Bacterial Endocarditis Following Homograft Replacement of the Aortic Valve

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SUMMARY
Endocarditis was encountered on an aortic homograft valve in 14 of 539 patients, giving a total incidence of 2.6%. It was an early postoperative complication in five patients (0.9%), and only one of these survived. Four hundred and six hospital survivors were followed for periods up to 76 mo. Nine of these patients (2.2%) developed infection of the homograft valve 11 to 66 mo postoperatively and four survived. Late endocarditis occurred more commonly in patients with a history of endocarditis prior to operation (P = 0.005). In only one of the nine patients with late endocarditis was the infection related to a peripheral leak around the graft. Most patients with late endocarditis rapidly developed severe homograft valve incompetence, which was the cause of death in four of the nine. Six patients were reoperated on and three of these survived.

Additional Indexing Words:
Homograft aortic valve incompetence

A HOMOGRAFT aortic valve is preferred in patients requiring aortic valve replacement at Green Lane Hospital.1 Between August 1962 and March 1969, 539 patients underwent initial homograft replacement of an aortic valve unassociated with other valvular surgery, and follow-up data are available on all but one of these. In 14 patients, endocarditis is known to have occurred on the homograft valve. In five the infection was apparent in the early postoperative period prior to dismissal from hospital; in nine it was a later event.

Four of the homograft valves were collected sterile and freeze-dried. The remainder were obtained using nonsterile technics and were sterilized with either beta propiolactone (9) or ethylene oxide (1) and then either freeze-dried or kept in Hank’s solution until used. Fragments of aortic wall trimmed from the graft at the time of operation were cultured in each instance, and all were reported free of infection. The development of endocarditis on the homograft valve could not be related to the mode of collection, sterilization, or storage of the valve in this series of patients.

Early Endocarditis
Five patients, aged 26 to 66 years, developed endocarditis early postoperatively, although this complication has not been encountered in the 255 patients operated on since March 1966. All had received antibiotics (penicillin, 1,250,000 units, and streptomycin, 1.25 g twice daily) following operation. None had a previous history of bacterial endocarditis, although microscopic examination of the surgically excised valve of one patient was indicative of relatively recent infection. Two patients underwent operation at a time when there was an unusual, unexplained, high incidence of infection following operation. In one patient, who sustained severe cerebral damage at the time of operation related to accidental failure of the perfusion apparatus, the endocarditis was a terminal unrecognized

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event associated with late breakdown of the sternal wound.

An unexpected degree of temperature elevation was present from the time of operation in one of these five patients and developed within 14 days in the others. Three patients experienced rigors, and clinical evidence of embolic phenomena was also present in three. None was noted to have splenomegaly.

In two patients the infecting organism (Streptococcus viridans in one, coagulase positive Staphyloccocus in the other) was isolated from multiple blood cultures during life. Blood cultures were negative in two patients while receiving antibiotics, and in one antemortem cultures were not obtained. The bacteriologic diagnosis in these three patients was made at autopsy. In two, micro-organisms were seen within the vegetations from which Klebsiella was cultured; in the other there was a fungus infection, probably Aspergillus.

One patient with Streptococcus viridans endocarditis was treated with penicillin for 1 mo and clinically cured. Four years later he remains well, requires no cardiac therapy, and is actively employed despite clinical and cineangiographic evidence of moderate aortic incompetence. The remaining four patients died with severe aortic incompetence despite appropriate antibiotic treatment and came to autopsy 1 to 6 weeks after operation. Noncalcified vegetations were found on the homograft valve in all. In two, the cusps were almost completely destroyed. Additional findings included an abscess surrounding but not involving the left coronary artery in one patient; in another there was a 6-mm rupture in the belly of the noncoronary cusp, as well as a localized deficiency in the lower suture line which communicated with a vegetation on the medial wall of the atrium. The graft host suture lines in other patients were intact. Cardiac valves, other than the aortic valve, showed no evidence of infection in any patient.

Late Endocarditis

Prior to April 1969, nine patients (table 1) were recognized to develop bacterial endocarditis on the homograft aortic valve as a late event 11 to 66 mo following operation. Over the period during which these patients underwent their initial operation, August 1962 to November 1967, a total of 406 patients had homograft replacement of the aortic valve and were dismissed from the hospital. They have been followed for periods up to 76 mo (table 2) and for a total of 933 patient years, giving an incidence of late bacterial endocarditis of one case per 104 patient years. The incidence of late endocarditis in the 406 patients was 2.2% and has not increased in those followed for longer periods (table 2).

A statistically significant difference \( P = 0.005 \) was noted between the incidence of late homograft valve infection in patients with a history of bacterial endocarditis prior to operation and those without such a history. Thus, among the 42 hospital survivors in this series with a previous history of bacterial endocarditis, four developed late homograft valve infection (10%) although none had evidence of active infection in the valve removed at operation. In contrast, only five patients out of 364 hospital survivors without a previous history of bacterial endocarditis (1.4%) have been noted to encounter this complication.

In general, the mode of presentation was that usually encountered with bacterial endocarditis. The only exception occurred in a patient (case 3, table 1) who received penicillin orally as prophylaxis against rheumatic fever. Although he gave a history of excessive sweating, neither this nor fever was observed during 2½ weeks' observation in the hospital, and he was not treated for endocarditis. Blood cultures obtained prior to reoperation for severe progressive aortic incompetence were subsequently positive, and the same organism was cultured from the surgically removed homograft valve. In one patient (case 9) the infection was due to Candida parakrusei. Reoperation was undertaken in the absence of severe aortic incompetence when it seemed that continuing medical treatment with amphotericin B would lead to important renal impairment. In the remaining seven patients the infection was caused by strepto-
# Table 1

## Late Homograft Valve Endocarditis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex/age</th>
<th>Initial disease*</th>
<th>Onset of endocarditis (mo postop.)</th>
<th>Possible predisposing factors</th>
<th>Organism</th>
<th>Degree of homograft incompetence</th>
<th>Duration (mo) of endocarditis to re-op. or death</th>
<th>Re-operation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M 27</td>
<td>AI</td>
<td>66</td>
<td>Carious teeth</td>
<td>Streptococcus viridans</td>
<td>Severe</td>
<td>1</td>
<td>Yes</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>F 60</td>
<td>AS/AI</td>
<td>37</td>
<td>-</td>
<td>Staphylococcus (coagulase negative)</td>
<td>Severe</td>
<td>7</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>M 17</td>
<td>AI</td>
<td>21</td>
<td>Carious teeth</td>
<td>Enterococcus</td>
<td>Severe</td>
<td>2</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>M 34</td>
<td>AI</td>
<td>35</td>
<td>-</td>
<td>Staphylococcus (coagulase positive)</td>
<td>Severe</td>
<td>2</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>F 50</td>
<td>AS</td>
<td>16</td>
<td>Bulky valve</td>
<td>Streptococcus viridans</td>
<td>?Severe</td>
<td>¼</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>M 47</td>
<td>AS</td>
<td>26</td>
<td>Diabetes mellitus</td>
<td>Staphylococcus (coagulase positive)</td>
<td>Moderate</td>
<td>-</td>
<td>No</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>M 51</td>
<td>AS</td>
<td>25</td>
<td>-</td>
<td>Streptococcus viridans</td>
<td>Severe</td>
<td>4</td>
<td>Yes</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>M 43</td>
<td>AS/AI</td>
<td>18</td>
<td>-</td>
<td>Streptococcus viridans</td>
<td>Severe</td>
<td>6</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>M 32</td>
<td>AI</td>
<td>11</td>
<td>Perivalvular leak</td>
<td>Candida parakrusei</td>
<td>Moderate</td>
<td>2</td>
<td>Yes</td>
<td>Alive</td>
</tr>
</tbody>
</table>

*AI = aortic incompetence; AS = aortic stenosis.
Table 2

Relation of Late Endocarditis to Length of Follow-up

<table>
<thead>
<tr>
<th>Months follow-up</th>
<th>&lt;12</th>
<th>12-23</th>
<th>24-35</th>
<th>36-47</th>
<th>48-59</th>
<th>60+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>406</td>
<td>334</td>
<td>220</td>
<td>118</td>
<td>52</td>
<td>12</td>
<td>406</td>
</tr>
<tr>
<td>No. of cases B.E.*</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>% incidence B.E.</td>
<td>0.2</td>
<td>0.9</td>
<td>1.4</td>
<td>0.8</td>
<td>0</td>
<td>8.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*B.E. = bacterial endocarditis.

cocci or staphylococci, all of which were sensitive to penicillin. Each patient received large doses of this drug parenterally for at least 4 weeks, sometimes with additional antibiotics. All were clinically cured of their infection after this period but despite this developed important homograft valve incompetence (table 1).

Four of the nine patients are alive 8 to 35 mo later, one (case 6) without reoperation who remains well with residual moderate incompetence, and the others following reoperation (repeat homograft valve replacement) which was required because of the development of severe aortic incompetence and uncontrollable heart failure in two, and renal damage from amphotericin B therapy in one (case 9). Five patients died, one from rupture of a mycotic basilar aneurysm, one from severe incompetence before surgery could be performed, and three (all in extremis) during or following reoperation for incompetence.

Reoperation was thus undertaken in six of the nine patients, and in two active infection was present in or around the valve at the time. One of these latter (case 3) died of arrhythmia postoperatively, but the other (case 9) remains well 12 mo later. No surviving patient has suffered recurrent endocarditis to date.

Examination of the homograft valve removed at operation or autopsy was possible in eight of the nine patients. In six, there was marked disorganization of the homograft valve cusps with extensive bulky calcified vegetations and cusp perforations in two instances. In two patients the leaflets were less affected; in one the left coronary cusp only was partially detached in association with a para-aortic abscess, and in the patient with Candida infection, the leaflets were uninvolved, as the infective focus lay adjacent to a large peripheral suture line leak behind and below the noncoronary sinus of the graft. Additional findings were a small chronic and uninfected peripheral leak between the homograft and host tissue in one patient (case 1) and a sterile abscess in the myocardium behind the origin of the aorta in another (case 4).

On the assumption that poor function of the homograft valve should predispose to late infection, the details of placement of the initial homograft were carefully reviewed and correlated with the findings at autopsy or reoperation. Malplacement was of prime importance in only one case (case 9), in which a large peripheral suture line leak was the focus of a Candida infection. It may have contributed in one other case (case 5), in which the valve was definitely too large for the host root and the leaflets were excessively redundant and folded. Other possible predisposing factors are listed in table 1.

Discussion

There has been a low (0.9%) incidence of bacterial endocarditis in the early postoperative period following homograft replacement of the aortic valve, and this complication has not been encountered since March 1966. The reason for the apparent absence of infection from this time is not clear and was not associated with any change in the routine antibiotic regimen of penicillin and streptomycin received by all these patients postoperatively.

Late homograft endocarditis has been slightly more common (2.2%). Such an illness is usually similar to endocarditis developing on the host's aortic valve, except that it almost always results in severe destruction of valve tissue and the rapid development of severe aortic incompetence, for which the only
effective treatment is a further valve replacement. It is noteworthy that all 14 infected valves in this series had been either chemically sterilized or freeze-dried. This treated leaflet tissue remains inert, is not replaced by host tissues, and is presumably more rapidly destroyed by the infection than living leaflet tissue.

Infection has also been encountered following replacement of the aortic valve with a Starr-Edwards prosthesis. In one large series this resulted in valve failure in 3.7% of patients surviving operation and followed for periods up to 52 mo. There appear to be two important differences between late endocarditis following prosthetic and homograft valve replacement. Firstly, with a prosthetic valve the infection is usually associated with a suture line leak around the device. In this homograft series there is only one example of late infection directly related to a peripheral suture line leak, despite the fact that such leaks have been relatively common around a homograft valve. Secondly, late endocarditis on a prosthesis is most difficult if not impossible to eradicate with antibiotics, while with a homograft valve the infection can nearly always be cured so that if and when reoperation is required the surgical field is usually clean.

In attempting to prevent this complication, we have not recommended the continuous use of prophylactic antibiotics on a long-term basis. Our experience with one patient (case 3) and that of others with patients on antirheumatic prophylaxis would not suggest that this approach is likely to be helpful. The awareness of the potential these patients have for the development of endocarditis on their homograft valve should alert one to the necessity for appropriate investigations in the case of an initially nonspecific febrile illness, particularly when associated with progressive aortic incompetence. Dental treatment, when necessary, should preferably be undertaken prior to operation. Following operation, regular dental care is advisable, and extractions and vigorous dental treatment should be performed under antibiotic cover, as should other surgical procedures likely to be associated with a bacteremia. Specific pyogenic infection should, of course, be treated with appropriate antibiotics. The finding in this series that late homograft valve infection is seven times more common in patients with a previous history of subacute bacterial endocarditis indicates the need for particular care in this group of patients.

These results show that late homograft valve infection is usually a lethal complication, because of the rapid development of severe incompetence and either the late referral of moribund patients or unwise procrastination in advising reoperation in the hope that continued antibiotic treatment and further decongestive therapy will improve the situation. Accordingly, it must be emphasized that reoperation should be undertaken immediately after incompetence is recognized to be severe and, if necessary, before the completion of a course of antibiotic therapy.

References
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