve replacement is an alternative to other prostheses and has been established in our department for 15 years.

Methods: Since 1992, 360 homografts (HG) have been implanted in adult patients (mean age 51.6 years, 72.8% male). Prospective follow-up was done on an annual basis.

Results: Thirty-day mortality was 5.0% (n = 17); after 5, 10, and 15 years, survival was 88.3%, 84.6%, and 76.0%, respectively. Out of 39 late deaths, 11 were valve-related (10 HG infections, 1 aortic aneurysm). Freedom from reoperation was 99.4% 1 year after operation; after 5, 10, and 15 years it was 94.1%, 78.2%, and 67.3%, respectively. Indications for HG explantation were graft infections (n = 20), calcification (n = 16), regurgitation > grade II (n = 17), perforation (n = 8), and paravalvular leakage (n = 1). Eleven transitoric ischemic attacks, 2 strokes, and 1 cerebral bleeding event were recorded. In echocardiography, the transvalvular pressure gradient changed from 10.55 to 15.02 (P = .004), 19.9 mmHg (P = .056), and 37 mmHg (not applicable) after 5, 10, and 15 years, respectively. Mean HG regurgitation was grade 0.49 before discharge and increased to 1.0 (P < .001), 0.91, and 2.5 after 5, 10, and 15 years, respectively. Ejection fraction increased from 61.9% to 64% after 5 years and to 66% after 10 years (P = .021) and then decreased to 63.5% after 15 years.

Conclusions: Comparing HG with other valve prostheses, survival and graft durability seem to be confirmed. They are vulnerable to infections. The hemodynamic performance is good, and hemorrhagic or thrombo-embolic events are rare.

INTRODUCTION

Using homografts (HG) for aortic valve replacement (AVR) is an alternative to mechanical or biological prostheses because anticoagulation medication can be avoided. Allograft heart valves are known for excellent hemodynamic performance and superior resistance to infections because these valves consist entirely of organic material.

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After the introduction of aortic valve replacement with HG in 1962 [Ross 1962; Barrat-Boyes 1969], the early preparation and preservation techniques did not generate satisfying long-term results until the establishment of antibiotic sterilization [Yacoub 1970] and cryopreservation techniques [Hehrlein 1971; O'Brien 1987; Schütz 1993; Fischlein 1995]. Following promising publications [Barrat-Boyes 1969; Yacoub 1995] describing good midterm results after HG implantation, we launched a program in our institution based on our in-house HG bank.

In the present publication we report on the prospective data concerning the outcome after HG implantation and the annual follow-up including all adult patients from our department; it is the biggest patient group in Germany, with the longest observation period of 15 years.

MATERIALS AND METHODS

Study Design

Since May 1992, 414 patients underwent AVR with HG in our department; patients with congenital heart diseases (n = 55) were excluded due to their additional complex cardiac alterations making a comparison with other patients difficult. Ninety-seven percent of the patients completed the annual follow-up including echocardiography, electrocardiograph (ECG), and history taking.

Homografts

The harvesting of the homografts was done from cardiac transplantation recipients. After treatment with an antibiotic cocktail containing amicacine, ciprofloxacine, vancomycine, amphotericine B, and metronidazole, they were stored in liquid nitrogen at –197°C, using dimethyl sulfoxide as a cryoprotectant [Schütz 1993]. Matching of blood groups or HLA class was not planned. Due to the lack of aortic HG (n = 283), pulmonary HG (n = 68) were utilized as an alternative, based on reports that supported the feasibility of their use [Gerosa 1994; Yacoub 1995].

Surgical Techniques

Between 1992 and 1995, the homografts (n = 75) were implanted using a subcoronary technique conserving the patient's aortic root. All others had root replacements, making a reimplantation of the coronary arteries necessary (n = 276). The procedures were done via a median sternotomy using cardiopulmonary bypass and moderate hypothermia (30 ± 2°C).

Table 1. Clinical Characteristics of All Patients Included

Indication for Surgery	n
Aortic valve stenosis	141
Aortic valve regurgitation	90
Combined aortic valve diseases	56
Native aortic valve endocarditit	44
Prosthetic infection	18
Replacement of pre-existing aortic prostheses	2
All	351

Echocardiographic Analysis

The following parameters were assessed for echocardiographic evaluation: end-diastolic diameter (EDD, mm) and ejection fraction (EF, %) for left ventricular function; peak pressure gradient via the homograft (mmHg), grade of regurgitation, and root diameter (mm) for information about the graft function. Definitions of structural alterations to grafts were made in accordance with Yacoub [Yacoub 1995]; regurgitation was graded as either absent, or mild, moderate, or severe. Stenosis was defined as moderate over a range of 30 mmHg to 50 mmHg and as severe when the gradient was >50 mmHg. In addition, the effects of the type of graft (aortic versus pulmonary), implantation technique (subcoronary versus root replacement), and patient gender were analyzed. Postoperatively, patients underwent ecocardiographic analysis before being discharged, and were re-interviewed and re-examined echocardiographically at the authors' outpatient department on an annual basis.

Data Acquisition and Analysis

Surgical results and follow-up data were reported in accordance with the recommendations of the Ad Hoc Liaison Committee in *Guidelines for Reporting Morbidity and Mortality After Cardiac Valve Interventions* [Akins 2008]. All recorded data were examined statistically using analysis of variance, *t* tests, chi-square test, the Wilcoxon test, and the Cox regression as appropriate for comparison of means. A *P* value <.05 was considered to be statistically significant. A Levene test was used to assess equality of variances. Survival and freedom from reoperation were calculated as cumulative events according to Kaplan-Meier and log-rank tests, with documentation of the patients at risk. Statistical analyses were carried out using SPSS 15.0.1 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Patient Demographics

Out of 359 adult patients, 351 were available for follow-up (97.8%). Of the patients, 253 were male (72.0%), and the mean age at the time of HG implantation was 51.6 years (range, 12 to 84 years), at a mean follow-up time of 182 months (range, 0 to 97.5 months). The indications for aortic valve replacement are shown in Table 1. Additional surgical procedures, singular or in combination, were necessary in 89 patients for replacement of the ascending aorta, in 15 patients for mitral valve operations, and in 42 patients for coronary bypass. Eighteen cases were reoperations after earlier AVRs with xenografts or mechanical prostheses.

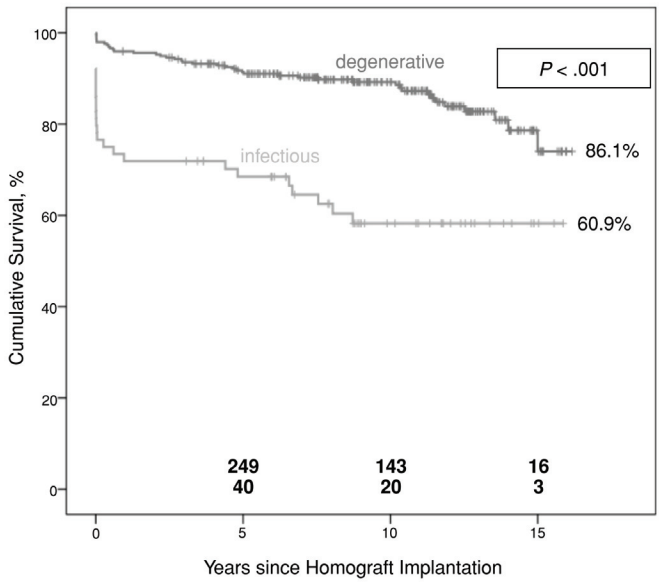

Figure 1. Kaplan-Meier graph depicting actuarial percent patient survival after homograft implantation comparing patients suffering from degenerative with infectious vitia. The early mortality (30 days) is included. Patients at risk are displayed at 5, 10, and 15 years in all similar figures. The significant difference between the groups resulted mainly from the first year after implantation.

Survival

Early mortality within 30 days after operation was 5.0%. Cumulative survival after 5, 10, and 15 years was 88.3%, 84.6%, and 76.0%, respectively. Out of 39 late deaths, 11 cases were rated as valve-related: 10 of these patients had HG infections, and 1 patient died after a dissection of the ascending aorta. In the univariate analysis of categorical factors influencing survival, the significant parameters are shown in Table 2. In particular, comparing degenerative with infectious vitia (Figure 1), it was noticed that survival was significantly lower in patients suffering from aortic valve endocarditis, but after 15 years 60% of those complex patients were still alive. Gender, aortic or pulmonary grafts, subcoronary implantation or root replacement, graft diameter, co-procedures such as coronary bypasses or replacement of the ascending aorta and rethoracotomy rate did not significantly influence the outcome.

Freedom from Reoperation

One year after operation, freedom from repeating the procedure was 99.4%; after 5, 10, and 15 years it was 94.1%, 78.2%, and 67.3%, respectively. Indications for HG explantation were degenerative calcification (n = 16), regurgitation > II° (n = 17), perforation (n = 8), and paravalvular leakage (n = 1). The main reason for HG replacement was graft infection (n = 20), which occurred in 15 patients primarily

Table 2. Univariate Analysis of Categorical Factors Influencing the Survival and the Freedom from Reoperation after Aortic Valve Replacement with Homografts

Factor	Compared Parameters	Higher Cumulative Survival Rate	Log-Rank Test (*P*)
Survival			
Age groups	12-44 years versus 45-64 years versus 65-83 years	12-44 years > 45-65 years > 65-83 years	<.001
Etiology	degenerative versus infectious	degenerative	<.001
New York Heart Association stage	I versus II versus III versus IV	I > II > III > IV	<.001
Urgency of intervention	elective versus urgent/emergency	elective	<.001
Freedom from Reoperation			
Gender	female versus male	female	.018
Age groups	12-44 years versus 45-64 years versus 65-83 years	65-83 years > 45-64 years > 12-44 years	.025
Graft origin	aortic versus pulmonary	aortic	.001

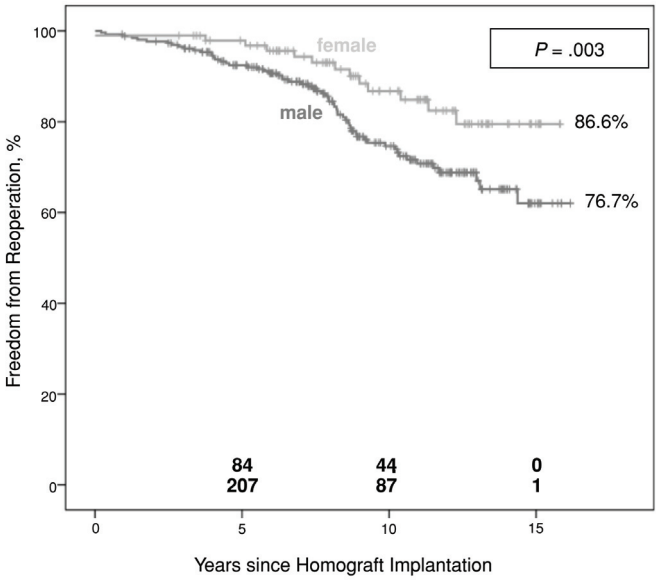

Figure 2. Freedom from reoperation showing significant differences between men and women. The 2 graphs are drifting apart continuously since operation.

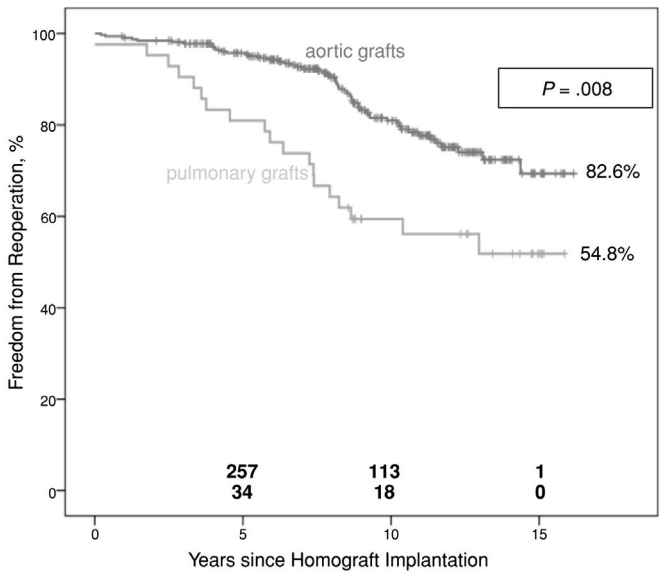

Figure 3. Patients who received pulmonary grafts had a higher incidence of graft failure leading to redo-procedure. Due to these circumstances, pulmonary grafts are not used for aortic valve replacement in our department anymore.

operated on due to degenerative aortic valve disease and in 5 patients with aortic valve endocarditis. One patient out of these had infective relapses after 3 months and 2 years leading to a second and third HG replacement. All others had HG infections 3 years after implantation or later.

In the univariate analysis, patient age, gender, graft origin, and graft size revealed significant results as shown in Table 2. Etiology and implantation technique did not reach statistical significance. Under multivariate criteria in Cox regression, men (P = .032) and patients with pulmonary grafts (P = .002) showed a statistically significant higher risk for HG explantation. In the log-rank test, the necessity for redo-AVR was significantly higher in men (n = 54 versus 7, P = .003) as well as in patients who received pulmonary grafts (n = 15 versus 46, P = .008) (Figures 2 and 3).

Ecocardiography Results

For assessment of the HG function the transvalvular pressure gradient was registered, which increased significantly from 10.55 mmHg after implantation to 15.02 mmHg (P = .004) after 5 years; to 19.9 mmHg (P = .056) after 10 years; and to 37 mmHg (not applicable) after 15 years (Figure 4). The degree of HG regurgitation was 0.49° before discharge, increasing significantly after implantation to 1.0° (P < .001), 0.91° (not significant) to 2.5° (not applicable) after 5, 10, and 15 years, respectively (Figure 6). To evaluate the left ventricular function after AVR, EF was measured planimetrically: it recovered from 61.9% to 64% after 5 years (not significant) and to 66% after 10 years (P = .04), then slightly decreased 15 years after implantation to 63.5% (not applicable). Significant

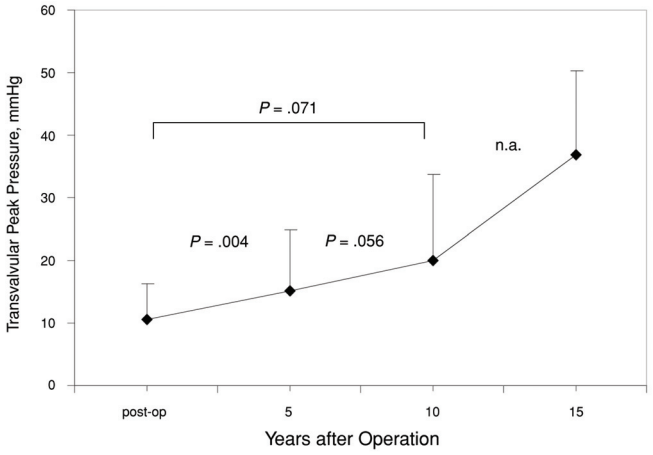

Figure 4. Analysis of echocardiographical data showing transvalvular peak pressure gradients during the observation period. The gradients increased continuously, which was interpreted as beginning graft degeneration.

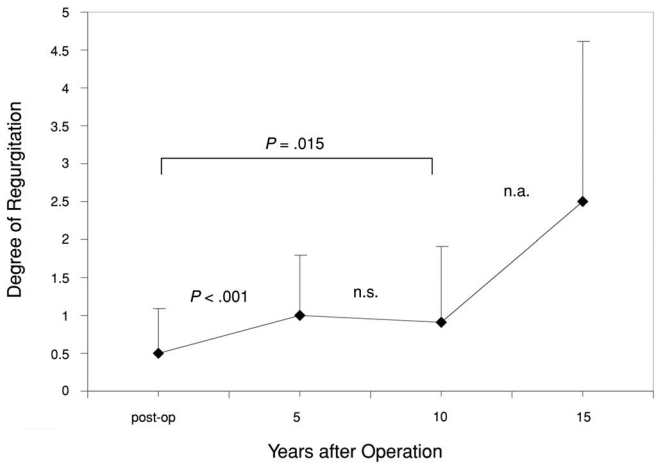

Figure 5. The degree of transvalvular graft regurgitation showing increasing values during follow-up.

results for changes in end diastolic diameter or aortic HG root diameter during follow-up could not be registered.

Bleeding and Embolism

During the observation period, 2 strokes and 11 transitory ischemic attacks (TIAs) were registered. Because anticoagulation therapy is not required after homograft implantation, some patients had ASS or cumarin therapy for other reasons, such as coronary artery disease or atrial fibrillation. Out of these, 1 patient who had intracerebral bleeding was treated with warfarin due to atrial fibrillation. Two cases had single episodes of upper gastrointestinal bleeding, and 4 patients suffered from epistaxis.

DISCUSSION

The intention of using HG for AVR in our department was to obtain excellent hemodynamic conditions, which should be superior to stented xenografts, and—following promising publications [O'Brien 1987; Yacoub 1995] about enhanced preservation methods—with improvement of the long-term durability.

The results presented in this paper, which are currently updated [Kilian 2004], are in support of our hypothesis that the survival rates are comparable to those of other authors reporting on homograft implantation [Yacoub 1995; Lund 1999; O'Brien 2001; Kilian 2004]. Survival rates after the implantation of xenografts were in a similar range [Frater 1998; Borger 2006].

Freedom from redo-AVR, a major issue of interest when comparing HG with xenoprostheses, was 63.3% after 15 years in this study for all age groups. O'Brien [O'Brien 2001] reported 47% freedom from reoperation within the same time period, and another author group achieved 55% after 15 years for HG [Lund 1999]. In comparison with stented porcine prostheses, however, Borger [2006] reported below 80% for patients younger than 65 years, and Frater [1998] showed a similar performance within the same time period (85.1% overall freedom from reoperation) for bovine pericardial prostheses. With regard to the patient age at the date of implantation, our data are at least comparable (Table 2).

In contrast to earlier publications regarding the use of pulmonary grafts for AVR [Gorczynski 1982; Gerosa 1994; Mair 1995], the incidence of graft failure was higher in patients receiving pulmonary grafts in contrast to aortic grafts, which led to the decision not to implant pulmonary grafts in aortic position in our institution anymore (Figure 3).

In ECG the annual follow-up data have demonstrated the excellent hemodynamic advantages of HG in contrast to stented valve prostheses, but show changes during the observation period: to investigate the graft function we annually measured the transvalvular systolic gradient and the grade of regurgitation. Interestingly the pressure gradient after the implantation was comparable to the gradients of native unaltered valves. It increased slowly during the observation period. Even after 10 years the gradients were still below the gradients known from stented valve prostheses [Jin 1996; Banbury 2002]. We interpret these changes in pressure gradients combined with increasing degrees of regurgitation (Figures 4 and 5) most likely as beginning graft degeneration, which may result later on in an elevated rate of HG explantations. According to Naegele [2000], the regurgitation rate in our institution was even higher in patients with pulmonary grafts. This was an additional reason to avoid the use of pulmonary grafts for AVR.

To evaluate changes in the left ventricular function after AVR, we could detect increasing values for the ejection fraction, which were interpreted as a ventricular recovery after restoring normal hemodynamic conditions following the HG implantation. This is in concordance with Jin [1996].

We noticed that graft infections after AVR leading to HG explantation (n = 20, 31.7%) or valve-related deaths caused by graft endocarditis (n = 10) were remarkably high in this patient cohort. The earliest case of graft infection leading to graft explantation occurred 3 months after implantation and may correlate with the graft preparation during the cryopreservation process. All other graft infections were registered much

later and were not brought in correlation with infections caused by graft preservation techniques or with the surgical procedure as such. On the contrary we prefer the use of HG in patients suffering from aortic valve endocarditis, infections of prosthetic heart valves, or endocarditis with aortic root abscesses [Gulbins 2002]. These indications for HG implantations have also been described earlier [Riberi 1997; Niwaya 1999; Naegele 2000]. Remarkably, we had to perform only 5 redo procedures (7.9%) when HG was used for treating aortic valve endocarditis in the first operation. Looking at the higher rate of HG explantations in men (Figure 2), it was noticed that men were more prone to graft infections during the follow-up time than women. We suspect that compliance to endocarditis prophylaxis may be gender related, similar to experiences reported from patients after heart transplantation [Hiemann 2008].

CONCLUSION

Our 15 years of follow-up demonstrate excellent hemodynamics in ecocardiography and a very low incidence for thrombo-embolic or bleeding events. After studying the literature, the age adjusted survival or the rate of redo operations is comparable to the respective rates after implantation of stented biological heart valves. Since HG in our study demonstrated a significant rate of graft infections even after long time intervals, a lifelong endocarditis prophylaxis should be absolutely mandatory. Our data further substantiate the fact that pulmonary grafts for AVR should be avoided.

We still use HG due to their good hemodynamic performance and the fact that they do not need anticoagulation. Finally, HG may even be life saving in patients suffering from acute endocarditis complicated with abscesses, valve destructions, or septal defects.

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REFERENCES

Akins CW, Miller DC, Turina MI, et al. 2008. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 135:732-8.

Banbury MK, Cosgrove DM 3rd, Thomas JD, et al. 2002. Hemodynamic stability during 17 years of the Carpentier-Edwards aortic pericardial bioprosthesis. Ann Thorac Surg 73:1460-5.

Barratt-Boyes BG, Roche AH, Brandt PW, Smith JC, Lowe JB. 1969. Aortic homograft valve replacement. A long-term follow-up of an initial series of 101 patients. Circulation 40:763-75.

Borger MA, Ivanov J, Armstrong S, Christie-Hrybinsky D, Feindel CM, David TE. 2006. Twenty-year results of the Hancock II bioprosthesis. J Heart Valve Dis 15:49-55.

Fischlein T, Schütz A, Haushofer M, et al. 1995. Immunologic reaction and viability of cryopreserved homografts. Ann Thorac Surg 60(2 Suppl):S122-6.

Frater RW, Furlong P, Cosgrove DM, et al. 1998. Long-term durability and patient functional status of the Carpentier-Edwards Perimount pericardial bioprosthesis in the aortic position. J Heart Valve Dis 7:48-53.

Gerosa G, Ross DN, Brucke PE, et al. 1994. Aortic valve replacement with pulmonary homografts: early experience. J Thorac Cardiovasc Surg 107:424-36.

Gorczynski A, Trenkner M, Anisimowicz L, et al. 1982. Biomechanics of the pulmonary autograft valve in the aortic position. Thorax 37:535-9.

Gulbins H, Kilian E, Roth S, Uhlig A, Kreuzer E, Reichart B. 2002. Is there an advantage in using homografts in patients with acute infective endocarditis of the aortic valve? J Heart Valve Dis 11:492-7.

Hehrlein FW. 1971. Preservation problems of homologous and heterologous aortic valve grafts [in German]. Thoraxchir Vask Chir 19:394-5.

Hiemann NE, Knosalla C, Wellnhofer E, Lehmkuhl HB, Hetzer R, Meyer R. 2008. Beneficial effect of female gender on long-term survival after heart transplantation. Transplantation 86:348-56.

Jin XY, Zhang ZM, Gibson DG, Yacoub MH, Pepper JR. 1996. Effects of valve substitute on changes in left ventricular function and hypertrophy after aortic valve replacement. Ann Thorac Surg 62:683-90.

Kilian E, Oberhoffer M, Gulbins H, Uhlig A, Kreuzer E, Reichart B. 2004. Ten years' experience in aortic valve replacement with homografts in 389 cases. J Heart Valve Dis. 13:554-9.

Lund O, Chandrasekaran V, Grocott-Mason R, et al. 1999. Primary aortic valve replacement with allografts over twenty-five years: valve-related and procedure-related determinants of outcome. J Thorac Cardiovasc Surg 117:77-90.

Mair R, Harringer W, Wimmer-Greinecker G, et al. 1995. Aortic valve replacement with cryopreserved pulmonary allografts: five years' follow-up. Ann Thorac Surg 60:S185-8.

Naegele H, Bohlmann M, Döring V, Kalmar P, Rödiger W. 2000. Results of aortic valve replacement with pulmonary and aortic homografts. J Heart Valve Dis 9:215-20.

Niwaya K, Knott-Craig CJ, Santangleo K, Lane MM, Chandrasekaran K, Elkins RC. 1999. Advantage of autograft and homograft valve replacement for complex aortic valve endocarditis. Ann Thorac Surg 67:1603-8.

O'Brien MF, Stafford G, Gardner M, et al. 1987. The viable cryopreserved allograft aortic valve. J Card Surg 2(1 Suppl):153-67.

O'Brien MF, Harrocks S, Stafford EG, et al. 2001. The homograft aortic valve: a 29-year, 99.3% follow up of 1,022 valve replacements. J Heart Valve Dis 10:334-44.

Riberi A, Caus T, Mesana T, et al. 1997. Aortic valve or root replacement with cryopreserved homograft for active infectious endocarditis. Cardiovasc Surg 5:579-83.

Ross DN. 1962. Homograft replacement of the aortic valve. Lancet 2:487-93.

Schütz A, Fischlein T, Haushofer M, et al. 1993. Homografts aus der eigener Herzklappenbank [Homografts from an own valve bank]. Zeitschrift für Transplantationsmedizin 5:194-8.

Yacoub M, Kittle CF. 1970. Sterilization of valve homografts by antibiotic solutions. Circulation 41(5 Suppl):II29-32.

Yacoub M, Rasmi NR, Sundt TM, et al. 1995. Fourteen-year experience with homovital homografts for aortic valve replacement. J Thorac Cardiovasc Surg 110:186-193.