Risk factors for the development of prosthetic valve endocarditis

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ABSTRACT  Risk factors for the development of prosthetic valve endocarditis (PVE) were analyzed in 2642 patients undergoing initial valve replacement at the Massachusetts General Hospital from 1975 to 1982.  Follow-up was available for 2608 patients (98.7%); the mean length of follow-up was 39.8 months.  PVE developed in 116 patients (4.4%).  The actuarial risk of PVE was 3.1% at 12 months and 5.7% at 60 months.  A Cox model was used to identify risk factors for PVE.  Recipients of multiple valves had a higher risk of PVE than single valves (p = .01).  There was no difference in the risk of PVE for patients receiving aortic valves vs those receiving mitral valves.  Recipients of mechanical valves had a higher risk of PVE than recipients of porcine valves in the first 3 months after surgery (p = .02), but the risk of PVE was higher for porcine valve recipients 12 months or more after surgery (p = .004).  Despite this difference in the time course of development of PVE, there was no significant difference in the cumulative risk of PVE by 5 years of follow-up between mechanical and porcine valve recipients.  Male sex was a risk factor for PVE within 12 months of aortic valve replacement (p = .008) but not thereafter; sex did not influence the risk of PVE after mitral valve replacement.  Older patients had a higher risk of late PVE after multiple (p = .04) or mitral valve replacement (p = .08), but not after aortic valve replacement.


PROSTHETIC valve endocarditis (PVE) is a serious but infrequent complication of cardiac valvular replacement.  The incidence of PVE has been previously estimated at 1% to 4%.  However, several prior studies may have underestimated the true incidence of PVE because of the lack of comprehensive follow-up information on operated patients or the use of nonactuarial methods of data analysis.  In other studies, the method of obtaining follow-up information and the number of patients lost to follow-up have not been detailed.  Some reports have used “linearized rates” to quantify the risk of PVE, stated as a percentage incidence per unit time.  However, as confirmed in a recent study, the risk of PVE is not constant with time but involves a higher risk period initially after surgery and a lower risk thereafter.

In this study, we wished to define the incidence of PVE over time in a large group of patients undergoing initial cardiac valvular replacement and to examine risk factors for the development of PVE.  Identification of patients at higher risk of developing PVE should allow testing of new measures for prevention of infection in specific high-risk groups.  In addition, clarification of risk factors for PVE may provide important insights into the pathogenesis of this infection.

Methods

Study population.  All patients undergoing initial valve replacement at the Massachusetts General Hospital between January 1, 1975, and December 31, 1982, were studied; prior cardiac surgery other than valve replacement did not exclude patient entry.  Information on each patient was entered into a computerized data base, preserving patient confidentiality.  Data gathered included demographic information, preoperative cardiac diagnosis and findings of catheterization, and detailed information about the operation, including date, duration of cardiopulmonary bypass, duration of aortic cross-clamping, operative procedure, site and type of valve replacement(s), and concomitant procedures performed.  Mechanical prostheses implanted during the study period included Starr-Edwards, Björk-Shiley, and St. Jude valves; porcine bioprostheses included Hancock and Carpentier-Edwards valves.

All patients received perioperative antibiotic prophylaxis for a period of 2 to 7 days.  The antimicrobial drugs used and the duration of therapy varied during the study period because of physician preference, patient allergy, and evolving concepts about optimal prophylaxis.  In the first 2 years of the study, the most common prophylactic regimen was intravenous oxacillin or nafcillin, followed by oral cloxacillin or dicloxacillin for a
total course of 5 to 7 days. In the later years of the study, a first-generation parenteral cephalosporin (cefazolin, cephalothin, or cephamycin) was frequently used for 2 to 5 days.

Follow-up of patients for the development of PVE was conducted between October 1, 1982, and October 1, 1983. Each patient or a relative was contacted by telephone to ascertain the current status of the valve recipient and to determine whether hospitalization had occurred in the interim since valve replacement. Physicians of patients were contacted if the patient could not be located or to verify the nature of subsequent hospital admissions. Detailed records of hospitalization, autopsy reports, or death certificates were examined as needed to substantiate the follow-up status of individual patients.

Patients who either died in the follow-up interval without PVE or who required a second valve replacement for reasons other than PVE were censored at the time of that event. The period of risk for PVE was calculated as the time between initial valve replacement and the earliest of the following: the date of death, the date of reoperation for reasons other than PVE, the date of telephone contact, or the date of onset of PVE.

Definitions. The diagnosis of PVE was accepted2-10 if at least two of the following three criteria were met: (1) a clinical illness compatible with bacterial endocarditis (two or more of: fever; new or changing heart murmur; presence of petechiae, splinter hemorrhages, Roth spots, Janeway lesions, or Osler nodes; unexplained emboli; unexplained anemia, elevated sedimentation rate, hematuria, or a positive test for rheumatoid factor); (2) two or more positive blood cultures for the same organism, either without an identifiable extracardiac source or, if associated with an identified extracardiac source, with evidence of valvular involvement by new or changing heart murmur, evidence of vegetations by echocardiogram or catheterization, or confirmation at surgery or autopsy; (3) histopathologic or microbiologic evidence of valvular infection at surgery or autopsy. Fifty-nine percent of our patients with PVE (68 of 116) were eventually pathologically.

The onset of PVE was taken as the earliest of: (1) the date of the first physician visit for an illness eventually proved to be PVE, (2) the date of the first positive blood culture for an organism eventually shown to be the causative pathogen of PVE, (3) the date of hospital admission for treatment of PVE.

Staphylococci were considered methicillin resistant if they were reported as resistant to methicillin or oxacillin by standard bacteriologic techniques or if they demonstrated the presence of methicillin-resistant subpopulations, as previously described.11

Data analysis. All statistical computations were performed with the Biomedical Programs statistical software (BMDP 1982). Two-way tables comparing the frequencies of categorical events without censoring were analyzed with the Pearson chi-square statistic. Life-table methods were used to compute the proportion of patients free of PVE at 3 month intervals, the corresponding monthly hazard rate and standard error, and the cumulative hazard function. The hazard rate at time t (in months) estimates the probability that a patient free of PVE at that time will develop PVE in the following month, and the cumulative hazard function estimates the cumulative probability of PVE over time. In this study, because the risk of PVE is relatively small, the mathematical expressions for the cumulative hazard function and the cumulative risk of PVE are virtually identical. Data in the figures are presented as the cumulative hazard function for PVE vs time. Actuarial estimates of the risk of PVE for two groups, without adjusting for any other risk factors or potentially confounding variables, were compared by the generalized Wilcoxon test.

Risk factors for the development of PVE were identified by means of a Cox regression model with a backward deletion algorithm. The following covariates were considered: sex, age, prior cardiac surgery, preoperative pulmonary capillary wedge pressure, position of valve(s) replaced, type of valve(s) implanted, duration of aortic cross-clamping and cardiopulmonary bypass, concomitant cardiac surgical procedures, and year of surgery. Cox regression models for the risk of early PVE (first 12 months after surgery) were fitted by censoring all patients free of PVE at 12 months. For analyzing the risk of late PVE, only patients who were free of PVE for more than 12 months were considered.

Results
During the study period, 2642 patients underwent initial valve replacement at the Massachusetts General Hospital; follow-up information was available after hospital discharge for 2608 patients (98.7%) and these constitute the study group. Thirty-four patients were lost to follow-up after valve replacement (21 male and 13 female; 19 aortic, nine mitral, and six multiple valve recipients). Duration of follow-up ranged from 0.5 to 103 months; mean follow-up was 39.8 months and the median was 38.0. The distribution by calendar year of patients operated on, lost to follow-up, and developing PVE is shown in table 1.

The age of the study group ranged from under 1 year to 86 years; the mean age was 59.2 years and the median was 61.0. Distribution by sex and by position of the implanted valve(s) is shown in table 2. Aortic valve replacement was more common in male patients and mitral valve replacement in female patients (p < .001). In the group with multiple valve replacements, 246 patients received aortic and mitral valves, 32 mitral and tricuspid, 17 aortic, mitral, and tricuspid, and one aortic and tricuspid. For single valve recipients, the type of valve inserted is shown by valve position in table 3.

The frequency of other surgical procedures done concomitantly with valve replacement was as follows:

<table>
<thead>
<tr>
<th>Year of operation</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
<th>Lost to follow-up</th>
<th>No. with PVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>204</td>
<td>208</td>
<td>412</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>1976</td>
<td>177</td>
<td>175</td>
<td>352</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>1977</td>
<td>173</td>
<td>168</td>
<td>341</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>1978</td>
<td>159</td>
<td>186</td>
<td>345</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>1979</td>
<td>163</td>
<td>183</td>
<td>346</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>1980</td>
<td>136</td>
<td>153</td>
<td>289</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>1981</td>
<td>144</td>
<td>154</td>
<td>298</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>1982</td>
<td>120</td>
<td>139</td>
<td>259</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>1276</td>
<td>1366</td>
<td>2642</td>
<td>34 (1.3%)</td>
<td>116 (4.4%)</td>
</tr>
</tbody>
</table>

*Percentage of 2608 patients with follow-up who developed PVE.
TABLE 2
Distribution of study group and incidence of PVE by valve position and sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Valve position</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AVR</td>
<td>MVR</td>
</tr>
<tr>
<td>Male</td>
<td>47/878</td>
<td>13/353</td>
</tr>
<tr>
<td>Female</td>
<td>8/419</td>
<td>28/657</td>
</tr>
<tr>
<td>Total</td>
<td>55/1297</td>
<td>41/1010</td>
</tr>
</tbody>
</table>

**AVR = aortic valve replacement; MVR = mitral valve replacement; TVR = tricuspid valve replacement.**

\(^{a}\) Numerator is the number of patients developing PVE in the follow-up interval; denominator is the number of patients with follow-up after hospital discharge. Percentage figures refer to incidence of PVE in each group.

corony artery bypass surgery in 587 of 2608 patients (23%), other procedures using prosthetic material (such as repair of aortic aneurysms, patch closure of atrial or ventricular septal defects, repair of aortic coarctation) in 81 patients (3%), associated valve procedures without valve replacement (such as valvuloplasty or valvulotomy) in 69 patients (3%), and miscellaneous associated procedures in 151 patients (6%).

**Incidence of PVE.** During the follow-up interval, 116 of 2608 patients (4.4%) developed PVE. The incidence of PVE by valve position and sex is shown in table 2. The cumulative hazard function for PVE is shown in figure 1. The actuarial risk of PVE was 3.1% at 12 months and 5.7% at 60 months.

**Bacteriology of infection.** The distribution of cases of PVE by infecting organism and by time of onset after surgery is shown in table 4. The distribution of organisms was similar in patients with onset of infection within 2 months of surgery, between 2 and 6 months after surgery, and between 6 and 12 months after surgery. Coagulase-negative staphylococci caused 22 of 38 (58%) and 41 of 72 (57%) cases of PVE during the initial 2 months and 12 months after surgery, respectively. Patients with onset of PVE more than 12 months after valve replacement showed a different pattern of infecting organisms, with streptococci and the fastidious gram-negative coccobacilli (such as *Actinobacillus, Cardiobacterium*, and *Hemophilus spp*) predominating. The distribution of infecting organisms did not differ by valve position, valve type, or sex.

The majority of infections caused by coagulase-negative staphylococci were caused by coagulase-negative staphylococci, with the majority of cases occurring within 2 months of surgery.

**TABLE 4**
Distribution of patients with PVE by time of onset after surgery and infecting organism

<table>
<thead>
<tr>
<th>Infecting organism</th>
<th>Time of onset after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 mo</td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td></td>
</tr>
<tr>
<td>staphylococci</td>
<td>22</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>2</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>4</td>
</tr>
<tr>
<td>Fungi</td>
<td>2</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2</td>
</tr>
<tr>
<td>Streptococci(^{a})</td>
<td>0</td>
</tr>
<tr>
<td>Enterococci</td>
<td>0</td>
</tr>
<tr>
<td>Fastidious gram-negative coccobacilli(^{b})</td>
<td>0</td>
</tr>
<tr>
<td>Other and mixed(^{c})</td>
<td>3</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
</tr>
</tbody>
</table>

\(^{a}\) Excludes enterococci.

\(^{b}\) *Actinobacillus, Cardiobacterium*, and *Hemophilus*.

\(^{c}\) Includes one patient infected with coagulase-negative staphylococci plus a second organism.
ative staphylococci (81%) began within 12 months of valve replacement. Thirty-six of 43 strains (84%) of coagulase-negative staphylococci causing infection within 12 months of surgery were resistant to methicillin as compared with three of 10 strains (30%) causing infection later (p = .001). The frequency of methicillin resistance did not differ between strains from cases in the first 6 months after surgery (83%) and strains causing infection in the period 6 to 12 months after surgery (85%).

**Incremental risk factors for PVE.** Recipients of multiple valves had a higher risk of PVE throughout the follow-up interval than recipients of single valves (p = .01) (figure 2). This higher risk was particularly evident in female subjects (p < .0001) but was not present in male patients. Within the group of multiple valve recipients, significant risk factors for the development of PVE included advancing age (p = .01), concomitant procedure at the time of valve replacement (p = .04), and possibly female sex (p = .08). When patients with onset of PVE less than 12 months after surgery were analyzed separately from those with later onset, advancing age was a significant risk factor for late PVE (p = .04) but not for early onset.

The time course of development of PVE was different for recipients of mechanical valves as compared with those of porcine valves (figure 3). Recipients of mechanical valves had a higher risk of PVE in the 3 months after surgery (p = .02) but recipients of porcine valves had a higher risk of infection 12 months or more after surgery (p = .004). These differences in risk persisted unchanged when potentially confounding variables were accounted for in the Cox model. Although the time course of development of PVE was different between recipients of mechanical and porcine valves, the cumulative risk of PVE was not significantly different by 5 years of follow-up.

There was no difference overall in the risk of PVE between recipients of aortic and mitral prostheses or between male and female subjects (table 2). However, significant interactions occurred between these variables in the Cox model. For aortic valve recipients, risk factors for PVE included male sex (p = .004) and possibly prolonged cardiopulmonary bypass time (p = .07). When infections during the year after surgery were analyzed separately from those occurring later, male sex was a significant risk factor for the development of PVE within 12 months of surgery (p = .008) but not later. Recipients of porcine valves were at higher risk of PVE than those of mechanical valves 12 months or more after surgery (p = .03). In addition, prolonged cardiopulmonary bypass time was a significant risk factor for the later development of PVE (p = .01).

For mitral valve recipients, those with porcine valve

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**FIGURE 2.** Cumulative hazard of PVE compared in multiple valve recipients and single valve recipients. Data points are mean values (±1 SEM). Figures in parentheses along the abscissa refer to the number of patients in each group being followed at the start of the subsequent interval.

**FIGURE 3.** Cumulative hazard of PVE compared in recipients of mechanical prostheses and porcine prostheses. Data points are mean values (±1 SEM). Figures in parentheses along the abscissa refer to the number of patients in each group being followed at the start of the subsequent interval.
replacements had a lower incidence of PVE in the year after surgery than those with mechanical valves (p = .02) but had a higher incidence later (p = .04). In the period more than 12 months after surgery, there was a tendency toward higher risk of PVE with advancing age (p = .08).

Discussion

Despite major advances in cardiovascular surgical technique and postoperative care and routine use of prophylactic antimicrobial agents, PVE continues to complicate the course of a small percentage of patients after cardiac valve replacement. Further advances in the prevention of this infection will depend on a better understanding of its pathogenesis and on risk factors for its development.

PVE has been recognized to be a time-related event, with a higher risk in the months shortly after surgery and a lower risk thereafter. "Early onset" PVE has been arbitrarily defined as occurring within 60 days of surgery; the pathogenesis of these infections has been attributed to events occurring either during or shortly after surgery. "Late onset" PVE has been defined as infection beginning 60 days or more after valve replacement. These infections have been attributed to contamination of the valve during bacteremia that results from incidental infection or from trauma to body surfaces colonized with microorganisms.

Prior estimates of the incidence of PVE have frequently overlooked the time-related nature of this infection. Comprehensive follow-up of the operated group has either not been attempted or the method and success of such follow-up has not been detailed. The use of nonactuarial methods to calculate the risk of PVE may lead to an underestimation of the true incidence because of a failure to recognize the importance of the duration of follow-up. Calculation of "linearized rates," presented as incidence of infection per unit time, blurs the distinction between the higher risk period after surgery and the lower risk period later.

In the present series, we sought to define carefully the incidence of PVE after initial valve replacement. We followed a large study population over an extended period of time and used a well-accepted definition for the presence of PVE. Using actuarial methods, we estimated the cumulative risk of PVE as 3.1% at 12 months and 5.7% at 60 months after surgery. Ivert et al. have recently analyzed the incidence of PVE after initial valve replacement at the University of Alabama in Birmingham, using methods of data analysis similar to our own. They confirmed the higher risk of PVE in the first 6 to 12 months after surgery and the lower risk thereafter. Their actuarial estimates of the risk of PVE, 3.0% at 12 months and 4.1% at 48 months, are similar to the cumulative risks in the present study.

Among our patients with PVE, the distribution of infecting organisms with time after surgery (table 4) showed several interesting differences from previous studies. In the past, Staphylococcus aureus, enteric gram-negative bacilli, and coagulase-negative staphylococci were the most frequent pathogens causing PVE with onset in the first 2 months after surgery. Among patients with onset of PVE later than 2 months after surgery, streptococci were the predominant cause of PVE, with S. aureus and coagulase-negative staphylococci remaining prominent. In the present series, S. aureus and enteric gram-negative bacilli rarely caused PVE during the initial 2 months after surgery, while coagulase-negative staphylococci became the predominant causative organisms. In addition, among the organisms causing our cases of PVE, those bacteria considered likely to have caused infection acquired outside of the hospital (streptococci, enterococci, and fastidious gram-negative coccobiocci) did not appear prominently at 2 months after surgery but rather only after a year had elapsed from valve implantation. The spectrum of infecting organisms was quite similar throughout the first 12 months after surgery, suggesting these cases may share a similar pathogenesis. Support for this hypothesis derives from the high frequency of methicillin resistance (84%) among coagulase-negative staphylococci causing PVE throughout the initial 12 months after surgery, as contrasted with the significantly lower frequency of methicillin resistance (30%) among strains causing PVE thereafter. Karchmer et al. have reported a similar distribution of methicillin resistance in coagulase-negative staphylococci from a multi-institutional study of PVE; they found methicillin resistance in 87% of strains from cases occurring within 1 year of surgery, as compared with 22% of strains from infections occurring later. Methicillin-resistant coagulase-negative staphylococci are infrequent isolates from cardiac surgical patients at the time of hospital admission but become common skin flora in these patients shortly after cardiac surgery, suggesting that methicillin resistance is, to a degree, a marker for hospital-acquired strains of coagulase-negative staphylococci. The frequency of methicillin-resistant coagulase-negative staphylococci as causes of PVE throughout the initial year after surgery suggests the possible nosocomial origin of these cases. Thus the distribution of the organisms causing our cases of PVE suggests that 12 months may be a
better break point for defining nosocomial (early onset) PVE than the previous definition of cases with onset within 2 months of surgery.

Several previous studies have examined risk factors for the development of PVE after valve replacement. Many of these studies had relatively small sample sizes or failed to analyze the differences found by statistical techniques. Recipients of multiple valves have been previously shown to be at higher risk for PVE than recipients of single valves. Some prior studies have suggested a higher incidence of infection in patients with aortic prostheses than in those with mitral prostheses, although one study suggested the opposite and two have shown no difference. One study suggested a higher risk of infection for porcine prostheses than for mechanical, but two larger studies failed to find any difference.

Ivert et al. carefully examined risk factors for PVE in a large study population with thorough follow-up. They found no difference overall in the incidence of PVE in patients with aortic or mitral prostheses. Patients with mechanical prostheses had a significantly higher risk of PVE than those with porcine prostheses in the initial 6 months after surgery, but the rates of infection were similar thereafter. These investigators identified four additional risk factors for the development of prosthetic valve infection: male sex, prolonged cardiopulmonary bypass time, antecedent native valve endocarditis, and black race.

The present series is the largest to date to examine incremental risk factors for the development of PVE by means of detailed statistical analysis. Our results confirm the enhanced risk of PVE among multiple valve recipients as compared with that of single valve recipients. This difference persisted when potentially confounding variables were taken into account in the Cox model. We found no difference overall between infection rates in patients with aortic and mitral prostheses, although the risk factors for infection within each group were different.

We confirmed the higher early risk of PVE in recipients of mechanical prostheses but showed that porcine valve recipients actually have a higher risk of late PVE. One possible explanation for the difference in our results compared with those of Ivert et al. is the larger sample size in the present study, particularly the larger number of porcine valve recipients. The differing time course for the development of PVE in patients with mechanical and porcine valves may indicate important differences in the pathogenesis of infection with these two valve types. Nevertheless, the absence of a significant difference between these two groups in the cumulative risk of PVE by 5 years of follow-up implies that the choice of a mechanical vs porcine prosthesis cannot be made at present on the basis of long-term risk of PVE.

We confirmed the influence of advanced age on the risk for PVE. However, we found that age predominantly affected the risk of PVE 12 months or more after surgery, particularly in recipients of multiple or mitral prostheses. Male sex was a risk factor for PVE on aortic prostheses in the 12 months after surgery but not thereafter; sex did not influence the risk of infection on mitral valve prostheses.

Explanations for the risk factors identified in the present study can only be speculative. More detailed analysis of the various groups will be necessary before the pathogenetic principles underlying the observed differences in the risk for PVE can be understood. Our results allow an accurate assessment of the risk for developing PVE at a major cardiovascular surgical center with current techniques and the identification of subgroups of patients at higher risk for PVE for whom new methods of infection prevention should be targeted.

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