Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period

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Objective: To compare early and late outcome of patients with prosthetic valve endocarditis treated medically versus surgically and to determine predictors of in-hospital death. We retrospectively reviewed patient's clinical records, including laboratory findings, surgery, and pathologic files, in an acute-care, 1200-bed teaching hospital.

Methods: One hundred thirty-three episodes of definite prosthetic valve endocarditis as defined by the Duke University diagnostic criteria occurred in 122 patients from January 1986 to December 2005. Logistic regression model was used to identify prognostic factors of in-hospital mortality. Long-term follow-up was made to assess late prognosis.

Results: Bioprostheses were involved in 52% of cases and mechanical valves in 48%. The aortic valve was affected in 45% of patients. *Staphylococcus epidermidis* was isolated in 23% of cases, *Streptococcus* spp in 21%, *S aureus* in 13%, and *Enterococcus* in 8%. Cultures were negative in 18% of cases. Twenty-six patients were treated medically and 107 with combined antibiotics and valve replacement. The operative mortality was 6.5% and the in-hospital mortality, 29%. Presence of an abscess at echocardiography, urgent surgical treatment, heart failure, thrombocytopenia, and renal failure were significant predictors of in-hospital death. Kaplan-Meier survival at 12 months was 42% in patients treated medically and 71% in those treated surgically ($P = .0007$). Freedom from endocarditis was 91% at the end of follow-up.

Conclusions: Prosthetic valve endocarditis is a serious condition with high mortality. Patients with perivalvular abscess had a worse prognosis, and combined surgical and medical treatment could be the preferred approach to improve outcome. (J Thorac Cardiovasc Surg 2010;139:887-93)

Prosthetic valve endocarditis (PVE) is a rare but severe complication of valve replacement and has been reported to occur with an incidence of 0.98 per 100 patient-years.[1] The cumulative incidence at 5 years is 3% and at 10 years is 5%,[2] with a case-mortality rate ranging from 25% to 59%,[3] despite improvements in prophylaxis, diagnosis, and treatment. The best therapeutic option in PVE is still debated. Although surgical therapy is said to represent the best choice,[4,5] medical therapy can be sufficient in some patients.[6]

The objective of this study was to describe the clinical features of patients with PVE, to determine predictors of in-hospital death, and to compare early and late outcome of patients with PVE treated medically versus surgically.

PATIENTS AND METHODS

The study was conducted at an acute-care, 1200-bed teaching hospital. The hospital has a department of cardiovascular surgery, a cardiology service, and a unit of infectious diseases and has been a reference center of cardiovascular surgery for other hospitals in the country. From January 1986 to December 2005, a total of 133 consecutive episodes of definite PVE as defined by Duke University diagnostic criteria[7] were treated at our institution. A retrospective review of the patient's clinical records, including laboratory findings, surgery, and pathologic files, forms the basis of the present report. The primary end points of the study were in-hospital death and survival at 12 months after combined medical and surgical treatment versus medical therapy alone. The study was approved by the Institutional Review Board.

Early PVE was defined as the diagnosis of PVE within 60 days of prosthetic valve implantation, and late-onset was defined as PVE occurring 2 or more months after valve replacement.[8] All patients were scheduled for 4- to 8-week antibiotic therapy. All operations were performed at the department of cardiovascular surgery of our hospital. Urgent surgery was defined as valvular replacement performed within 24 hours after hospital admission. Indications of surgery and the choice of the best valvular substitute were left to the discretion of the attending physician. Intraoperative decisions and the treatment protocols for these patients varied over the study period. Briefly, if the indication of surgical treatment was an urgent operation (<24 hours after admission), the infected prosthesis was substituted by a new one according

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Abbreviations and Acronyms
CI = confidence interval
NYHA = New York Heart Association
PVE = prosthetic valve endocarditis
RR = risk ratio

to criteria of the responsible surgeon, but in most cases the same model of prosthetic valve was used. The same occurred for endocarditis on a prosthetic mitral valve, except for a patient with recurrent mitral valve endocarditis in whom a mitral homograft was implanted. In patients with prosthetic endocarditis of the aortic valve in which surgery could be delayed 24 to 48 hours, a cryopreserved aortic root homograft from a tissue bank was inserted.

Medical records of patients were reviewed for data on age, sex, place of origin (our community or reference from other communities), preoperative functional class according to the New York Heart Association (NYHA) classification, previous endocarditis with native or prosthetic valves, and details of previous valve surgery, including intraoperative and perioperative data. The presence of congestive heart failure was based on characteristic signs and symptoms determined by clinicians at the individual sites. Neurologic abnormalities were defined as clinical signs of cortical and subcortical lesions (eg, hemiparesis, aphasia), brain stem lesion, meningitis, or altered consciousness. Abnormal laboratory findings included serum creatinine concentration > 133 μmol/L, white blood cell count < 3×10^9/L or > 16×10^9/L, and sedimentation rate > 40 mm/h. Complicated PVE was defined as the presence of a new or changing heart murmur, new or worsening heart failure, new or progressive cardiac conduction abnormalities, prolonged fever during therapy, or intracardiac abscess by echocardiography or the presence of pus by direct visualization at surgery or necropsy.[9] Uncontrolled infection was defined by persistent fever or persistent bacteremia or both after 1 week of appropriate antimicrobial chemotherapy.[10] Septic shock was defined as a persistent hypotension (systemic blood pressure $\leq$ 90 mm Hg) not due to cardiogenic shock and along with the presence of at least one of the following signs of perfusion abnormalities: oliguria, acute alteration of mental status, or lactic acidosis.[11] Relapse was defined as a fresh onset of clinical endocarditis with blood cultures positive for the initial pathogen within 12 months after hospital discharge. Reinfection was defined as a subsequent episode in which a different pathogen was isolated. The routine microbiologic screening also included fastidious organisms, anaerobes, fungi, and organisms from the HACEK group. Etiologic microorganism was defined as microorganism grown from blood or tissue culture sources determined to be the causative agent for the PVE episode.[12] Otherwise, the diagnosis of culture-negative PVE was established. In-hospital mortality was defined as death occurring during the initial hospitalization for infective endocarditis.

Transthoracic and/or transesophageal echocardiography as clinically indicated was performed. Vegetations were defined as circumscribed masses or clumps of echoes that arose from leaflet tips or prosthetic material, either as an irregular area of highly reflective leaflet thickening or as more discrete, pedunculated masses. Nonspecific valvular thickening was not interpreted as vegetations. An abscess was considered in the presence of abnormal echo-dense or echo-lucent areas within the valvular annulus or perivalvular tissue, confirmed by imaging in more than 1 echocardiographic plane, in the setting of valvular infection.[13]

The follow-up data for this study were procured in a 1-month period (June 2006). The patients were followed through visits in the outpatient clinic, direct telephone contact at home, or direct contact with their physicians. When follow-up was not possible, information on vital status (alive or death) and cause of death was obtained through the Social Security database.

Statistical Analysis

A logistic regression model was used to evaluate the effect of explanatory variables on in-hospital mortality. In both the univariate and multivariable analysis, continuous variables were categorized using the most clinically relevant cutoff points. Variables were entered into a stepwise backward multiple logistic regression model. Results are expressed as crude and adjusted odds ratios with 95% confidence intervals (CIs). All factors were adjusted by sex, age, year of diagnosis of PVE, referral hospital, and nosocomial infection after original valve replacement. Survival analysis was used to compare event rates during the follow-up period with comparisons made with the Kaplan-Meier method. Mortality rates for PVE were evaluated by plotting the survival distribution derived from Kaplan-Meier estimates, and differences in survival were assessed by the log-rank test. A Cox regression analysis was performed to assess the effect of the different variables on the risk of death. The risk ratio (RR) and the 95% CI were calculated. Data were analyzed using Stata statistical software (Release 8.0, Stata Corporation, College Station, Tex) and SPSS (version 11.5; SPSS Inc, Chicago, Ill).

RESULTS

A total of 133 episodes of PVE were diagnosed (112 patients had 1 episode, 9 patients had 2 episodes, and 1 patient had 3 episodes). There were 87 men and 34 women with a mean age of 59 years (95% CI: 56–62). During the same period, 6079 valve replacement operations were performed, with an incidence of PVE of 2.2%. Sixty-nine episodes occurred in patients who had bioprosthetic valve replacement and the remaining 64 in patients who had mechanical valve replacement. Location of infected prosthesis included aortic in 60 cases, mitral in 37, and mitroaortic in 36. Laboratory findings showed leukocytosis or leukopenia in 60% of the episodes, sedimentation rate > 40 mm/h in 24%, and serum hemoglobin < 10 g/dL in 8%. Echocardiography revealed vegetations in 63.1% of cases, prosthetic valve dysfunction in 71.4%, abscess in 39.3%, and aortoventricular dehiscence in 9.7%.

Of the 133 cases of PVE, there were 24 cases (18%) of early onset PVE and 109 (82%) of late-onset PVE. Mechanical PVE was more frequent in the early onset PVE group (78% vs 22%), whereas bioprosthetic PVE was more frequent in the late-onset group (58% vs 42%). Coagulase-negative staphylococci were observed most often in both early PVE (47%) and late PVE (29%) groups. *Staphylococcus aureus* was the second most frequent organism in early PVE (25%) and *Streptococcus viridans* in late PVE (19%). The percentage of methicillin-resistant *S aureus* was higher in early PVE (40%, 10/25) than in late PVE (23%, 3/13). Cultures were negative in 24 cases (18%). Complications during hospitalization occurred in 96 of the 133 episodes of PVE (72.2%), with a rate of 66.7% (16/24) in early PVE and 73.4% (80/109) in late PVE. Clinical features, microbiologic data, and complications in all episodes of PVE as well as in the groups of early and late PVE are shown in Table 1.

Thirty-nine patients died, for an in-hospital mortality rate of 29.3%. Causes of death included heart failure or

TABLE 1. Clinical characteristics, microbiologic data, and complications in 133 episodes of PVE

	All episodes	Early PVE	Late PVE
No. cases	133	24	109
Clinical features			
Fever	106 (79.7)	17 (70.8)	89 (84.0)
Heart failure	87 (65.4)	18 (75)	69 (63.3)
Systemic embolism	6 (4.5)	1 (4.2)	5 (4.6)
Splenomegaly	15 (11.3)	1 (4.2)	14 (12.8)
Osler nodes, Janeway lesions	7 (4.3)	1 (4.2)	4 (3.7)
New or changing murmur	85 (63.9)	13 (54.2)	72 (66.1)
Causative microorganisms	109 (81.9)	21 (87.5)	88 (80.7)
Coagulase-negative *Staphylococci*	36 (27.1)	9 (37.5)	27 (24.8)
Staphylococcus aureus	17 (12.8)	5 (20.8)	12 (11.0)
Methicillin-sensitive *S aureus*	12 (9.0)	3 (12.5)	9 (8.2)
Methicillin-resistant *S aureus*	5 (3.7)	2 (8.3)	3 (2.7)
Streptococcus viridans	21 (15.8)	1 (4.2)	20 (15.1)
Enterococcus	9 (6.8)	1 (4.2)	8 (7.3)
Diphtheroids	1 (0.7)	1 (4.2)	0
Gram-negative bacilli	4 (3.0)	0	4 (3.7)
Peptococcus spp	1 (0.7)	0	1 (0.9)
Candida spp	4 (3.0)	0	4 (3.7)
Miscellaneous	16 (12.0)	4 (16.7)	12 (11.0)
Negative culture	24 (18.0)	3 (12.5)	21 (19.3)
Complications during hospitalization	96 (72.2)	16 (66.7)	80 (73.4)
Respiratory failure	23 (17.3)	5 (20.8)	18 (16.5)
Severe heart failure	42 (31.6)	7 (29.2)	35 (32.1)
Renal failure	47 (35.3)	9 (37.5)	38 (34.9)
Third-degree atrioventricular block	13 (9.8)	2 (8.3)	11 (10.1)
Neurologic events	18 (13.5)	3 (12.5)	15 (13.8)
Uncontrolled infection	19 (14.3)	4 (16.7)	15 (13.8)
Septic shock	13 (9.8)	4 (16.7)	9 (8.2)

Data as absolute numbers and percentages in parenthesis. *PVE,* Prosthetic valve endocarditis.

TABLE 2. Results of univariate analyses: Risk factors for in-hospital death in 133 episodes of PVE

	Crude mortality		
	RR	95% CI	*P* value
Age > 75 y	1.6	0.6–4.3	NS
Year of PVE diagnosis 1986–1995	0.9	0.4–1.9	NS
Female gender	1.2	0.6–2.7	NS
Previous infective endocarditis	1.7	0.7–4.4	NS
Previous valve replacement	0.9	0.4–2.1	NS
Comorbidity	2.4	0.1–40.1	NS
Mechanical prosthesis implantation	1.1	0.5–2.4	NS
Involvement of the aortic valve	1.7	0.7–3.64	NS
Early PVE	1.9	0.8–4.92	NS
Onset < 3 mo of index operation	2.3	1.1–5.4	.044
Fever	2.0	0.7–5.9	NS
New or changing murmur	1.2	0.5–2.6	NS
Systemic emboli	2. 3	0.4–12.1	NS
White blood cell count < 3 × 10^9/L or >16 × 10^9/L	2.8	1.1–6.9	.023
Positive blood cultures	1.0	0.3–2.7	NS
Staphylococcus aureus infection	2.1	0.7–2.0	NS
Vegetation in the echocardiogram	1.5	0.6–3.2	NS
Abscess in the echocardiogram	3.5	1.6–7.8	.0016
Prosthesis regurgitation	0.9	0.4–1.9	NS
New valve dehiscence	2.2	0.7–7.2	NS
Left ventricular ejection fraction < 30%	17.0	1.4–210	.0082
Surgical treatment	0.5	0.2–1.2	NS
Urgent surgery	3.9	1.5–9.8	.0035
Abscess detected at surgery	2.7	1.1–6.5	.024
Respiratory failure	4.2	1.6–10.7	.0017
Renal failure	2.2	1.03–4.8	.038
Heart failure	9.7	4.1–22.9	.00001
Thrombocytopenia	4.5	1.0–19.6	.034
Third-degree atrioventricular block	1.6	0.5–5.1	NS
Neurologic events	2.2	0.8–5.9	NS
Complicated PVE	1.7	0.7–4.2	NS
Uncontrolled infection	14	4.3–46.2	.00001
Severe sepsis	10	1.9–50.9	.0009
Septic shock	41	5.1–332.3	.00001

PVE, Prosthetic valve endocarditis; *RR,* risk ratio; *CI,* confidence interval.

cardiogenic shock in 13 patients, multiorgan failure in 9, uncontrolled infection in 8, and other in 9. A total of 107 patients had surgical valve replacement during the acute phase of the disease. Urgent surgery was necessary in 51 cases (38.3%).

In the univariate analysis (Table 2), factors significantly associated with in-hospital death were onset of PVE within the first 3 months after the index valve replacement operation, leukopenia or leukocytosis, presence of an abscess detected by echocardiography or at surgery, left ventricular ejection fraction < 30%, urgent surgery, respiratory failure, renal failure, heart failure, thrombocytopenia, uncontrolled infection, severe sepsis, and septic shock. All these factors except thrombocytopenia were significant predictors of in-hospital mortality in the multivariate analysis (Table 3). In addition, the presence of third-degree atrioventricular block

TABLE 3. Results of multivariate analyses: Risk factors for in-hospital death in 133 episodes of PVE

	Adjusted mortality		
	OR*	95% CI	*P* value
Onset < 3 mo of index operation	7.0	1.02–47	.047
White blood cell count < 3 × 10^9/L or >16 × 10^9/L	4.8	1.5–15.4	.009
Abscess in the echocardiogram	3.2	1.3–7.8	.01
Urgent surgery	3.9	1.5–9.9	.02
Abscess detected at surgery	3.9	1.2–9.4	.019
Respiratory failure	4.5	1.5–13.2	.006
Renal failure	2.9	1.2–7.1	.018
Heart failure	11	4.3–39.8	.0001
Third-degree atrioventricular block	3.7	1.15–12	.028
Complicated PVE	2.6	0.8–7.8	.085
Uncontrolled infection	17	4.4–65.7	.0001
Severe sepsis	11	1.8–61.3	.008
Septic shock	42	4.9–356.8	.001

PVE, Prosthetic valve endocarditis; *OR,* odds ratio; *CI,* confidence interval. *All factors adjusted by: sex, age, year of PVE onset, referral hospital, nosocomial infection after original valve replacement.

TABLE 4. Demographic and clinical features between the surgically treated and nonsurgically treated groups of PVE

	Surgical, n (%) (n = 107)	Medical therapy only, n (%) (n = 26)	*P* value
Age, years, mean (SD)	57 (15)	66 (14)	.01
Male patients	75 (70.1)	15 (57.7)	.25
Diabetes mellitus	6 (5.6)	4 (15.4)	.11
Renal failure	1 (0.9)	1 (3.8)	.35
Neoplasms	3 (2.8)	2 (7.7)	.25
Intravenous drug users	2 (1.9)	0	.65
Immunosuppression	3 (2.8)	0	.52
Severe comorbidity	2 (1.9)	0	.65
Early PVE	17 (15.9)	7 (26.9)	.25
Fever	82 (76.6)	24 (92.3)	.10
NYHA functional class IV	40 (37.4)	4 (15.4)	.36
Staphylococcus aureus infection	14 (13.1)	4 (15.4)	.75
Complicated PVE	83 (77.6)	13 (50)	.007
Severe sepsis	4 (3.7)	5 (19.2)	.14

PVE, Prosthetic valve endocarditis; *SD,* standard deviation; *NYHA,* New York Heart Association.

during hospitalization and complicated PVE were also significant predictors in the logistic regression model.

In 26 episodes of PVE occurring in 25 patients, medical treatment only was indicated. One patient with 2 episodes of PVE received only medical treatment because prosthetic valve dysfunction was not observed. In the remaining 24 patients, surgical treatment was not performed for the following reasons: absence of prosthetic valve dysfunction in 10, severe sepsis in 5, cerebral embolism in 3, cardiogenic shock in 2, acute renal failure in 1, and unknown cause in 3. As shown in Table 4, demographic and clinical features of surgically treated and nonsurgically treated patients were similar, although medically treated patients were significantly younger and a significantly lower percentage of patients had complicated PVE as compared with the surgical group. Moreover, more patients in the surgical group were in NYHA functional class IV. The in-hospital mortality rate was 26% in the medical-surgical group versus 42% in the medical therapy alone group (P = NS).

Recurrent PVE was observed in only 12 cases (9%): a recurrent episode of valve infection was detected in 10 episodes and a relapse in 2. Fifty percent of patients were carriers of mechanical valve prosthesis, and 50% of biologic prosthesis (patients with multiple valve replacement in 60% of cases). Only 1 case had a positive culture in which *Candida albicans* was recovered.

The mean length of follow-up was 32.2 months (standard deviation 46.8, range 0–212 months). Freedom from endocarditis was 91% at the end of follow-up. Cumulative survival was 68% at 3 months, 64% at 6 months, and 63% at 12 months. Among the 94 patients who were discharged alive from the hospital, 26 (27%) died during a mean follow-up period of 31 months. As shown in Figure 1, 12-month survival was 71% in the medical-surgical group compared with 42% in the medical group (log-rank test 11.48, P = .0007). In the Cox regression analysis, surgical treatment was a significant predictor of survival (RR = 0.43, 95% CI 0.24–0.75, P = 0.003). Differences in survival regarding early and late PVE and study period (1986–1995 vs 1996–2005) were not observed.

DISCUSSION

Infection of intracardiac prostheses is a serious, often life-threatening complication of valve replacement surgery[14] despite prompt diagnosis, antibiotic therapy, and the frequent indication of replacement of the infected valve. The present study carried out in a large population of patients with PVE also documents the high morbidity and mortality of this condition.

One major problem when assessing the prognosis of PVE is that previous studies have included a spectrum of heterogeneous patients in whom the diagnosis of PVE was not proven. In the study of Kuyvenhoven and colleagues,[3] proven PVE was only documented in 39 of 70 episodes, whereas in the study of Yu and associates,[15] definite endocarditis was diagnosed in 42 of 74 patients. To allow valid interpretation of the data in our study, we included only patients with definite diagnosis of PVE according to Duke criteria.[7] In our population of patients with definite PVE

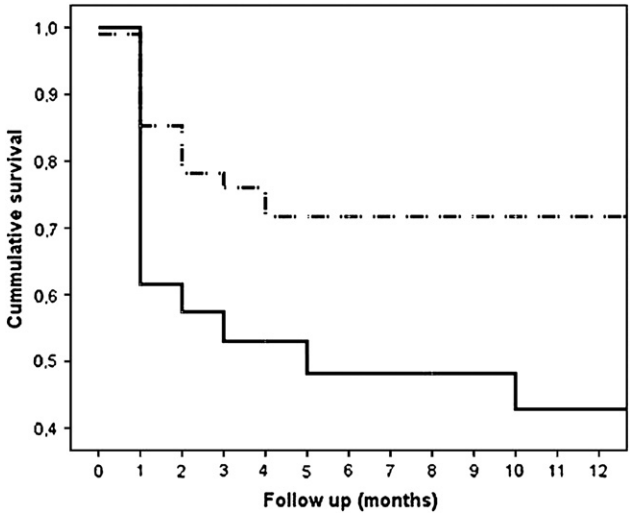

FIGURE 1. Long-term survival of patients with prosthetic valve endocarditis after combined medical and surgical treatment *(upper line)* or medical treatment alone *(lower line)*.

endocarditis in which patients with only bacteremia and no other major criteria of endocarditis were excluded, 18% of cases of PVE occurred within the first 60 days after valve replacement. This percentage is slightly lower than that reported in previous studies, in which about one-third of patients had early onset PVE and two-thirds had late-onset PVE.[16] Although our study showed a higher mortality in patients with early PVE (42%) compared with those with late PVE (26%), there were no statistically significant differences, which is in contrast with other studies.[6,10]

Due to the complexity of PVE, different clinical findings on admission and late complications may influence the outcome. Several studies have suggested that aortic prostheses[17] and infection of a mechanical valve[16] rather than a porcine valve are associated with a higher mortality, but other studies and our data showed no differences with regard to these variables. Leukocytosis or leukopenia on admission was the only variable significantly associated with in-hospital death. Although some studies have shown an association between abnormal white blood cell count and mortality in infective endocarditis,[6] as far as we are aware, this is the first study showing that this marker is an independent predictor of mortality in the setting of PVE.

According to microbiology, early PVE is caused by contamination of the artificial valve at the time of implantation or by perioperative bacteremia, so that the most frequently encountered pathogens in early PVE are coagulase-negative staphylococci, followed by *S aureus* and *Enterococcus*.[18] On the other hand, late PVE can be caused by different microorganisms.[19] In agreement with other studies, we found that coagulase-negative *Staphylococcus* was the most common causative microorganism for PVE, although recent studies showed an increase in PVE caused by *S aureus*.[14] A significant association between *S aureus* infection and mortality in PVE has been reported. In our study, a trend toward a higher mortality with staphylococcal infection was noted, but statistical significance in the multivariate analysis was not reached.

Echocardiographic findings have an important role in the diagnosis and management of PVE.[20] Echocardiographic signs include vegetations on and around the prosthetic valve, valve dysfunction (stenosis, regurgitation, perivalvular leak), and invasion of perivalvular tissue by abscesses and fistulae. Previous studies showed the association of periannular complications in endocarditis in the setting of prosthetic valve infection.[20] However, the role of echocardiography in predicting outcome has been poorly assessed. In the study of Habib and associates,[5] the presence of annular abscess was not associated with increased mortality. In our study, we observed a 29% rate of echocardiographic abscess in PVE patients, which is higher than the results obtained in other studies, which ranged from 12% to 19%.[6,12,21] The mortality of these patients was statistically significant in multivariate analysis. In a recent prospective multicenter study, abscess formation was included among the strongest predictors of mortality.[12] We also observed a worse prognosis in patients with a low ejection fraction. There are few comparable data in the literature concerning the ejection fraction as a predictor of outcome in patients with PVE.[22]

The optimal treatment in PVE is still debated, but surgery has become a mainstay in complicated PVE.[14,17,23] The high rate of subsequent valve failure in patients treated medically is an argument in favor of surgical treatment. However, the use and timing of surgery in an individual patient with PVE is often a difficult and complex clinical decision. Calderwood and colleagues[9] showed that patients not treated surgically during their initial hospital admission are at high risk of progressive prosthesis dysfunction and require careful follow-up. In contrast, early valve surgery appears to improve the prognosis of PVE. The superiority of surgical treatment compared with antibiotic treatment alone has been demonstrated in several studies, so that an aggressive medical-surgical approach is recommended.[9,15] In our study population, the surgery rate was relatively high when compare with data from the literature. The main cause was that about 65% of our patients were referred from other hospitals because of associated morbidity and a complicated clinical course of PVE. When we analyzed the outcome of patients according to the treatment received, in-hospital mortality was lower in the surgical group than in the medical group (26% vs 42%), although the differences were not statistically significant. Survival after 12 months of treatment, however, was markedly different in favor of surgically treated patients (71% vs 42%). Moreover, surgical treatment was an independent significant variable associated with favorable outcome in the Cox regression analysis (RR = 0.43, P = .003). Other studies have also assessed the benefits of

surgical treatment, but few of them have evaluated the impact of long-term survival.[5,6] In the study of Wang and associates,[12] a trend toward a benefit of surgical treatment was also reported. However, further studies are needed to define more clearly the role, timing, and effect of surgery in PVE.

Chronic heart failure is the most common cause of death in patients with PVE[5,9] and also the most frequent indication of surgical treatment in complicated infective endocarditis. Heart failure in PVE results predominantly as a consequence of valve destruction and secondary severe regurgitation leading to pulmonary edema. In our study, like others,[10] heart failure was one of the strongest predictors of in-hospital mortality. Uncontrolled infection, severe sepsis, and septic shock were predictors of death in the multivariate analysis, reflecting the importance of sepsis in the outcome of these patients. In addition, neurologic complications were related to an adverse outcome, as previous studies have pointed out.[12,24] On the other hand, and in contrast to other studies,[9,10] a relationship between complicated PVE and mortality was not observed.

After hospital discharge, the highest mortality rate was observed during the first 3 months. After this period, the survival of the patients remain stable and freedom from endocarditis was 92% at the end of the follow-up period. The differences between medical and surgical treatment in long-term outcome are similar to previous studies[5,15] and add evidence of the importance of combined surgical and medical treatment as the better treatment option in these patients. In fact, surgery was a significant protective factor for survival in the Cox regression analysis. In our patients, the medically treated group showed a higher in-hospital mortality rate than the surgically treated group, although differences were not significant. Although patients in the medical therapy only group were older, a significantly lower percentage was in NYHA functional class IV and had complicated bacterial endocarditis compared with the surgical group. Comorbidities in both groups were similar. Selection of surgical treatment should be considered in an early phase of the diagnosis of PVE and probably by a multidisciplinary team (cardiologists, specialists in infectious diseases, cardiovascular surgeons). The decision of operation should not be delayed as surgical mortality is related to the amount of anatomic damage, and it is well known that anatomic destruction reflects both aggressiveness of the causative pathogen and duration of the disease.

Our study has several shortcomings. First, a prospective randomized controlled trial remains the best way to evaluate the effectiveness of different strategies in the management of PVE but such a trial would take several years to recruit a sufficient number of patients from a single center or may have to involve multiple centers, leading to a nonhomogeneous group of patients and management protocols. Thus, a retrospective review is a reasonable approach for attempting to assess predictors of outcome in patients with PVE, although retrospective studies are clearly hampered by lack of randomization and therefore bias in the selection of treatment methods. However, our surgical team had no significant differences concerning intraoperative management, and there was a formal policy in our hospital during the study period. Second, our study was performed in a referral center; this may introduce a referral bias in the result obtained, which we tried to solve by introducing this variable in the multivariate analysis. Third, survivor treatment selection bias could be detected,[25] although there were no significant differences according to comorbidities or clinical situation between medical or surgical patients treated, and a significant number of patients in our study underwent urgent surgery. On the other hand, only patients who fulfilled the Dukes criteria for definite endocarditis were analyzed, which is in contrast to previous studies in which such a strict criterion was not used. Thus, our study is one of the largest single-center series published in the literature, and the present results may contribute to a better knowledge of the clinical course and outcome of this important disease.

In summary, the present findings, which should be interpreted considering the retrospective nature of the study, confirm that PVE is a serious condition with a high mortality. Patients with perivalvular abscess had a worse prognosis, and combined surgical and medical treatment could be the preferred approach to improve outcome.

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References

1. Arvay A, Lengyel M. Incidence and risk factors of prosthetic valve endocarditis. *Eur J Cardiothorac Surg*. 1988;2:340-6.
2. Rutledge R, Kim BJ, Applebaum RE. Actuarial analysis of the risk of prosthetic valve endocarditis in 1,598 patients with mechanical and bioprosthetic valves. *Arch Surg*. 1985;120:469-72.
3. Kuyvenhoven JP, van Rijk-Zwikker GL, Hermans J, et al. Prosthetic valve endocarditis: analysis of risk factors for mortality. *Eur J Cardiothorac Surg*. 1994;8:420-4.
4. Fariñas MC, Pérez-Vázquez A, Fariñas-Alvarez C, et al. Risk factors of prosthetic valve endocarditis: a case-control study. *Ann Thorac Surg*. 2006;81:1284-90.
5. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: who needs surgery? A multicentre study of 104 cases. *Heart*. 2005;91:954-9.
6. Akowuah EF, Davies W, Oliver S, et al. Prosthetic valve endocarditis: early and late outcome following medical or surgical treatment. *Heart*. 2003;89:269-72.
7. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med*. 1994;96:200-9.
8. Pérez-Vázquez A, Fariñas MC, García-Palomo JD, et al. Evaluation of the Duke criteria in 93 episodes of prosthetic valve endocarditis. Could sensitivity be improved? *Arch Intern Med*. 2000;160:1185-91.
9. Calderwood SB, Swinski LA, Karchmer AW, et al. Prosthetic valve endocarditis: analysis of factors affecting outcome of therapy. *J Thorac Cardiovasc Surg*. 1986;92:776-83.
10. Wolff M, Witchitz S, Chastang C, et al. Prosthetic valve endocarditis in the ICU. Prognostic factors of overall survival in a series of 122 cases and consequences for treatment decision. *Chest*. 1995;108:688-94.
11. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM

Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644-55.
12. Wang A, Pappas P, Anstron KJ, et al. The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort. *Am Heart J*. 2005;150:1086-91.
13. Daniel WG, Mugge A, Martin RP, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *N Engl J Med*. 1991;324:795-800.
14. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297:1354-61.
15. Yu VL, Fang GD, Keys TF, et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. *Ann Thorac Surg*. 1994;58: 1073-7.
16. Turina M. Prosthetic valve endocarditis. *Thorac Cardiovasc Surg*. 1982;30:350-3.
17. Wallace SM, Walton BI, Kharbanda RK, et al. Mortality from infective endocarditis: clinical predictors of outcome. *Heart*. 2002;88:53-60.
18. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318-30.
19. David TE. The surgical treatment of patients with prosthetic valve endocarditis. *Semin Thorac Cardiovasc Surg*. 1995;7:47-53.
20. Lengyel M. The impact of transesophageal echocardiography on the management of prosthetic valve endocarditis: experience of 31 cases and review of the literature. *J Heart Valve Dis*. 1997;6:204-11.
21. Anguera I, Miro JM, Evangelista A, et al. Periannular complications in infective endocarditis involving prosthetic aortic valves. *Am J Cardiol*. 2006;98: 1261-8.
22. Jassal DS, Neilan TG, Pradhan AD, et al. Surgical management of infective endocarditis: early predictors of short-term morbidity and mortality. *Ann Thorac Surg*. 2006;82:524-9.
23. Habib G, Thuny F, Avierinos JF. Prosthetic valve endocarditis: current approach and therapeutic options. *Prog Cardiovasc Dis*. 2008;50:274-81.
24. Chu VH, Cabell CH, Benjamin DK Jr, et al. Early predictors of in-hospital death in infective endocarditis. *Circulation*. 2004;109:1745-9.
25. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. *Circulation*. 2007;115: 1721-8.