SURGERY FOR ACQUIRED HEART DISEASE

SURGICAL TREATMENT OF PROSTHETIC VALVE ENDOCARDITIS

From 1975 through 1992, we reoperated on 146 patients for the treatment of prosthetic valve endocarditis. Prosthetic valve endocarditis was considered to be *early* (<1 year after operation) in 46 cases and *active* in 103 cases. The extent of the infection was prosthesis only in 66 patients, anulus in 46, and cardiac invasion in 34. Surgical techniques evolved in the direction of increasingly radical débridement of infected tissue and reconstruction with biologic materials. All patients were treated with prolonged postoperative antibiotic therapy. There were 19 (13%) in-hospital deaths. Univariate analyses demonstrated trends toward increasing risk for patients with active endocarditis and extension of infection beyond the prosthesis; however, the only variables with a significant ($p < 0.05$) association with increased in-hospital mortality confirmed with multivariate testing were impaired left ventricular function, preoperative heart block, coronary artery disease, and culture of organisms from the surgical specimen. During the study period, mortality decreased from 20% (1975 to 1984) to 10% (1984 to 1992). For hospital survivors the mean length of stay was 25 days. Follow-up (mean interval 62 months) documented a late survival of 82% at 5 postoperative years and 60% at 10 years. Older age was the only factor associated ($p = 0.006$) with late death. Nineteen patients needed at least one further operation; reoperation-free survival was 75% at 5 and 50% at 10 postoperative years. Fever in the immediate preoperative period was the only factor associated with decreased late reoperation-free survival ($p = 0.032$). Prosthetic valve endocarditis remains a serious complication of valve replacement, but the in-hospital mortality of reoperations for prosthetic valve endocarditis has declined. With extensive débridement of infected tissue and postoperative antibiotic therapy, the extent and activity of prosthetic valve endocarditis does not appear to have a major impact on late outcome, and the majority of patients with this complication survive for 10 years after the operation. (J THORAC CARDIOVASC SURG 1996;111:198-210)

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Prosthetic valve endocarditis (PVE) is a serious complication of cardiac valve replacement. Large studies of patients undergoing primary valve replacement have shown that despite the use of perioperative antibiotic therapy, the likelihood of PVE occurring during the first postoperative year has been approximately 3% and after the first postoperative years the risk of PVE appears to be approximately 1% per year.[1-6] Treatment with antibiotics alone can be an effective therapy for PVE, particularly for patients with infection limited to the leaflets of a bioprosthesis. However, most patients with infection of a prosthetic valve anulus will require replacement of the prosthesis in addition to

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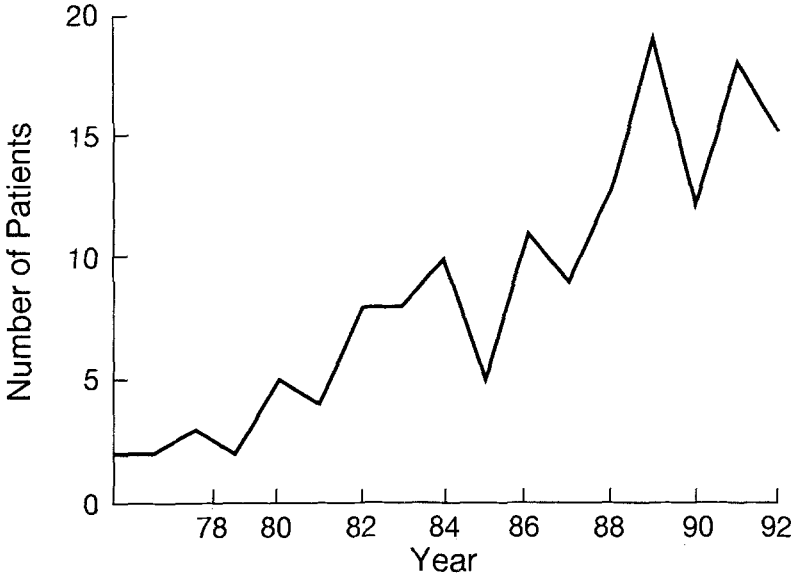


Fig. 1. Number of operations for PVE per year, 1975-1992.

antibiotic therapy, and many patients with "cured" PVE infection will eventually require reoperation. A combination of surgery for excision of infected tissue and valve rereplacement, along with intensive long-term antibiotic therapy, has often been successful in treating patients with PVE, but in-hospital mortality rates of reoperations for PVE have been 22% to 46% even at centers with extensive experience in valve surgery.[2, 7-12] Furthermore, eradication of infection has been inconsistent even with second operations, and late survival and reoperation-free survival have not been favorable even for patients who weather surgery for PVE.

However, a number of factors may have improved the outlook for patients with PVE. Improvements in myocardial protection have allowed surgeons to perform operations involving extensive débridement and complex cardiac reconstructions. The use of biologic materials for reconstruction, including aortic valve homografts, has increased and new generations of antimicrobial agents have been used. To assess the current status of surgical therapy for PVE, we reviewed the case histories of 146 patients who underwent reoperation for PVE from 1975 to 1992. Inclusion in this study was stopped in 1992 to allow at least a 2-year follow-up.

Patients and methods

Patient population. With the aid of a computerized cardiovascular information registry, we identified all patients (n = 146) who underwent a reoperation for the surgical treatment of PVE from 1975 through 1992. The number of operations performed for PVE during the period of the study has increased progressively (Fig 1). Although some patients had multiple operations for PVE, the operation examined was the first operation for PVE done at The Cleveland Clinic Foundation. Variables related to the previous operation, interval between operations, PVE illness, and the reoperation for PVE were examined for the association with early and late risk and are listed in Table I and Appendix I. To analyze changes in the patient population and effectiveness of treatment, patients were subgrouped according to the year of their PVE reoperation, 1975 to 1984 versus 1985 to 1992.

Definitions. *Early PVE* was defined as a reoperation for PVE within 1 year of the previous valve replacement, whereas *late PVE* applied to patients undergoing reoperation more than 1 year after the previous valve replacement.

Three criteria were used in the definition of *active PVE:* positive blood cultures within 2 months of operation, positive cultures of the surgical specimen removed at reoperation, or organisms identified by microscopic examination of the surgical specimen. A total of 103 patients fulfilled one of these criteria and were considered to have active endocarditis, whereas the remaining 43 were considered to have healed endocarditis.

Regarding extent of infection, patients were subgrouped according to the operative findings of the status of the prosthesis, the prosthesis-cardiac anulus interface, and the degree of myocardial invasion of infection. The patient was considered to have infection of the prosthesis only (66 patients) if a significant periprosthetic leak was not identified and myocardial invasion was not noted; a significant periprosthetic leak without extensive myocardial invasion was considered to indicate an anulus infection (46 patients); and tissue destruction beyond the

Table I. *In-hospital mortality according to surgical period*

	1975-1984			*1984-1992*		*Total*		
	No.	*%*	*p Value**	*No.*	*%*	*No.*	*%*	*P value†*
	9/44	20	0.079	10/102	10	19/146		
Early	4/11	36	0.046	3/35	9	7/46	15	
Late	5/33	15	0.524	7/67	10	12/100	12	0.591
Active	8/33	24	0.146	9/70	13	17/103	16	
Healed	1/11	9	0.451	1/32	3	2/43	5	0.052
Extent of infection								
Prosthesis alone	2/19	10	0.373	2/47	4	4/66	6	
Anulus	4/17	24	0.397	3/29	10	7/46	15	
Invasive	3/8	38	0.355	5/26	17	8/34	24	0.04
Surgical specimen culture positive								
No	4/29	14	0.071	2/65	3	6/94	6	
Yes	5/15	33	0.483	8/37	22	13/52	25	0.001

**p* Value for comparison of mortality per variable for the two surgical periods.
†*p* Value for difference in mortality for each variable for entire patient group.

prosthesis-tissue interface was considered to indicate invasive infection (34 patients). Patients with multiple infected valves were classed according to the valve with the most extensive infection.

In-hospital death (early mortality) was defined as death before hospital discharge regardless of the duration of hospitalization. Late death was defined as death after discharge from the operative hospital stay.

Results

Bacteriology and pathology. The organisms identified at culture either of the blood (106 patients) or of the surgical specimen (52 patients) are listed in Appendix II, separated according to early versus late infection. In three patients cultures were negative but microscopic examination of the surgical specimen revealed the organisms. Examination of organisms according to whether they were linked to healed or active PVE showed that healed status was more common after enterococcal (5/11) and streptococcal (8/27) infection. On the other hand, PVE was considered healed in only three of the 31 cases of *Staphylococcus aureus* PVE and in none of the eight cases of fungal endocarditis.

Pathologic conditions detected at operation differed on the basis of the time of the infection and the prosthesis type. Of the 46 patients with early PVE, 20 (43%) had infection of the anulus, 18 (39%) had invasive infection, and only 8 (17%) had infection of the prosthesis only. On the other hand, of the 100 patients with late PVE, 58 had involvement of the prosthesis only; 49 of those infections involved bioprostheses, 3 homografts, and 6 mechanical valves. Of 71 late infections of bioprostheses, 49 (69%) involved the prosthesis only; of 26 infections involving late mechanical valve PVE only, 6 (23%) were limited to the prosthesis. Including both early and late infections, there were 90 instances of bioprosthesis infection with involvement of the prosthesis only, 53 (95%), annular infection, 18 (20%), and invasive infection, 19 (21%). For patients with infected mechanical valves ($n = 54$) the infections were distributed as follows: prosthesis in 10 (18%), anulus in 28 (52%), and invasion in 15 (28%). The majority of patients (26/49, 53%) with late infections of bioprostheses were considered to have had healed infections at the time of the operation, and the mean interval between the onset of PVE and the reoperation was 21 ± 24 months.

Operative technique. As surgical experience increased operative techniques evolved. Except in seven patients operated on in the early years of the study, cardioplegia was used for myocardial protection in all patients, with a trend toward blood cardioplegia in more recent years. Progressively more radical débridement of cardiac tissues was carried out combined with reconstruction of cardiac structures with biologic materials, such as autologous or bovine pericardium. Valve replacement was accomplished with mechanical valves ($n = 52$), bioprostheses ($n = 76$), and homografts ($n = 13$). In five patients the valve was not replaced: four patients had repair of a periprosthetic leak and one underwent thrombectomy. All patients with active PVE were treated with long-term intravenous antibiotic therapy (4 to 6 weeks after the operation).

In-hospital mortality. Nineteen (13%) in-hospital deaths occurred. The mode of death was intraoperative myocardial failure in four, postoperative

myocardial failure in six, multisystem organ failure in three, persistent sepsis in two, and myocardial infarction, renal failure, cerebral hemorrhage, and pulmonary embolus in one each. Compared according to the surgical periods, the in-hospital mortality decreased from 20% (9/44) during the 1975-1984 period to 10% (10/102) during the 1985-1992 period ($p = 0.079$).

Univariate analyses of the association of preoperative and operative variables with in-hospital mortality are listed in Table I and Appendix I. For the entire duration of the study, the variables with an association ($p < 0.1$) with mortality were preoperative heart block, surgical specimen culture positive for microorganisms, coronary artery disease, preoperative left ventricular function, year of operation, active PVE, invasive infection, and fever for 1 to 3 days before the operation. Inclusion of these variables in a logistic regression model identified preoperative heart block ($p = 0.0047$), positive surgical specimen culture ($p = 0.0179$), coronary artery disease ($p = 0.0423$), and abnormal left ventricular function ($p = 0.0223$) as associated with increased in-hospital mortality.

For some patient subsets, in-hospital mortality rates for the 1975-1984 and 1985-1992 time frames were compared with univariate testing (see Table I). In the more recent time frame, there was a significant decrease in mortality for patients with early PVE and nonstatistically significant trends toward a decreased risk for patients with active PVE; prosthesis, anulus, or invasive infection; patients with organisms cultured from the surgical specimen; and for the entire group.

Patients undergoing operation during the 1985-1992 period were examined as a separate subset, and logistic regression analysis identified preoperative left ventricular function ($p = 0.0012$) and positive culture of the surgical specimen ($p = 0.0119$) as the only factors associated with mortality during that time frame.

Perioperative morbidity included reoperation for bleeding in 15 patients (10%), pacemaker placement in 20 (14%), renal failure in 10 (7%), respiratory failure in 9 (6%), stroke in 4 (3%), myocardial infarction in 2 (1%), and wound infection in 3 (2%). For hospital survivors the mean length of hospital stay was 25 days.

Late results. Follow-up at a mean postoperative interval of 62 months documented late survival (survival of in-hospital survivors) of 82% at 5 years and 60% at 10 postoperative years (Fig. 2, *A*). That produced an overall survival (including in-hospital deaths) of 71% at 5 years and 52% at 10 postoperative years.

Thirty-six late deaths occurred, with the mode of death being congestive heart failure ($n = 10$), undocumented but probable cardiac death ($n = 4$), sudden death ($n = 3$), death at cardiac reoperation ($n = 3$), stroke ($n = 3$), arrhythmia ($n = 2$), renal failure ($n = 2$), and acute myocardial infarction, sepsis, endocarditis, and bleeding ($n = 1$ each). Only five deaths were clearly not related to heart disease, endocarditis, or valve disease. They were caused by ruptured aneurysm in two patients, cancer in two, and trauma in one.

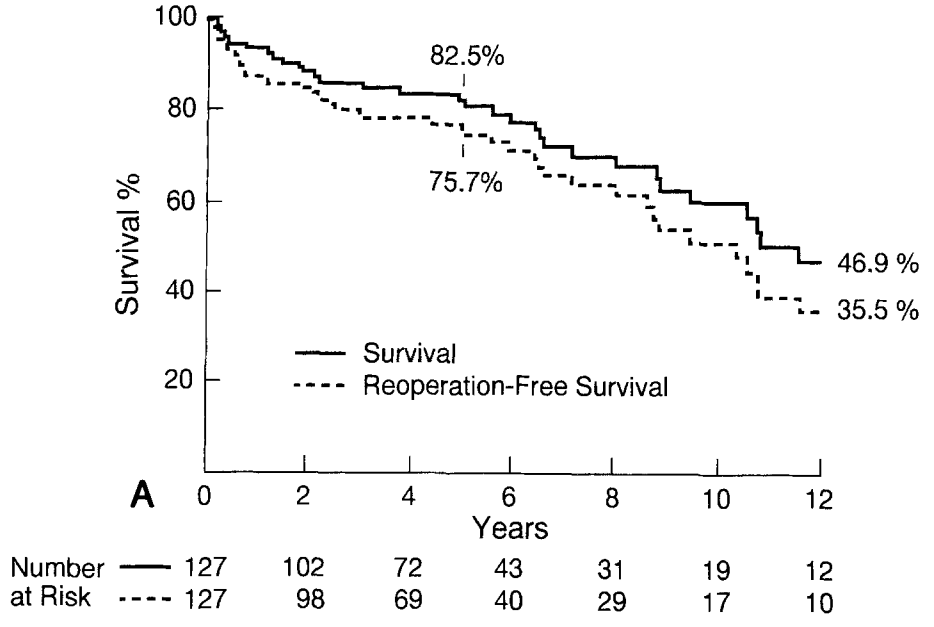
Of the 127 in-hospital survivors of the initial PVE operation, 19 had a subsequent valve reoperation. The late reoperation-free survival of those 19 patients was 76% at 5 postoperative years (Fig. 2, *B*). Eight patients underwent reoperation within 1 year of their original PVE operation (three with organisms identified in the blood or surgical specimen), and 11 underwent a second operation more than 1 year after their original PVE operation, organisms being identified in two of those patients. Four of the 19 patients had a further reoperation, and one patient had two more reoperations. For the 19 patients who required one operation or more after the initial operation for PVE, the 5-year survival was 59% after that second PVE operation. All patients with a known recurrence of endocarditis after their PVE operation underwent a second operation.

Examination of the variables in Table I and Appendix 1 did not demonstrate a significant difference in late survival or reoperation-free survival on the basis of the time of the infection (early vs late) (Fig. 3), activity of the infection (active vs healed), or the extent of the infection at operation (Fig. 4). For the entire group of patients, the type of valve used for rereplacement did not influence late outcome, and evaluation of the patients who underwent reoperation for isolated aortic valve PVE did not demonstrate an advantage for any valve type (Fig. 5).

Multivariate testing by means of Cox regression analysis showed that only advanced patient age was associated with decreased late survival ($p = 0.006$). Multivariate testing in regard to reoperation-free survival showed that only fever in the immediate preoperative period (1 to 3 days before the operation) was associated with decreased late reoperation-free survival ($p = 0.032$).

Discussion

The number of patients operated on each year for PVE at our institution has been increasing as a



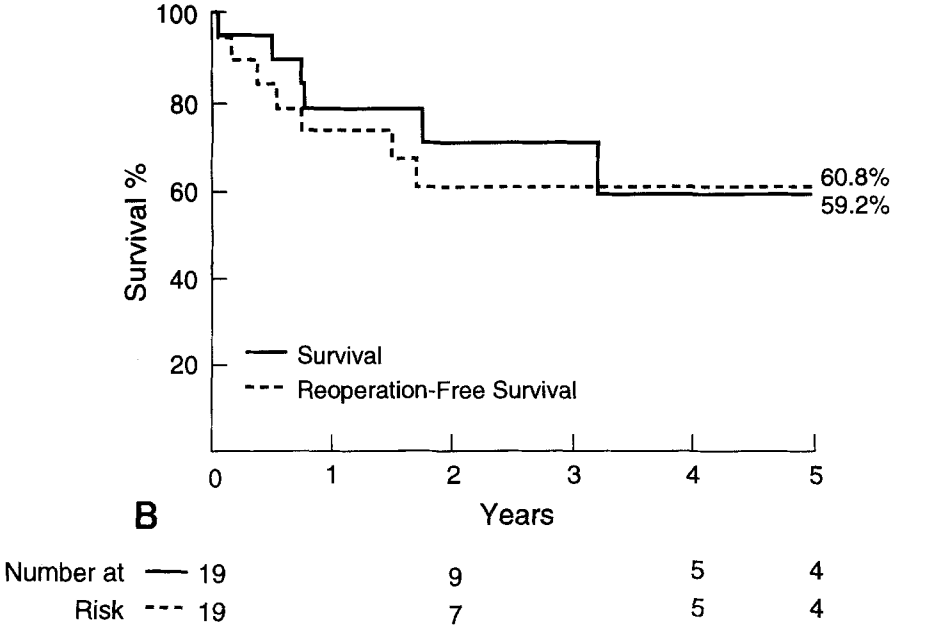


Fig. 2. Late survival and reoperation-free survival for the in-hospital survivors of operations for PVE **(A)** and for the 19 patients who underwent subsequent reoperation **(B)**.

result of multiple influences, including the large numbers of patients who now have had successful valve replacement and who are at risk for PVE, regional referral patterns, and an aggressive attitude toward the surgical treatment of patients with PVE. Yet even this relatively large single-institution series contains only 146 patients distributed over a 17-year time frame. In-depth statistical analysis in all studies of PVE is difficult because of the small patient numbers. Therefore our observations have pertained to some not statistically significant trends, as well as statistically significant results of univariate and multivariate analyses.

Bioprostheses and mechanical valves differed with

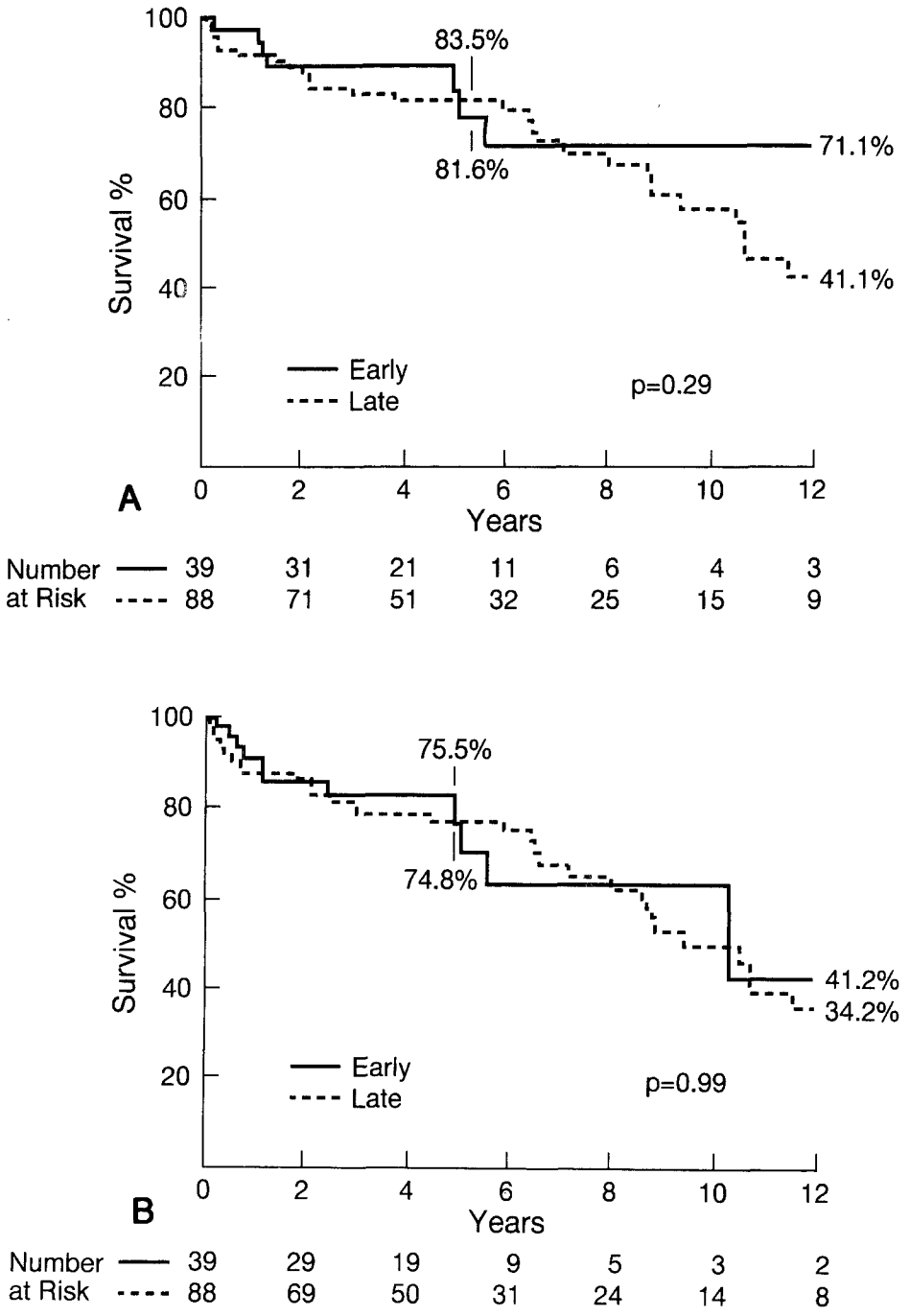


Fig. 3. Early versus late infection did not appear to influence late survival **(A)** or reoperation-free survival **(B)**.

regard to the type of disease found at reoperations for PVE. Patients with late infections of bioprostheses frequently had involvement of only the prosthesis (69%), whereas infection was limited to the prosthesis in only 23% of patients with late PVE involving a mechanical valve. For both types of prostheses, annular and invasive infections predominated, with only 17% of early infections being limited to the prosthesis.

The bacteriologic characteristics of the series were consistent with previous studies of PVE. Gram-positive organisms predominated. *Streptococcus* and *Enterococcus* were common causes of late PVE but were not common in the early setting.

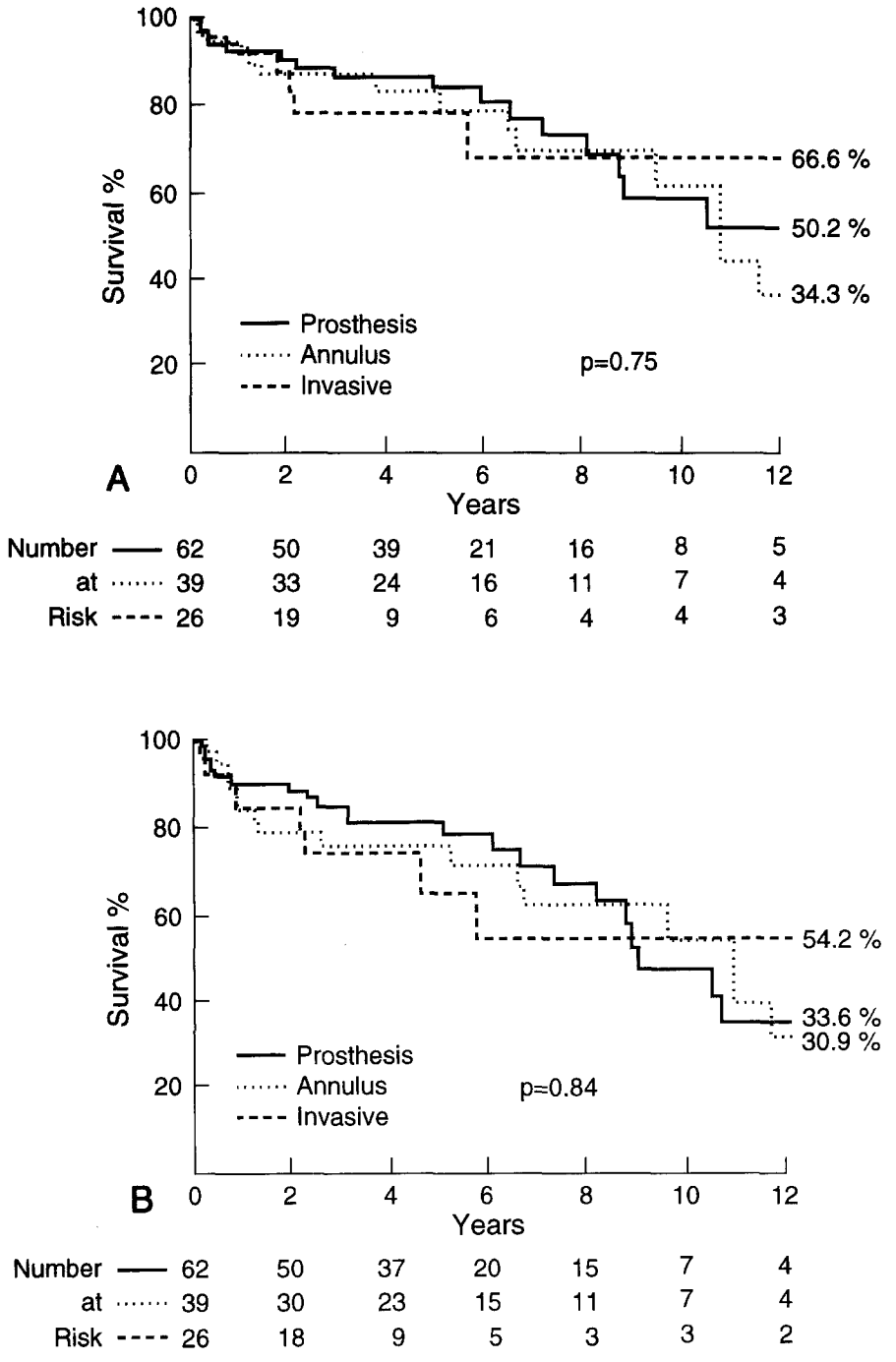


Fig. 4. Late survival (**A**) did not appear to be influenced by the extent of the infection found at operation. The trend toward decreased reoperation-free survival in patients with invasive infection (**B**) was not statistically significant ($p = 0.84$).

Patients rarely were reoperated on for "healed" PVE if the organisms were *Staphylococcus aureus* (3/31) or fungus (0/8), illustrating the difficulty in eradicating these organisms with antibiotic treatment alone. The majority of patients who underwent surgical treatment for healed PVE were patients with late infections of bioprostheses, and the causative organisms were most likely to be *Enterococcus*

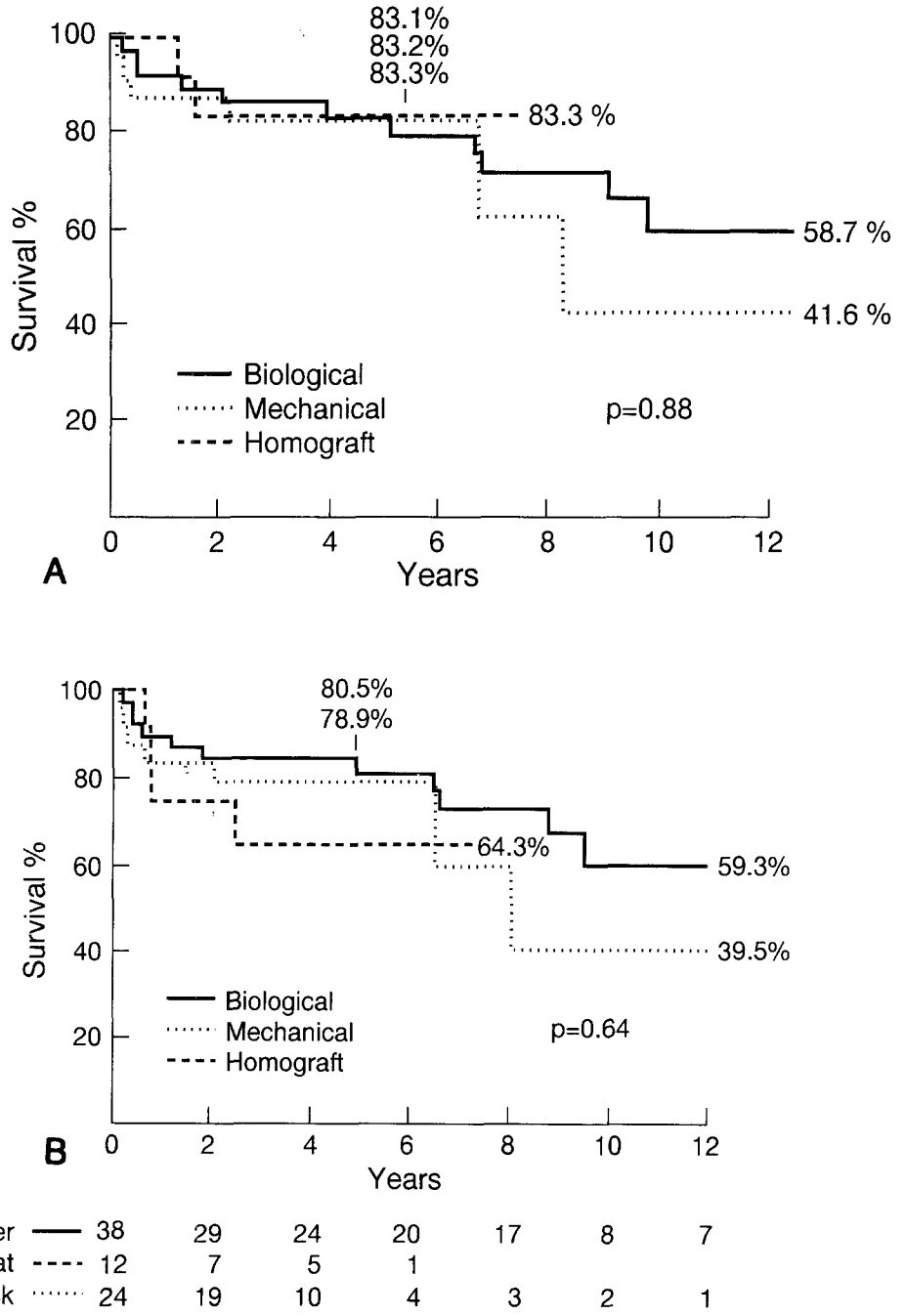


Fig. 5. For patients with aortic valve PVE, late survival (**A**) and reoperation-free survival (**B**) were equivalent regardless of the type of prosthesis used.

or *Streptococcus.* Other authors have noted that this subgroup may often be successfully treated with antibiotic therapy, at least temporarily.[13] However, it is also clear that even endocarditis involving only the bioprosthesis hastens the failure of those valves, inasmuch as the interval between the onset of PVE and the time of reoperation was just under 2 years in our series.

In-hospital mortality clearly decreased (20% to 10%) when the two time periods of the study (1975-1984 vs 1984-1992) were compared. Although the risk for patients in both high- and low-risk

subgroups decreased, most notable was the improved survival for patients in high-risk categories. In particular, the decrease in mortality in operations for early endocarditis was statistically significant and there were strong trends toward a decreased mortality for patients with active PVE and invasive disease. The trend in surgical technique has been toward more extensive operations. It is probable that effective myocardial protection, as well as increased surgeon experience, accounts for this improvement in in-hospital risk.

During the 1984-1992 time frame, our surgical technique evolved in the direction of more extensive débridement of myocardial tissue and the use of biologic materials for reconstruction. The fact that 14% of patients required new pacemaker placement is some indication of the extent of tissue removal. The specific measures that are necessary to eradicate infection vary from case to case, and publications by Ergin and associates[14] and David[15] have illustrated some approaches to specific anatomic problems. We have found that division of the superior vena cava allows precise exposure of the mitral valve and aortic valve and may be extremely helpful when bivalvular infection extends to the fibrous trigone of the heart.[16] We prefer autologous pericardium for cardiac reconstruction, but if that is not available bovine pericardium has been used with success.

The use of aortic valve homografts for the treatment of aortic valve PVE is another concept that has been suggested by multiple investigators.[9, 12, 17-19] Our use of homografts for this indication began in 1988. Although we have reported the use of only 13 homografts in this series, through the middle of 1994 we have placed another 20 homografts during reoperations for PVE.[20] Early series of patients receiving homografts for aortic root infections involving prosthetic valves reported high in-hospital mortality rates,[12, 17] but the risk appears to have decreased with increased experience.[18, 20]

The presence of PVE injects uncertainty into the long-term result of valve replacement, and in the past patients have been noted to have had unfavorable rates of late death, recurrence of infection, and reoperation. In a study of 49 patients with PVE by Larbalestier and associates,[10] 22% died in the hospital and another 22% died after hospital discharge, for a total survival of approximately 50% at 5 years. Jault and associates[11] noted a 54% survival at 6 postoperative years with a 26% incidence of reoperation. Calderwood and coworkers[8] noted a 23% in-hospital mortality, with 75% of the survivors of combined medical and surgical treatment still alive 4 years after the operation. A more recent series reported by David and colleagues[21] reviewed 24 patients with PVE who had a 12.5% in-hospital risk and a 56% 5-year survival. Clearly the issue is not resolved once the patient leaves the hospital after surgery for PVE.

In this study we found a late survival (survival of in-hospital survivors) of 82% at 5 years and, including in-hospital mortality in the calculations, a 5-year survival of 71%. Subsequent reoperation was performed for 15% of in-hospital survivors. It is difficult to know what to compare these results with, because late survival after valve reoperation for indications other than PVE is not a well-studied subject. Late mortality in this series was largely cardiac related, although rarely was it clearly related to infection. Of the 19 patients who underwent reoperations after their PVE operation, there were only five in whom active infection was demonstrated as the cause of that second operation; two of these infections occurred 3 or more years after the PVE operation, possible examples of reinfection rather than persistent infection. These observations may mean that the infections were eradicated and that the reoperations that were needed were engendered by bland periprosthetic leaks. However, an alternative explanation is that persistent infection did cause periprosthetic leaks leading to a second operation but that organisms could not be cultured, perhaps because of long-term antibiotic therapy. It is our hope that a more radical approach to reoperations for PVE will result in a higher rate of cure of infection. Realistically, although we have shown that in-hospital risk has decreased, the late results do not yet seem to place patients undergoing reoperation for PVE in a "normal" post-valve replacement survival mode.

We did not document an improvement in late survival on the basis of surgical period. However, there were trends toward older age and an increased prevalence of coronary artery disease for patients in the more recent surgical period, alterations in the patient population that may have blunted the influence of improved surgical results. It is noteworthy that the time of infection (early vs late), the activity of the infection, and the extent of the infection at reoperation did not influence late survival or late reoperation-free survival. We would like to think that this occurred because aggressive reoperation eradicated the infection more often and improved the survival of those patients in high-risk categories.

Other authors have presented evidence that the use of aortic valve homografts in the treatment of PVE improves long-term outcome.[12, 18] We believe this may be true, and we currently use aortic valve homografts in the treatment of patients with aortic valve and aortic root infection. However, the data from this study do not demonstrate an improved long-term outcome for the small numbers of patients who did receive homografts. Furthermore, with extensive débridement at reoperation and the use of intensive long-term antibiotic therapy, valve rereplacement for PVE with standard prostheses is not a futile gesture, inasmuch as patients undergoing reoperation with bioprostheses and mechanical valves had a late 5-year survival of 83%.

Finally, persistence appears to be of value in the treatment of PVE. For the 19 patients who required one or more reoperations after their PVE operation, survival was still 59% at 5 postoperative years.

REFERENCES

1. Blackstone EH, Kirklin JW. Death and other time-related events after valve replacement. Circulation 1985;72:753-67.
2. Grover FL, Cohen DJ, Oprian C, et al. Determinants of the occurrence of and survival from prosthetic valve endocarditis: experience of The Veterans Affairs Cooperative Study on Valvular Heart Disease. J THORAC CARDIOVASC SURG 1994;108:207-14.
3. Calderwood SB, Swinski LA, Waternaux CM, et al. Risk factors for the development of prosthetic valve endocarditis. Circulation;1985:72:31-7.
4. Karchmer AW. Prosthetic valve endocarditis: a continuing challenge for infection control. J Hosp Infect 1991;18(A):355-66.
5. Bloomfield P, Wheatley DJ, Prescott RJ, et al. Twelve year comparison of a Björk-Shiley mechanical heart valve with porcine bioprostheses. N Engl J Med 1991;324:573-9.
6. Akins CW, Carroll DL, Buckley MJ, et al. Late results with Carpentier-Edwards porcine bioprosthesis. Circulation 1990;82(Suppl):IV65-74.
7. Piehler JM, Blackstone EH, Bailey KR, et al. Reoperation on prosthetic heart valve: patient-specific estimates of in-hospital events. J THORAC CARDIOVASC SURG 1995;109:30-47.
8. 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.
9. Miller DC. Predictors of outcome in patients with prosthetic valve endocarditis (PVE) and potential advantages of homograft aortic root replacement for prosthetic ascending aortic valve-graft infections. J Card Surg 1990;5:53-62.
10. Larbalestier RI, Kinchla NM, Aranki SF, et al. Acute bacterial endocarditis: optimizing surgical results. Circulation 1992;86:68-74.
11. Jault F, Gandjbakhch I, Chastre JC, et al. Prosthetic valve endocarditis with ring abscesses: surgical management and long-term results. J THORAC CARDIOVASC SURG 1993;105:1106-13.
12. Haydock D, Barratt-Boyes B, Macedo T, et al. Aortic valve replacement for active infectious endocarditis in 108 patients: a comparison of freehand allograft valves with mechanical prostheses and bioprostheses. J THORAC CARDIOVASC SURG 1992;103:130-9.
13. Tornos P, Sanz E, Permanyer-Miralda G, et al. Late prosthetic valve endocarditis: immediate and long-term prognosis. Chest 1992;101:37-41.
14. Ergin MA, Raissi S, Follis F, et al. Annular destruction in acute bacterial endocarditis: surgical techniques to meet the challenge. J THORAC CARDIOVASC SURG 1989;97:755-63.
15. David TE. The surgical treatment of patients with prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:47-53.
16. Lytle BW. Surgical treatment of prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7: 13-9.
17. Glazier JJ, Verwilghen J, Donaldson RM, Ross DN. Treatment of complicated prosthetic aortic valve endocarditis with annular abscess formation by homograft aortic root replacement. J Am Coll Cardiol 1991;17:1177-82.
18. McGiffin DC, Kirklin JK. The impact of aortic valve homografts on the treatment of aortic prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7: 25-31.
19. Kirklin JK, Kirklin JW, Pacifico AD. Aortic valve endocarditis with aortic root abscess cavity: surgical treatment with aortic valve homograft. Ann Thorac Surg 1988;45:674-7.
20. Camacho MT, Cosgrove DM. Homografts in the treatment of prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:23-37.
21. David TE, Bos J, Christakis GT, et al. Heart valve operations in patients with active infective endocarditis. Ann Thorac Surg 1990;49:701-5.

Discussion

Dr. D. Craig Miller *(Stanford, Calif.)*. I agree with you, Dr. Lytle, that if you use a tissue valve the infection tends not to be as invasive as with a mechanical valve. That leads to a more general question, which I admit is not the topic of your paper: If a biologic valve becomes infected, is the infection more likely to be successfully eliminated with medical therapy alone than would an infection affecting a mechanical valve?

Dr. Lytle. I think the infection is more likely to be

controlled. A very common scenario, however, was that when we reoperated for patients who had a healed infection, it was usually a leaflet infection on a bioprosthesis that was treated successfully with antibiotics; then usually within 1 to 2 years (the mean interval between treatment and operation was 21 months), these bioprostheses had to be operated on. These valves often can be treated successfully and can be sterilized, but their failure rate is accelerated by the occurrence of endocarditis.

Dr. Miller. You do not mind substituting an old healed case of PVE for an active one, do you?

Dr. Lytle. I think operating on healed PVE is preferable to operating on active PVE.

Dr. Miller. Agreed. Second, I think you might have tilted the playing field in your definition of *early* PVE, which you defined as 1 year postoperatively. If I remember correctly, the infectious disease group at The Massachusetts General Hospital and the Mayo Clinic, as well as the Alabama cardiovascular surgeons and our group at Stanford, have all come up with a fairly generally promulgated definition of *3 months.* Would early versus late become or emerge as more significant had you used the more conventional definition of *early* PVE?

Dr. Lytle. I don't know. We did that because most infections occur within the first year. We did not review the organisms that were involved, but in our experience infections developing within 1 year of operation were most often nosocomial infections that were acquired at the time of the hospitalization. Even if the infection takes 6 or 8 months to develop, the distribution of the organisms is more characteristic of early than late infections.

When we looked at the onset of early PVE according to month, most infections occurred in the first 6 months. I do not agree that 3 months is the correct time to designate as an early infection. I think 6 months is reasonable, but the reason we chose 1 year is that at 1 year the incidence appeared to decrease. The incidence was low between 1 year and 18 months to 2 years after operation.

Dr. Miller. I am surprised that the organism did not emerge as an important factor. In North America, *Staphylococcus epidermidis* did not emerge as strongly as *Staphylococcus aureus* did in the previous Brisbane series. Do you have any comments regarding that?

Dr. Lytle. Pathologic characteristics differed according to the organism. We had no cases of healed PVE when fungal organisms were involved, and of 31 cases of *Staphylococcus aureus* PVE, only three were considered to be healed. However, I believe the reason that those were not risk factors for either early or late death is that we were extremely aggressive in cutting out the infection.

Dr. Miller. That leads right into my next question. You failed to show a demonstrable salutary effect of homografts. You did mention that this might be due to the small number of patients with homografts (the studies stopped in 1992); alternatively, could it be the skewed distribution of early versus late or active versus healed PVE? Data from Brisbane, Australia, indicate that a homograft valve re-replacement eliminates the high early-phase hazard but has no real salutary effect on the late constant hazard of PVE. This leads me to the cases of fungal valve endocarditis. What would you do today? Is there any doubt that a homograft aortic root replacement is the best course of action?

Dr. Lytle. We have written a separate article that deals specifically with fungal endocarditis, and we do believe that a homograft is important. Our best results with fungal endocarditis, and we have only about 14 cases, have been with the use of a homograft, treatment with amphotericin, and lifelong treatment with oral azole agents.

This leads to another point—the concept of long-term oral suppressive therapy. That is critical in patients with fungal endocarditis. Some of our patients with fungal endocarditis have done well for years, stopped taking their oral antifungal agents, had recurrent fungal endocarditis at that time, undergone a reoperation, and been all right after the second operation. With fungal endocarditis, the optimal treatment is to use a homograft and to prescribe antibiotics forever.

Whether that also applies to bacterial endocarditis is hard to say. One of the problems, particularly for methicillin-resistant *Staphylococcus,* is the lack of availability of a good oral agent. Also, we tend not to have cultured organisms from patients having reoperations for late PVE. However, I think the plan for fungal endocarditis in the aortic position ought to be a homograft aortic valve replacement and lifelong antifungal therapy.

Dr. Miller. I agree. Inasmuch as we share your dilemma, how do you differentiate between recurrent and residual PVE postoperatively? We have used a simple definition: If it is the same organism, it is probably residual; if it is a different organism, it is recurrent. What is your opinion?

Dr. Lytle. It is difficult to make the distinction. We had an early phase, within 1 year of the operation for PVE, in which a couple of patients had positive cultures. Then there were some late cases of PVE, only one or two of which had positive cultures. Thus I do not know how to distinguish between recurrent and reacquired infection. That is the reason that we dealt with reoperation rather than documented recurrence of an infection. It may be that for many of these patients operated within 1 year the need for reoperation is generated by persistent infection that we are unable to detect.

Our answer to the whole question of PVE is that we are just getting more comfortable with radically débriding the infected tissue. Following the principles of cutting out the infection, closing the holes, and replacing the valve seems to work pretty well.

Dr. Augustin Arbulu *(Detroit, Mich.).* You say that reoperation is not futile in this group of patients, and I do agree with you, but I would like a clarification. Are you including in this statement persons who are addicted to drugs and are actively using drugs?

Dr. Lytle. We do not have a large population of persons addicted to drugs in our care. We do have some anecdotal experience. The combined medical-social aspects of that problem have worked out favorably in about half of these patients on whom we have operated.

Dr. Arbulu. In my experience, as reported in one of my previous publications, reoperation is a futile exercise in persons addicted to drugs who are continuing to use the drugs.

You suggest that the homograft may be the answer in

fungal endocarditis. On the basis of my experience, I do agree with you that in fungal endocarditis antifungal treatment should be for life, but what is the basis for your enthusiasm with regard to homografts and fungal endocarditis?

Dr. Lytle. We have operated on eight patients with fungal endocarditis and aortic root infections, and three of those patients had infection of the aortic root and some sort of ascending aortic graft. All of those patients are currently alive without reoperation, except for one who had a fungus that was insensitive to every antibiotic that we tried, both in vitro and in the patient. Thus among the seven patients who had a fungal infection for which we had an antifungal agent, there have been no recurrences. I think that it is encouraging enough to warrant our use of this type of therapy.

Dr. Arbulu. Are they receiving antifungal agents currently?

Dr. Lytle. Yes, they will all be taking azul agents orally forever.

Dr. Arbulu. I share that enthusiasm when we use a mechanical prosthesis in valve replacement for fungal PVE. The problem in our experience is that as we approach the fifth year of follow-up all of the patients die. It will be interesting to see what happens in your series.

Dr. Glenn D. Pennington *(St. Louis, Mo.).* Dr. Lytle, you indicated that many of these operations involved extensive débridement and then reconstruction. You mentioned using Peri-Gard vascular graft material (Bio-Vascular, St. Paul, Minn.), but do you have a preference for material? Do you use cryopreserved homograft? Is there any relationship to infection?

Dr. Lytle. My personal choice is autologous pericardium. If the patient has been operated on a number of times, there will not be much autologous tissue left, or the infection may extend into the pericardium. Those are the circumstances under which we have used Peri-Gard vascular graft material. We have not had enough homograft material available to be able to use it with these kinds of intracardiac reconstructions. Homograft material may be a reasonable substitute, but autologous pericardium works well and is my preference.

Appendix I. *Preoperative and operative variables*

	No. of patients	*No. of in-hospital deaths*	*% of in-hospital deaths*	*P value*
Previous operation				
Endocarditis				
No	116	17	14.7	0.365
Yes	30	2	6.7	
Location of prosthesis				
Aortic	96	14	14.6	0.815
Mitral	30	3	10.0	
Multiple	20	2	10.0	
CABG				
No	122	14	11.5	
Yes	24	5	20.8	0.315
No. of operations				
1	115	16	13.9	
2	21	1	4.8	
>3	10	2	20.0	0.378
Valve type				
Mechanical	53	8	15.1	0.751
Biological	90	11	12.2	
Homograft	3	0	0	
PVE illness				
Interval between initial				
≤1 yr	117	19	16.2	
>1 yr	29	0	0.0	0.014
Congestive heart failure				
No	41	4	9.8	
Yes	105	15	14.3	0.465
Fever				
No >3 days	118	12	10.2	
Yes 1–3 days	28	7	25.0	0.056
Blood culture				
No	40	4	10.0	
Yes	106	15	14.0	0.117
Preoperative morbidity				
No	125	14	88.8	0.154
Yes	21	5	76.2	
PVE operation				
Gender				
Male	106	15	14.2	0.506
Female	40	4	10.0	
Age				
<40	23	2	8.7	
40-70	99	14	14.1	0.931
>70	24	3	12.5	
Year of operation				
1975-1984	44	9	20.4	0.079
1985-1992	102	10	9.8	
Time between operations				
<1 yr	46	7	15.3	0.591
>1 yr	100	12	12.0	
*Preop. morbid event				
No	35	3	8.6	
Yes	111	16	14.4	0.565
AV block				
No	140	15	10.7	
Yes	6	4	66.7	0.003

Appendix I. *(continued)*

	No. of patients	*No. of in-hospital deaths*	*% of in-hospital deaths*	*P value*
Thromboembolism				
No	118	13	11.0	
Yes	28	6	21.4	0.206
LV function				
Normal	102	6	5.9	
Mild	18	3	16.7	
Moderate	15	6	40.0	
Severe	6	1	16.7	0.002
Type of operation				
Aortic	86	12	14.3	
Mitral	31	4	12.0	
Multiple	24	2	8.3	0.778
Nonreplacement	5	1	20.0	
Type of valve				
Biologic	76	10	13.2	
Mechanical	52	8	15.4	
Homograft	13	0	0.0	0.327
Staph. aureus				
No	115	12	10.4	
Yes	31	7	22.6	0.127
Fungus				
No	138	18	13.0	
Yes	8	1	12.5	0.999
CAD				
No	115	11	9.6	
Yes	31	8	25.8	0.031

CABG, Coronary artery bypass grafting; *PVE,* prosthetic valve endocarditis; *AV,* atrioventricular; *LV,* left ventricular; *CAD,* coronary artery disease.

*Preoperative morbidity includes stroke, renal function, cardiac event, shock, myocardial infarction, and respiratory failure.

Appendix II. *Organisms*

	Early (46 patients)	*Late (100 patients)*
Staph. epidermidis	20	17
Staph. aureus	11	20
Streptococcus	5	22
Enterococcus	1	10
Gram negative	9	9
Fungus	3	5
Culture negative	2	23
Multiple organisms	11	