Clinical and Hemodynamic Studies in Patients with Homograft Mitral Valve Replacement

By Anthony F. Graham, M.D., John S. Schroeder, M.D., Pat O. Daily, M.D., and Donald C. Harrison, M.D.

SUMMARY
Debate continues regarding the long-term clinical and hemodynamic benefit of homograft replacement of the diseased mitral valve. The results of valve replacement with mitral homografts in the 120 patients who have had operation at the Stanford Medical Center from May 1967 to November 1970 are given. The operative mortality rate has been 5% and the late mortality rate 6%. Anticoagulants were stopped 6 weeks following surgery and there has been only one thromboembolic complication. Ninety percent of the surviving patients are improved clinically. Thirteen of these patients have been restudied 25 to 41 months after receiving homograft mitral valve replacement. Hemodynamic studies showed a 43% decrease in mean left atrial pressure and 42% decrease in mean pulmonary artery pressure with a 10% increase in mean resting cardiac output. Early diastolic gradients between the left atrium and left ventricle averaging 3.0 mm Hg at rest and 6.0 mm Hg during moderate exercise were present. Left ventricular angiography showed a trace of mitral insufficiency in three patients, moderate to severe in three others, and poor contractility in three other patients with normal homograft function. Mitral insufficiency, when present, was thought to result from poor mounting of the homograft on the metal strut rather than primary deterioration of the valve leaflets. These data indicate that fresh homograft replacement of the mitral valve provides good long-term clinical and hemodynamic benefit in most patients.

Additional Indexing Words:
Anticoagulants
Aortic valve homograft
Mitral insufficiency
Thromboembolism

The search for the ideal form of prosthetic mitral valve has been pursued enthusiastically because of the high complica-
tion rate of the earlier forms of metal and plastic prostheses.1-3 The homograft mitral valve appears to answer two of the major problems involved with these earlier valves, i.e., thromboembolism and bleeding associated with anticoagulation. Earlier reports have been conflicting as to the long-term clinical and hemodynamic value of the homograft valve. Gianelly and others4-7 showed good initial hemodynamic and clinical improvement. However, Suzuki et al.8 recently stated that in their series all homograft valves had to be replaced within 25 months following surgery.

This review will present the results of long-term follow-up on a large series of patients who have had mitral homograft replacement.

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at Stanford University Medical Center. Furthermore, it will assess specifically their clinical state, complications after valve replacement, incidence of mitral insufficiency, and significance of the mitral diastolic gradients.

**Methods**

A total of 120 patients have undergone homograft mitral valve replacement surgery at the Stanford University Medical Center between May 1967 and November 1970 under the direction of Dr. Norman E. Shumway. In this group, nine patients had both mitral and aortic homograft replacement and one had tricuspid, mitral, and aortic homografts. The age range of the group was 7 to 70 years (average 44 years) with a female to male ratio of 2 to 1. All patients were in class III or IV of the New York Heart Association classification and all had preoperative hemodynamic assessment by right and left heart catheterization. At surgery, the diseased mitral valve was replaced with a fresh aortic homograft valve which had been obtained and prepared under sterile conditions and mounted on a Teflon-covered titanium strut with an internal diameter of 27–29 mm. Anticoagulants were stopped 6 weeks after surgery. The patients were then routinely followed at 6-month intervals.

Thirteen of the 23 patients who have survived for more than 2 years have been restudied. These patients were all 25 to 41 months postoperative at the time of study. There were nine females and four males with an age range from 32 to 70 years. At the time of operation, two patients had mitral insufficiency secondary to ruptured chordae tendineae, six had pure mitral stenosis, and five had mixed stenosis and insufficiency due to rheumatic heart disease. Each patient had received a single fresh aortic homograft in the mitral position, and one patient (I.O.) had also received a homograft in aortic and tricuspid positions. For follow-up study, each patient was admitted to the hospital and the following studies were performed: clinical examination, ECG, phonocardiogram, echocardiogram, and right and retrograde left cardiac catheterization. Five patients had transeptal left heart catheterization, and the others had simultaneous pulmonary wedge and left ventricular pressure measurements to assess diastolic gradients across the homograft mitral valve. All patients except I.O. had left ventricular cineangiography to assess competency of the homograft valve and left ventricular contractility.

**Results**

The operative mortality (within 30 days) for the 120 patients was 5% (table 1). Several of the early deaths were due to left ventricular outflow obstruction and associated left atrial thrombus formation probably due to malpositioning of the homograft valve. This complication has not occurred recently, and the operative mortality rate in the last 100 cases was 3%. There have been seven late deaths to date which represent one death per 255 months of patient follow-up. The most common cause of death in this small group has been progressive left ventricular failure without evidence of homograft valve dysfunction (table 1).

Of the 107 patients still alive, 100 are now in functional class I or II. The remaining seven are either class III or IV. Of this group four had left ventricular failure without

**Table 1**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>17</td>
<td>13</td>
<td>61</td>
<td>29</td>
<td>120</td>
</tr>
<tr>
<td>Operative deaths</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>LV outflow obstruction and LA thrombus</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Arrhythmias</td>
<td>1</td>
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<td>Cerebral hypoxia</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>Late deaths</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Primary LV failure</td>
<td>3</td>
<td></td>
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<td></td>
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<td>LV failure with mitral insufficiency</td>
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<td></td>
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<td></td>
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<td>Infective endocarditis</td>
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Abbreviations: LV = left ventricular; LA = left atrial.
Hemodynamic Data*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age (yr)</th>
<th>Lesion</th>
<th>Months post-op</th>
<th>Rhythm</th>
<th>PA press (a/d/m)</th>
<th>PW or LA press (a/v/m), mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>1. R.C.</td>
<td>M, 70</td>
<td>MI</td>
<td>41</td>
<td>AF</td>
<td>(52/20/35)</td>
<td>(63/36/50)</td>
</tr>
<tr>
<td>2. A.P.</td>
<td>F, 52</td>
<td>MS</td>
<td>39</td>
<td>AF</td>
<td>(38/14/22)</td>
<td>(84/32/-)</td>
</tr>
<tr>
<td>3. M.K.</td>
<td>F, 60</td>
<td>MI</td>
<td>34</td>
<td>NSR</td>
<td>(72/26/45)</td>
<td>(72/36/47)</td>
</tr>
<tr>
<td>4. L.B.</td>
<td>F, 60</td>
<td>MS</td>
<td>34</td>
<td>AF</td>
<td>(25/12/19)</td>
<td>(38/21/29)</td>
</tr>
<tr>
<td>5. D.D.</td>
<td>F, 37</td>
<td>MS</td>
<td>37</td>
<td>AF</td>
<td>(50/27/34)</td>
<td>(83/45/64)</td>
</tr>
<tr>
<td>6. J.D.</td>
<td>F, 43</td>
<td>MS</td>
<td>28</td>
<td>NSR</td>
<td>(41/16/26)</td>
<td>(72/32/-)</td>
</tr>
<tr>
<td>7. F.C.</td>
<td>F, 57</td>
<td>MS</td>
<td>27</td>
<td>AF</td>
<td>(45/17/23)</td>
<td>(71/32/48)</td>
</tr>
<tr>
<td>8. K.N.</td>
<td>M, 32</td>
<td>MS</td>
<td>25</td>
<td>AF</td>
<td>(104/50/63)</td>
<td>-</td>
</tr>
<tr>
<td>9. E.W.</td>
<td>F, 50</td>
<td>MS</td>
<td>27</td>
<td>AF</td>
<td>(61/31/39)</td>
<td>(109/50/70)</td>
</tr>
<tr>
<td>10. I.O.†</td>
<td>F, 36</td>
<td>AS</td>
<td>40</td>
<td>AF</td>
<td>49/20/28</td>
<td>60/32/43</td>
</tr>
<tr>
<td>12. D.C.</td>
<td>M, 45</td>
<td>MS</td>
<td>25</td>
<td>NSR</td>
<td>(36/18/-)</td>
<td>(65/34/-)</td>
</tr>
</tbody>
</table>

*Preoperative in parentheses.
†Patient had aortic, mitral, and tricuspid homografts.
‡MI graded 0 to +4.

Abbreviations: MI = mitral insufficiency; MS = mitral stenosis; TI = tricuspid insufficiency; TS = tricuspid stenosis; AS = aortic stenosis; AF = atrial fibrillation; NSR = normal sinus rhythm; PA = pulmonary artery; LA = left atrial; PW = pulmonary wedge; LV = left ventricular; CI = cardiac index; a = a wave; v = v wave; m = mean; s = systolic; d = diastolic; ed = end-diastolic.

Clinical evidence of homograft valve dysfunction. The other three patients have been reoperated 6 to 25 months following surgery. Two were found to have severe mitral insufficiency, one due to a paravalvular leak and the other secondary to Candida albicans endocarditis. The other patient had moderate mitral insufficiency and severe left ventricular failure and died at the time of reoperation to replace the homograft. There have been two patients with infected valves in the entire series, and one of these patients died. Thromboembolism has been proven in only one case in the entire group (see below).

Apical systolic murmurs have been heard in 30% of the patients and in most was first noted shortly after surgery.

In the 13 patients restudied, all were functionally class I or II at the time of postoperative evaluation. All had improved since surgery except that two patients (R. C. and D. D.) had noted recent increasing fatigue. There was one thromboembolic episode in this group (K. N.). There were no other complications following surgery, and many patients were asymptomatic and not receiving any cardiac medications. Nine of 13 patients were still in atrial fibrillation. In ten

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patients, clinical evidence of pulmonary hypertension and right-sided failure, which had been present before surgery, had disappeared. Two patients (A. P. and L. B.) had clinical evidence of mild tricuspid insufficiency which had been present preoperatively. In all the patients the first sound at the apex was composed of two prominent components. Ten of the 13 patients studied had soft apical systolic murmurs. These were variable in timing, being early, late, or pansystolic. Several patients had early diastolic flow murmurs (A.P., D. D., and D. C.) which were later shown to be associated with a moderate mitral insufficiency. Only one patient (K. N.) had an isolated diastolic murmur. An opening snap was not heard in any patient. A presystolic gallop ($S_1$) was heard in one patient (D. D.).

Review of the cardiac series showed a decrease in heart size and clearing of pulmonary vascular congestion in 85% of the patients, but in several there was residual left atrial and right ventricular enlargement. Phonocardiography confirmed the murmurs and documented the two prominent components of the first heart sound heard clinically. This finding is in agreement with the recent work of Gianelly who stated that the first component was due to the closure of the homograft valve leaflets occurring in early systole. The origin of the second component remains unclear. Echocardiography showed the movement of the homograft mitral valve ring and its leaflets. These movements are of normal amplitude but have a characteristic square-wave appearance as previously described. The rapid posterior motion of the valve leaflets corresponds with the first heart sound.
Changes in mean left atrial pressure at rest (A.) and mean pulmonary artery pressure (B.). The preoperative values are at the left of each panel and the postoperative values on the right. Left atrial pressure and pulmonary artery pressure decrease after surgery (see text).

**Hemodynamics**

The hemodynamic data on the 13 patients restudied are summarized in table 2. Mean left atrial pressure postoperatively was 13 ± 3.3 mm Hg in 12 patients and 27 mm Hg in another (A. P.) (fig. 1A). This is a decrease of 43% from the values before valve replacement. Postoperatively the mean pulmonary artery pressure was 19 ± 5.4 mm Hg (fig. 1B) which is a decrease of 42%. Diastolic gradients across the mitral valve were measured by transeptal left heart catheterization (five patients) or via simultaneous pulmonary artery wedge and retrograde left ventricular pressure measurements. Small diastolic gradients were present across the homograft mitral valve in each patient, but all reached diastasis. The mean diastolic gradient at rest for the whole group was 4.5 mm Hg and rose to 7.7 mm Hg during exercise. In the ten patients with little or no mitral insufficiency the mean diastolic gradient at rest and during exercise was 3 and 6 mm Hg, respectively. In three of these cases (L. B., J. D., and K. N.) the insufficiency was only shown on angiography (+1). In two others (D. C. and A. P.) there was moderate insufficiency (2+) on angiography with V waves as high as 36 mm Hg at rest. In one patient (D. D.) there was severe mitral insufficiency shown on angiography (4+) and V waves rising to 55 mm Hg with exercise. In the seven other patients left ventricular angiography showed normal homograft valve function. Left ventricular contractility was poor in three of these patients (R. C., F. C., and E. W.) in spite of normal homograft mitral valve function.

Patient I. O. had undergone triple valve replacement and was found to have mild insufficiency of mitral, aortic, and tricuspid homograft valves. Case K. N. presented with a femoral artery embolus following the recent onset of atrial fibrillation. He was found to have an apical rumbling diastolic murmur on physical examination. Catheterization revealed a mitral diastolic gradient of 5 mm Hg at rest rising to 17 mm Hg with exercise, and diastasis was not reached. Left ventricular angiography showed grade 1 mitral insufficiency. The history and catheterization findings were thought to represent a left atrial thrombus with outflow obstruction and a mild degree of mitral insufficiency. However, at reoperation 25 months following insertion of the homograft valve, the leaflets appeared normal with only mild central insufficiency but no fusion of the commissures (fig. 2). There was no clot in the left atrium. Microscopic examination showed a mild inflammatory infiltrate around the base of the valve and increased numbers of fibroblasts in the leaflets (fig. 3). The diastolic gradient may have been partially due to a small valve ring (27 mm) and an inaccurate measurement of pulmonary wedge pressure.

The mean resting cardiac output of the patients studied was 2.3 liters/min/m², an increase of 10% since surgery. There was a further increase to a mean of 3.4 liters/min/m² with exercise. This small change in cardiac output and poor exercise response for the group is partially accounted for by those patients with moderate mitral insufficiency (A. P. and D. D.), as well as those with primary left ventricular failure and normal valve function (R. C., F. C., and E. W.). The arteriovenous oxygen difference at rest for the group fell an average of 25% to 5 vol/100 ml and with exercise remained...
Mitral homograft from ventricular side showing mild degree of central insufficiency due to poor coaptation of leaflets (patient K.N.).

Discussion

The replacement of diseased heart valves with homografts dates back to the work of Lam et al. in 1952, followed by Murray et al. in 1956, who placed free aortic homografts in various positions including the mitral. Lower, Stofer, and Shumway in 1961 next reported the use of the autologous pulmonary valve as a replacement for the mitral valve. The initial experiences were troubled with complications of stenosis of the homograft and left ventricular outflow obstruction, as well as frequent reports of valve deterioration. Various methods of sterilization of the grafts have elevated at an average of 10 vol/100 ml which represented a decrease of 15% since surgery.
been employed including high-energy irradiation, freeze-drying, storage in formaldehyde or β-propiolactone, and preparation and storage in an antibiotic medium. It is now thought that several of these sterilization methods may contribute to late deterioration and calcification of the valves. Problems with poor coaptation of the leaflets and commissure support, producing severe mitral regurgitation, have led to the introduction of a ring with struts to which the homograft is sewn at the time of surgery. The results of our whole series show that there has been satisfactory clinical improvement in patients having homograft mitral valve surgery. To date the late mortality rate has been low (one death per 255 months of patient follow-up), and the cause of death in these patients was often unrelated to homograft valve dysfunction (see fig. 1). In addition to the symptomatic improvement following surgery, these patients have been free from embolic complications with one exception. This is a major advantage over the other forms of prosthetic valves which have 10 to 30% reported incidence of thromboembolism within 5 years. They have also avoided the risks associated with long-term anticoagulant therapy.

In patients restudied, hemodynamic data show that there has been a significant decrease in both pulmonary artery and left atrial pressures since surgery. There has been no major dysfunction of the homograft valve in our patients. Although small early diastolic gradients do exist across these valves, this may be related to the size of the valve ring onto which the homograft is sewn at the time of surgery. These diastolic gradients (3.0 mm Hg at rest and 6.0 mm Hg with exercise) are slightly less than with other forms of prosthetic valves. To date there has been no proven organic stenosis of a homograft mitral valve.

Mitral insufficiency occurred to varying degrees in six patients and had been present since shortly after surgery in four of these. Review of left ventricular angiograms show prolapse of the valve leaflets into the left atrium just prior to left ventricular ejection in eight patients (fig. 4). This was associated with a trace of insufficiency in three patients. With the onset of left ventricular ejection there was further bulging of the valve leaflets into the atrium, and they remain in this position until end-systole (fig. 5). At this point in most patients, there is no evidence for insufficiency of the valve. We postulate that the bulging of the leaflets into the atrium in early isovolumic ventricular contraction is related to the lack of papillary muscle support of these valves. In case D. D. there was actually prolapse of one of the leaflets resulting in severe mitral regurgitation.

Figure 4
Left ventricular cineangiogram (right anterior oblique) from patient L.B. End-diastole showing valve ring (X) with prolapse of homograft leaflets into left atrium (Y) and central mitral regurgitation (Z).

Figure 5
Left ventricular cineangiogram (right anterior oblique) from patient L.B. End-systole showing valve ring (X) with prolapse of homograft leaflets (Y) but no mitral regurgitation.
In addition, the central regurgitation seen in early systole may result from poor leaflet coaptation, secondary to curling of the valve leaflets, which actually improves with increasing intraventricular pressure. This would explain the lack of initial insufficiency during the ejection phase of systole in most of these patients. In certain patients with more significant mitral insufficiency, there appears to be slight retraction of the leaflets (see fig. 2) as shown at reoperation in case K. N. Histologic examination of this valve showed only a few inflammatory cells around the base of the valve and fibroblasts in the leaflet (see fig. 3), but no leaflet degeneration. This makes it unlikely that the insufficiency was due to primary deterioration of the valve. This lack of valve deterioration may be related to the technique of using fresh valves prepared only in an antibiotic solution. A more likely explanation for varying degrees of mitral insufficiency is poor mounting of the valve on the ring at the time of surgery. Small differences in surgical technique may prevent coaptation of leaflet edges and allow small degrees of mitral insufficiency. This would explain why some murmurs have been present since the time of surgery.

Left ventricular angiography demonstrated the poor correlation between homograft valve function and left ventricular contractility in three patients. In those patients (R. C., F. C., and E. W.) who showed normal valve function there was evidence of poor contractility as well as elevated left ventricular end-diastolic pressures. This may be due to longstanding left ventricular dysfunction secondary to rheumatic mitral valvular disease.20 Other causes of left ventricular dysfunction, i.e., coronary artery disease, intraoperative myocardial infarction, and systemic hypertension, must be considered in these patients. Thus, ultimate prognosis of these patients does not always depend on valve function alone. The poor response in cardiac output to exercise may also be partially explained by the above nonvalvular related causes.

Conclusion

Review of our series of mitral valve homografts shows both a low operative (5%) and late mortality rate (6%). There has been clinical improvement in the majority of patients and they have been free of both the complications of thromboembolism and the risks of anticoagulants. Mitral diastolic gradients are smaller than with other forms of prosthetic valves. Mitral insufficiency when present is frequently mild and usually not related to primary degeneration of the valve leaflets. This may be corrected by better technique in mounting the valve at the time of surgery. These clinical results as well as the detailed postoperative hemodynamic data presented indicate that fresh stent homograft mitral valve replacement offers satisfactory long-term function.

References


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