Homograft replacement of the mitral valve: Eight-year results

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Objective: The objective of this study was to assess whether the mitral homograft represents a valuable alternative for complete or partial mitral valve replacement.

Methods: Since 1993, 104 patients underwent mitral homograft replacement surgery. The mean age was 38 ± 15 years. The causes of mitral valve disease were rheumatic disease ($n = 76$), infective endocarditis ($n = 24$), and others ($n = 4$). Sixty-five of these procedures were total homografts, and 39 were partial homografts.

Results: The mean follow-up was 52 ± 35 months (maximum, 117 months). Overall hospital mortality was 4 (3.8%) of 104 patients and 2.5% versus 8.7% for patients without endocarditis and with endocarditis, respectively ($P < .19$). There were 9 late deaths (cardiac, 4; noncardiac, 5). There have been 5 early (<3 months) and 10 late reoperations. Of the remaining 77 patients, New York Heart Association class was I in 61, II in 14, and III in 2. Four patients had endocarditis, and 5 had an ischemic or hemorrhagic event. Freedom from major cardiac events was $71\% \pm 6\%$ at 8 years (partial at 81% vs total at 63% , $P < .19$). Among patients with a total homograft, freedom from major cardiac events was $61\% \pm 9\%$ and $85\% \pm 8\%$ at 6 years in patients younger than and older than 40 years, respectively ($P = .09$).

Conclusion: The risk of early dysfunction related to a mismatch between the mitral homograft and the patient's valve is the main pitfall of the technique. Beyond that stage, the results were comparable with those of bioprostheses in a cohort of young patients.

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Following the original work by Sievers and colleagues,¹ we described, in 1992, a technique of mitral homograft implantation in a case report.² Two years later, we published a series of 43 patients who underwent partial or complete homograft replacement of the mitral valve.³ Since that time, there have been several articles concerning early results of mitral valve replacement with a homograft,⁴⁻⁸ including some negative reports.⁹⁻¹¹ The aim of this study was to establish the midterm results of partial and total mitral homografts on the basis of our experience.

Methods

A total of 104 patients (67 female patients) underwent mitral homograft replacement between February 1993 and July 2002. The mean age was 38 ± 15 years (range, 10-69 years). The causes of mitral valve disease were rheumatic disease ($n = 76$), infective endocarditis ($n = 24$), systemic lupus erythematosus ($n = 1$), marasmic endocarditis ($n = 1$), congenital disease ($n = 1$), and degenerative disease ($n = 1$). Assessment of valve function showed insufficiency

($n = 38$), stenosis ($n = 52$), and mixed disease ($n = 14$). All patients had an anatomic contraindication for valve repair.

Twenty-four patients had undergone previous mitral valve operations (repair, $n = 21$; replacement, $n = 3$). Associated procedures included aortic valve homograft ($n = 7$) or repair ($n = 5$), tricuspid valve homograft with a mitral homograft ($n = 2$) or repair ($n = 3$), reduction of left atrial cavity ($n = 1$), closure of atrial septal defect ($n = 1$), and coronary artery bypass grafting ($n = 1$). Informed consent was obtained from all patients. The rationale for choosing a homograft was as follows (either isolated or combined): age less than 18 years ($n = 14$), woman of child-bearing age ($n = 38$), contraindication to oral anticoagulation ($n = 48$), and acute endocarditis ($n = 24$).

Operative Technique

The operative technique has been described previously.³ All mitral homografts were cryopreserved and were obtained from the Assistance Publique de Paris tissue Bank at Hopital Saint Louis. The operative strategy was decided at the time of inspection. In case of diffuse disease, a total homograft was performed ($n = 65$). In case of a localized lesion (calcification or abscess) with a remaining normal or subnormal valve, a partial homograft was used ($n = 39$). The partial homograft techniques were anterior leaflet reconstruction with a patch of homologous leaflet ($n = 10$) and hemivalve replacement ($n = 29$). In case of a hemivalve, the tailoring of the mitral valve followed the segmentation described by Carpentier and associates¹²: transplantation of A1 and P1 or A3 and P3 with the commissure and corresponding papillary muscle. The grafted segment was larger than the resected part so as to provide some excess tissue.

Among patients operated on for rheumatic disease, 26 received a partial and 50 received a total homograft (32% and 68%, respectively). Among patients operated on for infective endocarditis, 13 received a partial and 11 received a total homograft (57% and 43%, respectively; $P < .09$ vs rheumatic disease).

In all patients prosthetic ring annuloplasty was performed. The size ranges used were Carpentier size 36 ($n = 2$), size 34 ($n = 13$), size 32 ($n = 27$), size 30 ($n = 18$), and size 28 ($n = 3$) and Duran ring size 29 ($n = 11$) and size 27 ($n = 19$). The mean cardiopulmonary bypass time was 116 ± 38 minutes, and the mean cross-clamp time was 103 ± 35 minutes.

Follow-up

Intraoperative transesophageal and postoperative transthoracic echocardiography was performed in all patients. Clinical follow-up was obtained directly from the patient, his or her general physician and cardiologist, or both.

Statistical Analysis

Quantitative variables were expressed as means $\pm$ SD. Comparisons between groups used the Mann-Whitney U test for quantitative variables and the χ^2 or Fisher exact tests for qualitative variables. Analysis of late results was performed on the 3 following end points: survival, survival taking into account only cardiac-related deaths, and a composite end point (freedom from major cardiac events) associating survival with neither cardiac-related death nor reoperation. Cumulative survival was determined for these 3 end points according to the Kaplan-Meier method. Uni-

variate analysis of the predictive factors of event-free survival used a log-rank test for qualitative variables. The analysis of reoperation alone was performed according to the actual method.¹³ All analysis was performed with SAS statistical software (release 6.11, SAS Institute Inc, Cary, NC).

Results

Hospital Events

Hospital mortality ($n = 4$). Overall hospital mortality was 4 (3.8%) of 104 patients. These comprised 2 (2.5%) of 80 patients without endocarditis and 2 (8.7%) of 24 patients with infective endocarditis ($P < .19$). Causes of death were mitral homograft failure, cerebrovascular accident, pulmonary infection, and biventricular failure. Homograft failure resulted in a prolapse caused by either a superficial implantation of the papillary muscles or a large homograft, and the patient died before reoperation could be attempted.

Early reoperations ($n = 5$). There were 5 early reoperations within 3 months because of early valve dysfunction. In 3 patients the mechanism of the early failure was a leaflet restriction related to a deep implantation of the papillary muscles or to an undersized homograft. In these 3 patients intraoperative echocardiography had revealed a moderate degree of mitral regurgitation that had been considered acceptable.

In another case a leaflet suture dehiscence occurred at the 10th postoperative day in a patient who had undergone replacement of an infected prosthesis in a dilated left ventricle. Sizing of the homograft had been roughly estimated from the prosthesis size. In another patient rupture of chordae to the anterior leaflet occurred, probably as a result of chordal erosion by the suture material used for papillary muscle implantation.

The early reoperation rate was higher for total (4/65 [6.1%]) compared with partial (1/39 [2.6%]) homografts ($P < .41$). This patient receiving a partial homograft had complex lesions that required the use of 2 segments of homograft.

Other complications. The following complications were observed: transient cerebrovascular accident ($n = 1$), acute pancreatitis ($n = 1$), pericardial effusion ($n = 5$) with one tamponade, and atrial flutter ($n = 2$).

Postoperative echocardiography. Intraoperative echocardiography revealed either no or trivial regurgitation in all but 3 patients who were reported as having moderate but acceptable regurgitation. There were no patients with mitral stenosis, and the mean gradient immediately postoperatively was 4 ± 1 mm Hg, whereas the mean orifice area was 2.3 ± 0.4 cm².

Late Results

Follow-up was obtained for 99 (95.1%) of 104 patients, and a recent follow-up of less than 12 months was available in 88 patients. The mean follow-up period was 52 ± 34

Figure 1. Eight-year results after mitral homograft implantation: survival (all deaths, 80%; cardiac deaths, 91%), freedom from reoperation (81%), and freedom from major cardiac events (71%).

months, and the maximum follow-up period was 117 months.

Late mortality ($n = 9$). Nine late deaths occurred. Four were cardiac related: recurrent infective endocarditis, pulmonary embolus, congestive heart failure, and bleeding during a reoperation. Five deaths were noncardiac related: laryngeal carcinoma, bronchial carcinoma ($n = 2$), HIV-related sepsis, and trauma. At 8 years, freedom from all causes of death was $80\% \pm 6\%$, and freedom from cardiovascular deaths was $91\% \pm 3\%$ (Figure 1).

Late reoperations ($n = 10$). Ten patients required a late reoperation. The time range of reoperation was 18 to 96 months (mean, 53 months). Seven patients presented with predominant mitral stenosis, and 3 had predominant mitral regurgitation. According to the actual method, $81\% \pm 5\%$ of the patients were free from reoperation at 8 years. Kaplan-Meier analysis showed that $71\% \pm 6\%$ of the patients were free from major cardiac events at 8 years (Figure 1).

The causes for late reoperation were homograft degeneration in 8 patients and recurrent endocarditis in 2 patients. In homograft degeneration the valve appeared to be severely fibrosed, with leaflet and chordal thickening and retraction. Occasionally, commissural, as well as chordal, fusion was observed. Localized calcium deposits were also found on the leaflet and at the papillary muscle implantation sites. The papillary muscle invariably appeared to be completely healed, with a fibrosed scar. There were no cases of chordal or papillary muscle rupture.

The freedom from major cardiac events of partial homografts at 7 years was 81% versus 63% for total homografts ($P < .19$; Figure 2). The freedom from major cardiac events was $76\% \pm 10\%$ in the endocarditis group in comparison with $70\% \pm 7\%$ for the nonendocarditis group

Figure 2. Freedom from major cardiac events (cardiac death and reoperation) was 81% for partial homografts and 63% for total homografts at 7 years ($P < .19$). The difference is related to a larger number of events in the early postoperative period among patients with a total homograft.

($P < .65$). Among patients with a total homograft, the freedom from major cardiac events was lower in patients younger than 40 years of age compared with patients older than 40 years of age ($61\% \pm 9\%$ vs $85\% \pm 8\%$ at 6 years, respectively; $P < .09$; Figure 3). The instantaneous risk of reoperation is represented in Figure 4.

Endocarditis ($n = 4$). There were 4 patients with endocarditis, including 2 drug addicts, all of whom had undergone operations for endocarditis. One patient died before a reoperation could be attempted. One patient was treated successfully medically. Two patients underwent reoperation, including a patient with combined replacement of both the mitral and the tricuspid valve with 2 separate homografts.¹⁴ Recurrence of endocarditis was associated with large and obstructive vegetation with no chordal rupture. The underlying homograft was slightly degenerated in both cases.

Thromboembolic and hemorrhagic events ($n = 5$). Three patients had late transient ischemic attacks while in atrial fibrillation without neurologic sequelae. One patient had a thrombus on the prosthetic ring, which resolved without reoperation. Two patients had severe bleeding (muscular hematoma and gastrointestinal bleeding) related to anticoagulation therapy. Both were successfully treated medically.

Functional result. Of the 77 patients alive without reoperation, 61 were in New York Heart Association class I, 14 were in class II, and 2 were in class III. Three patients had successful pregnancies.

Echocardiographic study. Echocardiography was performed by the transthoracic approach in 71 of 77 patients

Figure 3. Freedom from major cardiac events (cardiac death and reoperation) in patients with total homografts was $61\% \pm 9\%$ versus $85\% \pm 8\%$ at 6 years in patients younger than and older than 40 years of age, respectively ($P < .09$).

Figure 4. Instantaneous risk of reoperation (actual estimation), showing a peak of reoperation during the first postoperative year (which does not exist with bioprostheses) and a progressive increase over 8 years (comparable with the fate of bioprosthetic valves).

and showed an insufficiency graded 0 or 1 ($n = 60$), 2 ($n = 9$), or 3 ($n = 2$). Five patients had mild mitral stenosis with an orifice area of less than 1.5 cm^2 , and 66 patients had no stenosis. The mean gradient across the valve was $5.6 \pm 2.4 \text{ mm Hg}$, with a mean orifice area of $1.7 \pm 0.4 \text{ cm}^2$.

Histopathology

Early explants. Microscopic examination of the early explants revealed that the normal architecture of the valve in 3 layers was preserved (Figure 5). A subacute inflammatory cell infiltrate was noted in most cases, consisting mainly of macrophages. There was evidence of edema and thickening of the endocardium. This was interpreted as a sign of mild

Figure 5. Histologic aspect of a mitral homograft leaflet early after implantation (2 months). Subacute inflammatory reaction with edema and macrophage infiltration, resulting in thickening of the endocardium with preservation of the normal trilaminar architecture, is shown.

Figure 6. Histologic aspect of a mitral homograft leaflet 5 years after implantation. Extensive fibrosis and complete acellularity is shown, with discrete areas of calcification identified by the purple staining.

immunologic cell-mediated rejection. In some cases a fibrotic process was already present.

Late explants. Examination revealed severe leaflet fibrosis with degeneration and hyalinization. Discrete areas of calcification were noted (Figure 6). The leaflet tissue most frequently appeared to be completely acellular. The chordae and their attachments, although slightly thickened and fibrotic, were essentially normal, with a central core of collagen and a lightly thickened endocardium. The papillary muscles were fibrosed with sporadic areas of viable muscle, and significant calcium deposits were frequently observed at this level.

Discussion

Our results show that homograft replacement of the mitral valve can be achieved with an acceptable hospital mortality (3.8%), although early valve failure constitutes a potential pitfall of the technique. Almost all early reinterventions were directly or indirectly linked to a mismatch between the size of the homograft and that of the patient's valve. The mechanism of regurgitation was more frequently a restricted leaflet motion (type III) than a leaflet prolapse (type II).¹⁵ A leaflet suture dehiscence was observed in one patient who had previously undergone replacement with a prosthesis. The difficulty in assessing the size of the homograft led us to consider the presence of a prosthesis as a relative contraindication for the use of a mitral homograft.

In this series the method of valve sizing relied on the postulate that all the elements of the mitral valve are normally proportioned: leaflet dimensions, length of the chordae, and diameter of the orifice. With increasing size of the valve, all the elements would increase according to a fixed ratio. Thus our original theory was that a precise measurement of a single component of the mitral valve would allow us to accurately size the valve. In this series the selected criterion was the height of the anterior leaflet. This parameter was chosen because it was available before the operation on the patient's mitral valve by using transesophageal echocardiography and on the homograft by means of a direct measure by the technicians at the tissue bank.

Soon it appeared that the height of the anterior leaflet provided only a rough estimate of the valve size. Some limitations have been identified: (1) the simultaneous harvesting of the aortic valve led to the resection of some tissue on the anterior leaflet of the mitral valve remaining attached to the aortic homograft, leading to an underestimation of the true dimensions of the mitral homograft; (2) the measurement of the patient's anterior leaflet height was biased by the limits of echocardiography, which did not offer a strictly anteroposterior cross-section of the mitral valve, leading to an overestimation of the valve size; and (3) because of pathologic involvement of the recipient's valve, the size of the anterior leaflet did not necessarily correlate with the dimensions of the homograft, which should be selected.

A simple alternative to the sizing method described above would be to give up the preoperative assessment of the patient's valve and to use as the sole parameter the diameter of the mitral orifice calibrated intraoperatively with an obturator as for a prosthetic valve replacement. The mitral homografts would be indexed at the tissue bank according to the annulus diameter. The causes of valve disease in this series (mitral stenosis and acute bacterial endocarditis) do not produce any annular dilatation, and the assessment of the diameter should truly reflect the dimensions of the mitral valve.

The risk of reoperation for early failure seems to be lower with the partial homograft (2.6%) compared with that seen with the complete homograft (6.2%). This could be due to the fact that the importance of sizing is less critical than for a complete graft. Indeed, by using the remaining parts of the native valve, the reference point technique¹⁵ could be used for guiding the implantation of the partial homograft.

There was no case of systolic anterior motion, despite the systematic use of a small-sized prosthetic ring. As opposed to myxoid valves, there is no excess tissue in mitral homografts, and the risk for obstruction of the left outflow tract is low. Furthermore, once inserted, the homograft leaflets are somewhat restricted, and the tension exerted on the chordae usually prevented the excursion of the anterior leaflet in systole toward the outflow tract.

The papillary muscle implantation technique used in our series was an intraventricular fixation in a side-to-side position on the recipient papillary muscle.³ As opposed to other series,^{9,16} there was no instance of papillary muscle rupture. A rapid healing process was observed, resulting in a stable and fibrotic attachment of the papillary muscles. Although rarely encountered (<5% of the cases), a limit of the technique has been recognized: the subdivision of the recipient papillary muscle in multiple underdeveloped heads raised significant technical difficulties and should be considered as a contraindication for homograft implantation.

The adjunction of a prosthetic mitral ring to the mitral homograft has been critical. As for mitral valve repair, it undoubtedly improved the stability of the results. Ring annuloplasty resulted in an increased surface of contact between the leaflets, which reduced the traction exerted on the subvalvular apparatus, thereby facilitating the consolidation of papillary muscle anastomosis.

The most frequent cause of late valve failure was the degeneration of the homograft. Its functional consequences were more often a stenosis than regurgitation. The combination of a small-sized prosthetic ring with a fibrotic involvement of the homograft probably accounted for the stenosis. Surprisingly, there were no late cases of ruptured chordae in this series, and the degenerative process invariably progressed toward thickening and fibrosis rather than fragilization and dystrophy. These changes vary from that of the degeneration of aortic homografts, in which it is common to observe a pellucid aspect of the cusps.

The valves used in this series were stored with cryopreservation, and only sporadic calcium deposits were observed, as opposed to the massive calcification reported for mitral homografts preserved with other techniques (glutaraldehyde or formaldehyde).¹⁷ Similarly to microscopic findings on aortic homografts, the mitral valves explanted late were completely acellular. Once cryopreserved and inserted, it seems that the mitral homograft does not retain any viability.

Mitral homograft endocarditis occurred only in patients who had undergone operations for endocarditis. Although the use of a mitral homograft did not eliminate the risk for endocarditis, the management of this complication was made easier, and reoperation could occasionally be avoided.

The comparison of the outcome of partial versus total homografts showed that beyond the early postoperative period, the risk of death or reoperation was similar in the 2 groups. Obviously, with a partial homograft, the remaining portion of the autologous valve was spared by the degenerative process, which should have improved the late outcome. On the other hand, the quality of the remaining part of the valve was occasionally suboptimal, particularly in cases of rheumatic disease, and was in itself the source of reoperation in a few cases.

On the whole, the mitral homograft offered a survival without reoperation of 71% at 8 years in this series. The vast majority of the patients were asymptomatic and had a normally functioning mitral valve. Thus, except for the early period, the fate of the mitral homografts appear to be comparable with that of mitral bioprostheses in a cohort of young patients (Figure 4). It is known that the longevity of bioprostheses in the mitral position is inferior to that of their aortic counterparts because of the abrupt closure of the mitral valve in systole.¹⁸ The present study suggests that this observation is also true for the longevity of the homografts.

Finally, as is the case for aortic homografts,¹⁹ the durability of the mitral homograft seems to be related to the patient's age. At younger than 40 years of age, the freedom from cardiac events was lower among patients with a total homograft in our series (Figure 3). In the pediatric group mitral valve replacement with a biologic valve still raises a difficult problem because the bioprostheses have a very limited durability, and it appears that the mitral homograft degenerates rapidly also in children.¹¹

Conclusion

Homograft replacement of the mitral valve can be achieved with reliable long-term results in a large series of patients. The partial homograft technique significantly enhances the possibilities of valve repair, particularly in patients with acute bacterial endocarditis,²⁰ and offers good durability. The mitral homograft carries a greater risk of early dysfunction than does a bioprosthetic valve. Beyond the first postoperative year, the 8-year follow-up of mitral homografts appears to provide results comparable with those of mitral bioprostheses in a cohort of young adults. Relative contraindications for the procedure have been identified and include unfavorable anatomy of the recipient papillary muscles, redo patients already subjected to prosthetic mitral valve replacement, and young recipients who are still growing. Optimal valve sizing is critical, and the method used in the past needs to be changed for a direct intraoperative

measurement of the annulus. By following these guidelines, we believe that it is possible that the results of the mitral homograft can be further improved. Meanwhile, the bioprosthesis and, in particular, the bovine pericardial valve²¹ remain the gold standard for mitral valve replacement with a biologic substitute.

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