Clinical Outcome and Long-Term Prognosis of Late Prosthetic Valve Endocarditis: A 20-Year Experience

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A prospective study of the clinical characteristics and evolutionary patterns of 59 cases of late prosthetic valve endocarditis (LPVE) that occurred between January 1975 and December 1994 was performed. Of these 59 cases of LPVE, 48 involved mechanical valves and 11 involved biological valves. Etiologies were as follows: streptococci, 41% of cases; staphylococci, 25%; enterococci, 13%; and miscellaneous, 21%. Echocardiography documented vegetations in 21 patients, paravalvular abscesses in 10, and prosthetic leaks in 34. Emboli occurred in 22 patients, and heart failure in 19 patients. Forty-two patients received medical treatment alone, and 17 received medical treatment and underwent valve replacement surgery. The in-hospital mortality rate was 25%; staphylococcal infection caused 67% of deaths, streptococcal infection caused 5%, and other etiologies caused 23% (P = .0004). After adjustment for age and type of prosthesis, multiple logistic regression revealed an odds ratio for death due to nonstreptococcal infections of 9.67. The overall survival rate was 59% at 5 years and 52% at 10 years. During follow-up, 17 patients needed new valves. At the end of follow-up, only 13 patients remained alive and had the same prosthesis that they had at the time of the diagnosis of LPVE.

In recent years, improvements in the diagnosis and management of prosthetic valve endocarditis have occurred, but the disease is still a serious clinical problem [1–4]. Infective endocarditis involving prosthetic valves has been classically divided into two forms: early and late. Early endocarditis is caused by contamination of the valve during or soon after surgery; the infection is normally caused by staphylococci or gram-negative rods, and the prognosis is poor [1–5]. Antibiotic prophylaxis during valve replacement surgery and careful attention to infection control in the immediate postoperative period have probably reduced the incidence of this type of endocarditis, although the risk is still substantial [6–8].

Late endocarditis is caused by contamination of the valve secondary to bacteremia, as occurs in native valve endocarditis. Its incidence may increase in the near future because the number of individuals with prosthetic valves is increasing, and although the prognosis of this form of endocarditis is better than that of the early form [9, 10], there are still doubts regarding the best therapeutic approach.

From January 1975 to December 1994, we prospectively studied all cases of late prosthetic valve endocarditis (LPVE) that occurred at our institution. In the present study, we analyze these cases as well as our data from a previous study [10] with a special emphasis on clinical outcome and long-term prognosis.

Patients and Methods

From January 1975 to December 1994, 533 consecutive cases of infective endocarditis were diagnosed at our hospital. Of these 533 cases, 59 (11%) occurred ≥12 months after valve replacement and were considered LPVE. The diagnosis of LPVE was made when two of the following criteria were present: (1) two or more blood cultures positive for the same microorganism; (2) clinical findings consistent with LPVE including fever, embolic or vascular phenomena, and signs of prosthetic dysfunction; and (3) histopathologic evidence of valvular infection during autopsy or operation. After transesophageal echocardiography (TEE) was introduced at our institution in 1990, the presence of clear-cut vegetations on echocardiograms was also considered diagnostic criterion.

All patients received antimicrobial treatment according to antimicrobial susceptibility patterns; survivors received further treatment for 6 weeks on the basis of an established protocol. Replacement of the prosthetic valve during the active phase of the disease (defined as the first treatment period) was considered in the following situations: staphylococcal or fungal infections, moderate to severe heart failure due to prosthetic dysfunction, repetitive emboli and severe periprosthetic damage, or echocardiographically evident abscesses.

Death was associated with valve replacement surgery when it occurred within 30 days after the procedure. A relapse was defined as a new episode of endocarditis that appeared during the first 3 months after treatment was stopped and was caused by the initial infectious agent. Recurrence was defined as a...
new episode of endocarditis that occurred later and/or was caused by a different organism.

Survivors were prospectively followed up, and blood specimens for culture were taken 1 and 3 months after discharge. The disease was considered cured when the patient remained without clinical signs of infection and the blood cultures were negative. Thereafter, patients were evaluated yearly. Patients with mild or moderate perivalvular leaks were followed up by means of clinical evaluation and echocardiography every 3 to 6 months according to the severity of the dysfunction. Surgery during follow-up was considered in cases of severe or progressive prosthetic dysfunction leading to symptoms of heart failure.

Statistical methods. Descriptive statistics, including means, SDs, maximal and minimal values for continuous variables, and frequencies for categorical variables, were calculated. In-hospital mortality was assessed by bivariate analysis with the χ² test and by multiple logistic stepwise regression for the maximal likelihood ratio. Survival on the basis of both mortality and the need for surgery during follow-up was analyzed by the Kaplan-Meier method. Survival rates were compared by the Tarone test. A P value of ≤ .05 was considered significant.

Results

Description of case series and diagnosis of infective endocarditis. Our series consisted of 59 cases of LPVE that were diagnosed from January 1975 to December 1994. There were 38 men and 21 women; the ages of the patients ranged from 18 to 81 years (mean ± SD, 47 ± 16 years). The mean time ± SD from prosthetic implantation to the diagnosis of endocarditis was 4.6 ± 3 years (range, 1–15 years). Forty-eight patients had mechanical valves, and 11 had biological valves. Prostheses were aortic in 26 patients, mitral in 24, and mitral and aortic in 9. The mean time ± SD from the beginning of clinical symptoms to diagnosis was 24 ± 27 days (range, 1–150 days). A portal of entry was identified in 20 patients (dental, 10; digestive, 2; cutaneous, 3; urinary, 2; and intravenous, 3).

The etiologies of LPVE are shown in table 1. Four patients had negative blood cultures; the diagnosis was confirmed for two during surgery, and two had biological prostheses and echocardiographically definite vegetations.

The diagnosis of LPVE was made according to the above-mentioned criteria. Our diagnosis was validated by using the diagnostic criteria recently proposed by Durack et al. [11]. According to these new criteria, the diagnosis of endocarditis in our series was definite in 52 cases: surgical confirmation, 17; two major criteria (positive blood cultures and either new prosthetic dysfunction or definite vegetations on echocardiogram), 15; and one major (18 positive blood cultures and two clear echocardiographic signs) and three minor (including embolic phenomena in all) criteria, 20.

The remaining seven cases would have been classified as possible endocarditis; cultures of several blood specimens from seven patients were positive, and all seven had clinical histories suggestive of endocarditis but did not have embolic or vascular phenomena. Transthoracic echocardiography (TTE) did not reveal any abnormalities, and TEE was not available at the time of diagnosis. All patients received treatment for endocarditis, and their infections resolved.

Echocardiographic data. Fifty-five patients underwent echocardiography. Four patients died before results of the echocardiographic examination were obtained; all four had staphylococcal endocarditis and presented with severe neurological damage due to intracerebral hemorrhage.

Thirty-four patients underwent TTE only, and 21 patients whose infections were diagnosed after 1990 underwent both TTE and TEE. Echocardiographic findings are summarized in table 2. Twenty-one patients had vegetations; five of these patients had emboli. Abscesses were diagnosed for 10 patients: 1 died before surgery was attempted, 5 underwent operations and survived, and 4 were medically treated and survived (2 of whom underwent operations during follow-up). Prosthetic dysfunction was diagnosed for 34 patients: 16 underwent operations, 3 died, and 15 were medically treated and survived (8 of whom underwent operations during follow-up).

TEE was more sensitive than TTE for the diagnosis of vegetations (67% vs. 19%, respectively), abscesses (38% vs. 0, respectively), and prosthetic dysfunction (86% vs. 43%, respectively). TEE revealed no abnormalities for only one patient; this procedure was performed when this technology first became available at our hospital.

Clinical outcome. All but one patient presented with fever. Embolic episodes were diagnosed for 22 patients (cerebral, 11; splenic, 4; renal, 2; peripheral, 1; vertebral, 1; and multiple, 3). In 14 cases, the embolic episodes were present at the time of admission or developed within 3 days of hospitalization. In seven cases, the embolic episodes occurred before the second
week of hospitalization. One patient died suddenly of brain hemorrhage during the sixth week of hospitalization; a ruptured mycotic aneurysm rather than an embolism was the likely cause. Nine patients died of cerebral embolism; eight of these patients had *Staphylococcus aureus* infection, and two underwent splenectomy to remove splenic abscesses. The remaining patients recovered from their embolic episodes without clinical sequelae.

Heart failure developed in 19 patients. Fourteen of these patients underwent surgical treatment. Surgery was not attempted in the other five patients because of an advanced neoplasm (1), age of 81 years and refusal of aggressive treatment (1), and resolution of heart failure with medical treatment (3; these cases were judged to be secondary to tachyarrhythmia and anemia rather than to prosthetic dysfunction).

Forty-two patients received medical treatment alone, and 17 received medical treatment and underwent valve replacement surgery. The reasons for surgery were heart failure due to prosthetic dysfunction in 14 patients (4 of whom also had annular abscesses), fungal or staphylococcal infection in 2, and severe dysfunction of the prosthesis and perianular abscess in 1.

Fifteen patients died in the hospital (10 [24%] of the patients who received medical treatment alone and five [29%] of the patients who received medical and surgical treatment; difference not significant); the in-hospital mortality rate was 25%. The mortality rate was related to the type of microorganism causing LPVE (*streptococci*, 5%; *staphylococci*, 67%; and other organisms, 23%; *P* = .0004). After adjustment for age and type of prosthesis, multiple logistic regression showed that the odds ratio for death due to nonstreptococcal infections was 9.67 (95% CI, 2.66–35.2). In nine cases, death occurred as a result of brain embolism and hemorrhage; eight of these patients had these conditions at the time of admission. Five patients died after surgical treatment; in three of these cases, the operation was the fourth procedure for valve replacement. One patient died of heart failure and advanced colonic neoplasm.

An uneventful clinical course (defined as easy control of the infection with antibiotic therapy and absence of embolic episodes or heart failure) occurred in 22 patients. The rate of uneventful clinical courses was associated with the type of microorganism causing LPVE (*streptococci*, 67%; *staphylococci*, 0; and other organisms, 23%; *P* = .0002). Clinical courses according to etiologic agents are shown in table 3.

**Follow-up.** All 44 survivors were followed up, and blood specimens for culture were taken 1 and 3 months after discharge. The median follow-up period was 54 months (range, 2–248 months). At the beginning of follow-up, 27 patients had mild or moderate prosthetic dysfunction. The overall survival rate, including in-hospital deaths, was 59% at 5 years and 52% at 10 years; this rate was not different for patients who received medical treatment alone and patients who received medical and surgical treatment during the active phase of disease (figures 1 and 2). The survival rate, excluding in-hospital deaths, was 80% at 5 years and 63% at 10 years.

During follow-up, 11 patients died. The cause of death was associated with valve replacement surgery in five patients (pump failure, 3; and technical problems, 2 [for whom the operation was the third and the fourth procedure, respectively]). Death was sudden and unexpected (no previous evidence of prosthetic dysfunction or heart failure) in two patients, and death was due to congestive heart failure in four patients for whom valve replacement surgery was not attempted because of old age or associated diseases.

Of the 44 survivors, 17 patients (61% at 7 years; figure 3) needed new valves due to prosthetic dysfunction. Fourteen of these patients had been cured by antibiotic therapy alone and were discharged from the hospital with signs of mild prosthetic dysfunction but without signs of heart failure. Thirteen patients underwent valve replacement surgery during the first 12 months of follow-up. The need for valve replacement surgery depending on the type of prosthesis at the time of diagnosis of LPVE is shown in figure 4.

Recurrent endocarditis occurred in three patients who were drug addicts. Two of these patients received medical treatment and survived the second episode of infective endocarditis, and the third patient underwent valve replacement surgery and died during the postoperative period.

At the end of follow-up, only 13 patients remained well and had the same prosthesis that they had at the time of the diagnosis of LPVE.

**Discussion**

The incidence of LPVE is most likely to increase in the near future. Although LPVE was classically defined as occurring >2 months after surgery, Karchmer et al. [12] pointed out that infections related to valve replacement surgery can manifest clinically throughout the first 12 months after the procedure. Therefore, in an attempt to ensure that all patients in the study really had LPVE, we considered only those instances occurring

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Table 2. Echocardiographic findings for 55 patients with late prosthetic valve endocarditis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. (%) patients with finding</th>
<th>TTE only (n = 34)</th>
<th>TTE and TEE (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetation</td>
<td>7* (21)</td>
<td>4 (19)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Abscess and/or pseudoaneurysm</td>
<td>2 (6)</td>
<td>0</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Prosthetic dysfunction</td>
<td>16 (47)</td>
<td>9 (43)</td>
<td>18 (86)</td>
</tr>
</tbody>
</table>

*NOTE.* TTE = transesophageal echocardiography; TEE = transthoracic echocardiography.

* Five bioprostheses and two mechanical valves.

1 Three bioprostheses and 11 mechanical valves.

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Table 3. Clinical courses of late prosthetic valve endocarditis in 59 patients according to etiologic agents.

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>No. of cases</th>
<th>Emboli</th>
<th>Heart failure</th>
<th>Surgical treatment</th>
<th>In-hospital death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viridans group</td>
<td>18</td>
<td>4 (22)</td>
<td>4 (22)</td>
<td>3 (17)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Streptococcus bovis</td>
<td>3</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>2</td>
<td>0</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1</td>
<td>0</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Enterococci</td>
<td>8</td>
<td>4 (50)</td>
<td>1 (13)</td>
<td>1 (13)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Staphylococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-positive</td>
<td>12</td>
<td>10 (83)</td>
<td>2 (17)</td>
<td>1 (8)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td>3</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>0</td>
</tr>
<tr>
<td>HACEK group*</td>
<td>4</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>4 (100)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Other*</td>
<td>4</td>
<td>0</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>4</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>22 (37)</td>
<td>19 (32)</td>
<td>17 (29)</td>
<td>15 (25)</td>
</tr>
</tbody>
</table>

* Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella species, and Kingella kingae.

As can be seen from our data, the clinical outcome of LPVE depends on the etiologic agent. The prognosis of infections due to streptococci (excluding Streptococcus agalactiae and Streptococcus pneumoniae) is good; our overall mortality rate was 5% (one of 21), and the rate of uneventful clinical courses was 67%. Therefore, we believe that prosthetic valve infections due to these microorganisms can be managed medically unless severe dysfunction of the prosthesis, normally related to a late diagnosis, is present. In our series, only three patients required

Figure 1. Overall survival rates, including in-hospital and follow-up deaths, among 59 patients with late prosthetic valve endocarditis. Bars represent the confidence interval for each period.

Figure 2. Overall survival rates among 59 patients with late prosthetic valve endocarditis according to the type of treatment (medical or surgical) during the active phase of disease. Bars represent the confidence interval for each period.
surgery during the active phase of disease. In these cases, the mean time from clinical symptoms to diagnosis was 28 days.

On the contrary, *S. aureus* endocarditis is a devastating disease; emboli are common and are likely to involve the brain [5, 15–17]. In our series, cerebrovascular accidents occurred in 10 of 12 patients with *S. aureus* LPVE; these accidents were hemorrhagic and the cause of death in eight patients. These cases could result from either hemorrhagic transformation of an infarct or septic arteritis with or without aneurysm as recently described [18]. Anticoagulation probably plays a major role in hemorrhagic infarcts [19].

Although surgery can be useful for patients with a history of cerebral emboli [20], severe brain hemorrhages contraindicate valve replacement surgery, and in fact, all 10 of our patients died of their brain damage. Cerebrovascular accidents occur very early in the course of LPVE, as has been previously described [21]. Our findings, in agreement with those of other researchers [22], suggest that patients presenting with staphylococcal endocarditis and no emboli should undergo surgical treatment on an urgent basis in an attempt to improve their prognosis. The most adequate therapeutic approach for patients with endocarditis due to other less common organisms seems to be antibiotic treatment and surgery as soon as complications arise.

During our study, no major changes occurred in the clinical presentation of LPVE. In addition, no major advances in either antibiotic treatment or surgical treatment occurred. The most relevant advance was the introduction of TEE. LPVE can be diagnosed now with more confidence because vegetations can be seen with TEE, whereas they were very difficult to detect with TTE.

The major contribution of TEE is that it improves diagnosis; more important, it allows the diagnosis to be made earlier, thus allowing decisions about therapeutic strategies to be made more rapidly (especially in acute cases). In addition, the documentation of perivalvular abscesses or pseudoaneurysms [23–25] provides important prognostic information because most patients will require surgery; however, as occurred in four of our cases, sometimes bacteriologic cure can be achieved with antibiotic therapy alone.

Long-term follow-up reveals that the clinical course of most survivors will be influenced by the presence of endocarditis. Most patients who receive medical treatment will require valve replacement surgery because of progressive prosthetic dysfunction. As has been previously recognized [26], this finding is more likely for patients with biological valves, probably because they need surgery during the active phase of infection less frequently. Our data suggest that a more aggressive surgical approach for patients with mild to moderate prosthetic dysfunction could result in increased duration of survival. Unfortunately, we have no data to substantiate this contention, and the available literature does not provide evidence about the net effect of earlier operations on prognosis.

The decision to operate may be quite individualized for these patients, some of whom have undergone more than one previous cardiac operation and may have a very high surgical risk [27]. Late death due to heart disease is not uncommon, probably reflecting the natural history of chronic valvular heart disease in patients who have undergone several procedures to replace cardiac valves. Our survival results are in agreement with those of Lytle et al. [28]. Recurrences are uncommon, although they are the rule in patients who are intravenous drug addicts.

Since prosthetic valve endocarditis is such a serious disease, every effort should be made to provide prophylaxis and an early diagnosis. We believe that if prophylaxis is given, the incidence of streptococcal infections will decrease; early diagnosis should reduce periprosthetic damage and the need for surgical treatment. Unfortunately, less can be done to reduce the incidence of the most severe form of the disease: staphylo-
coccocal infection. At present, only early surgery (before cerebral complications occur) seems to be reasonable treatment. For those patients presenting with severe neurological damage, the prognosis remains ominous.

References