Prosthetic valve endocarditis: management strategies and prognosis

A ten-year analysis in a tertiary care centre in Tunisia

S. Rekik, I. Trabelsi, A. Znazen, I. Maaloul, M. Hentati, I. Frikha, M. Ben Jemaa, A. Hammami, S. Kammoun

Background. Prosthetic valve endocarditis (PVE) is a rare and serious complication after heart valve replacement; its optimal management strategy, though, still needs to be defined.

Objective. To study the clinical, microbiological and echocardiographic characteristics of PVE and to analyse the influence of the adopted therapeutic strategy (medical or surgical) on short- and mid-term outcome in a tertiary care centre in a developing country (Tunisia).

Methods. All cases of PVE treated in our institution between 1997 and 2006 were retrospectively analysed according to the modified DUKE criteria.

Results. A total of 48 PVE episodes were diagnosed (30 men and 18 women), mean age was 37.93 years. Twenty-eight patients (58.33%) were exclusively medically treated, whereas 20 (41.66%) were treated by a combined surgical and medical strategy. Indications for surgery were haemodynamic deterioration in eight patients (40%), annular abscess in six (30%) and persisting sepsis

in six (30%). In comparison with those from the medical group, operated patients had a longer delay to diagnosis ($p=0.025$), were more frequently in heart failure ($p=0.04$) and experienced more early complications ($p=0.011$); they also more frequently had prosthetic dehiscence ($p=0.015$), annular abscesses ($p=0.039$) and vegetations >10 mm ($p=0.008$). Conversely, no differences were found between the groups in terms of age, sex, or nature of involved organisms. In-hospital mortality for the medical group was 14.28% and for the surgical group 35% ($p=0.09$).

Conclusion. PVE is a very serious condition carrying high mortality rates regardless of the adopted strategy. Our study demonstrates that, in selected patients, medical treatment could be a successful and acceptable approach. (*Neth Heart J* 2009;17: 56-60.)

Keywords: prosthetic valve endocarditis, surgery, medical treatment, mortality

S. Rekik
I. Trabelsi
M. Hentati
S. Kammoun

Department of Cardiology, University Hospital Hedi Chaker, Sfax, Tunisia

A. Znazen
A. Hammami

Department of Microbiology, University Hospital Habib Bourguiba, Sfax, Tunisia

I. Frikha

Department of Cardiovascular Surgery, University Hospital Habib Bourguiba, Sfax, Tunisia

I. Maaloul

M. Ben Jemaa

Department of Infectious Diseases, University Hospital Hedi Chaker, Sfax, Tunisia

Correspondence to: S. Rekik
Department of Cardiology, University Hospital Hedi Chaker, Sfax, Tunisia
E-mail: sofienerek@yahoo.fr

Prosthetic valve endocarditis (PVE) constitutes a rare but life-threatening complication after heart valve replacement, occurring with an approximate overall incidence of 0.1 to 4% per year,¹ and carrying a high mortality risk ranging from 20 to 80% of affected patients.²

In the absence of guidelines based on prospective randomised studies,³ the optimal therapeutic strategy is still being widely discussed. Thus, whereas some authors still believe in an exclusively medical approach to PVE,¹ a majority agree to consider a combined medical and surgical approach to be the best attitude.

Our aim in this study was to describe clinical, echocardiographic and microbiological characteristics of PVE in a tertiary care centre in a developing country (main referral centre in a 1.2 million people region, Sfax, Tunisia, North Africa) and to analyse the influence of the therapeutic strategy (surgery versus medical treatment) on outcome in affected patients.

Methods

Patients

All suspected cases of PVE admitted to our institution between 1997 and 2006 were included; the patients' medical records were carefully reviewed and the diagnosis of endocarditis was qualified as definite or possible according to the DUKE criteria.⁴ A total of 48 cases (31 men and 17 women) were ultimately collected, all occurring on mechanical prostheses. Our institution is the main referral centre in a 1.2 million population region (Sfax, Tunisia); however the diagnosis of IE is almost always made in our centre, with very limited numbers of patients referred for management of an already diagnosed IE.

Various parameters were collected for each patient, including the predisposing heart condition, initial clinical presentation, biological data, results of microbiological tests (we typically performed three to six sets of aerobic and anaerobic blood cultures). When blood cultures remained negative, specific analyses were performed including additional sets for blood cultures on enriched media and serological tests for *Coxiella burnetii*, *Brucella*, *Mycoplasma pneumoniae*, *Chlamydiae* spp, fungi, *Aspergillus* and *Bartonella*, echocardiographic features, duration of antibiotic treatment, time and type of surgery, nature and position of the prosthesis as well as the short- and mid-term evolution.

Definitions

PVE was qualified as definite or possible according to the Duke criteria⁴ modified by Li.⁵ Pathological criteria

include either demonstrable microorganisms or pathological lesions compatible with active endocarditis. For a clinical diagnosis of endocarditis, two major criteria, one major and three minor criteria, or five minor criteria were needed. Major criteria are positive blood cultures of a typical microorganism, and evidence of endocardial involvement (positive echocardiogram or new valvular regurgitation). Minor criteria are fever, vascular phenomena (arterial embolism, septic pulmonary infarct, mycotic aneurysm), immunological phenomena (glomerulonephritis, Osler's nodes, Roth spots, Janeway lesions), a suggestive echocardiogram, and microbiological evidence (positive blood culture but not meeting the major criterion). PVE was classified into early PVE when occurring within 12 months after surgery; beyond that, they were called late PVE.

Treatment

For all patients in the medically treated group, antibiotic treatment was initiated at admission and continued intravenously for at least four weeks. The initial choice of antibiotics was directed by the clinical context and suspected causative organism. All operated patients were initially treated with antibiotics.

Statistics

The statistical analysis was performed using the SPSS 15.0 statistical package (Chicago, Illinois). Continuous variables are presented as means $\pm$ standard deviations (SD) and categorical variables as percentages. Con-

Table 1. Clinical characteristics and complications.

	Surgical group (n=20)	Medical group (n=28)	P value
Age (years $\pm$ SD)	35.85 $\pm$ 14.6	39.48 $\pm$ 19.65	NS
Males	14 (70)	17 (60.7)	NS
Early PVE	8 (47.05)	12 (38.7)	NS
Delay to diagnosis (days $\pm$ SD)	15.46 $\pm$ 15.35	7.22 $\pm$ 7.13	0.022
Valve location			
- Mitral	10 (50)	14 (50)	NS
- Aortic	6 (30)	8 (28.57)	NS
- Both	3 (15)	6 (21.42)	NS
- Tricuspid	1 (5)	0 (0)	NS
Antibiotics duration (days $\pm$ SD)	67.25	33.73	0.026
In hospital stay (days)	39.05	38.28	NS
Identified source (%)	11 (55)	15 (53.57)	NS
Definite PVE (%)	20 (100)	23 (82.14)	NS
Total early complications	10 (50)	4 (14.28)	0.011
Neurological complications	4 (20)	1 (3.5)	NS (0.088)
Persisting sepsis	7 (35)	7 (25)	NS
Renal failure	2 (10)	3 (10.7)	NS
Heart failure	8 (40)	4 (14.28)	0.04
Death	7 (35)	4 (14.28)	NS (0.09)

PVE=prosthetic valve endocarditis, SD=standard deviations, NS=non-significant. Percentages in brackets.

tinuous variables were compared with Student's *t* test, and categorical variables with the χ^2 test or Fisher's exact test, where expected values were <5 . A two-sided *p* value of 0.05 was established as the level of statistical significance for all tests.

Results

Clinical characteristics

During the study period, 182 patients were admitted to our institution for IE; among those 48 had a PVE (31 men and 17 women), 43 of which (i.e. 89.6% of the whole group) were classified as definite. Among the 48 cases, only three have been referred for management of a diagnosed IE, two from a primary care hospital and one from another cardiology department without onsite cardiac surgery facilities. The remaining 45 cases were mainly referred from the emergency department for a suspected IE based on clinical and biological arguments.

Mean age was 37.93 ± 17.59 years (ranging between 18 and 73 years). In 20 cases (41.66%) the PVE was classified as early and in 28 cases (58.83%) as late. Surgery was needed in 20 patients (41.6%): 12 had early PVE (i.e. 54.54%) and eight had late PVE (i.e. 30.7%). Mean delay to surgery was 14.85 days.

Indications for surgery were haemodynamic deterioration in eight patients (40% of the cases), annular abscesses in six (30%), and persisting sepsis despite appropriate antibiotic treatment in six (30%).

Clinical characteristics of the included patients are summarised in table 1. In comparison with those from the medical group, operated patients had a longer delay to diagnosis ($p=0.025$), were more frequently in heart failure ($p=0.04$) and experienced significantly more early complications ($p=0.011$). The duration of the antibiotic treatment was significantly longer in the operated group ($p=0.026$). Conversely, no differences were found between the groups in terms of age, sex, or incidence of renal failure.

Eleven patients died during hospitalisation (i.e. 22.91% global mortality); mortality tended to be higher in the surgical group with a close to significant difference ($p=0.09$) (table 1).

Microbiology

Blood cultures were positive in 18 cases (37.5%). Patients with negative blood culture results received prior antibiotic treatment in 73.33% of cases (22 out of 30). In 19 cases, causative microorganisms were identified either by serology (3 cases) or leaflet culture (2 cases). Therefore, the infective agent was identified in 23 cases (47.91%). Detailed features of causative organisms are shown in table 2. *Staphylococcus* spp were the most commonly isolated organisms (30.4%) followed by gram negative rods and *Streptococcus* spp. Gram negative rods included a case of *Escherichia coli*, a case of *Klebsiella pneumoniae*, and two cases of *Acinetobacter baumannii*.

The group 'others' contained *Ketococcus* (1), *Aspergillus* (1), *Enterococcus* (1), *Coxiella* (1) and *Brucella* species (1). No significant differences were noted between the two groups, either in terms of rate of PVE with negative culture or in terms of nature of the involved organisms.

Echocardiographic data

The most significant echocardiographic parameters are listed in table 3. Operated patients more frequently had prosthetic dehiscence ($p=0.015$), annular abscesses ($p=0.039$) and vegetations >10 mm ($p=0.008$) than those medically managed. No significant differences were found in terms of all the other studied data.

Follow-up

The mean follow-up was 28.37 ± 33.54 months. During that period, four patients, all in the medical group, underwent surgery for major valvular regurgitation and only one recurrent endocarditis was registered 24 months after discharge, also in the medical group; this patient was conservatively treated with success. There was only one late sudden death, occurring in the surgical group.

Discussion

Notwithstanding the progress made regarding diagnostic and therapeutic modalities in infective endocarditis, PVE remains a serious complication associated with a heavy mortality.⁶ Generally, a medical

Table 2. Microbiological features.

	Surgical group (n=20)	Medical group (n=28)	P value
<i>Staphylococcus</i> spp	4 (20)	3 (10.71)	NS
<i>Streptococcus</i> spp	2 (10)	2 (7.14)	NS
<i>Bartonella</i> spp	3 (15)	0 (0)	NS
Gram negative rods	1 (5)	3 (10.71)	NS
Others	2 (10)	3 (10.71)	NS
Negative blood cultures	11 (55)	14 (50)	NS

NS=non-significant. Percentages in brackets.

Table 3. Echocardiographic characteristics.

	Surgical group (n=20)	Medical group (n=28)	P value
Vegetations	15 (75)	14 (50)	NS
- Mitral	8 (40)	11 (39.28)	NS
- Aortic	6 (30)	3 (10.71)	NS
- Tricuspid	1 (5)	0 (0)	NS
Vegetations >10 mm	8 (40)	2 (7.14)	0.008
Rope rupture	1 (5)	2 (7.4)	NS
Annular abscess	5 (25)	1 (3.7)	0.039
Prosthetic dehiscence	7 (35)	3 (10.7)	0.015

NS=non significant. Percentages in brackets.

treatment combined with surgery is considered the approach of choice in this situation.

Surgical treatment has already proven superior to a strategy based solely on antibiotics in various studies; therefore, an aggressive approach is often recommended. In a classic analysis by Calderwood et al.,⁷ isolated initial medical treatment was the only independent variable associated with poor outcomes. In the series by Yu et al.⁸ the mortality of the patients treated medically was 53% versus 23% for those undergoing surgery. In a more recent series Akowuah et al.,⁹ reported similar results with 46% mortality for the medical group versus 26% for the surgical one.

Conversely, in our series, mortality was paradoxically higher in the surgical group (35 vs. 14.28%); which seems in contrast to the results of the majority of publications^{7,10,11} supporting the combined approach. These findings might be, at least partly, explained by the particular characteristics of our operated population, mainly by the significantly longer delay to diagnosis (15.46 vs. 7.22 days; $p=0.02$). That delay might, indeed, have had a determining impact, being at the origin of a significantly higher rate of early complications (50 vs. 14.28%; $p=0.011$), and a more significant loco-

regional invasion resulting in more frequent prosthesis dehiscence (35 vs. 10.7%; $p=0.015$) and more annular abscesses (25 vs. 3.7%; $p=0.039$). Hence, the haemodynamic status of this group of patients was more unstable with 2.5-fold more heart failure than in the patients in the other group which, in itself, could have precipitated surgical intervention in this group.

Nevertheless, regarding global in-hospital mortality, our results (22.91% mortality rate), despite high rates in the surgery group (35%), were similar to major published data (table 4), which could be explained by two singular characteristics of our series.

Firstly, our patients were significantly younger (37.93 years) than those studied in previous publications which were quite exclusively conducted in occidental populations where initial predisposing heart conditions were mainly degenerative, occurring in relatively old patients. This means that the mean age in previously reported series^{3,9,14} was usually around 60 years. Our series was conducted in a developing country where rheumatic fever, which is still endemically prevalent in children, was predominantly the cause of the initial surgically treated valvular disease. Hence, our patients were considerably younger when

Table 4. Comparative results of some series of prosthetic valve endocarditis.

Series (first author)	Year	Patients (n)	Overall hospital mortality rate (%)	Medical hospital mortality rate (%)	Surgical hospital mortality rate (%)
Calderwood ⁷	1986	116	23	NA	NA
Yu ⁸	1994	74	46	56	23
Kuyvenhoven ¹²	1994	70	27	26	30
Schulz ¹³	1996	24	20	17	21
Habib ³	2005	104	21	25	17
Akowuah ⁹	2003	66	33	46	24
Sohail ¹⁴	2006	55	36	48	28
Present study	2007	48	22.91	14.28	35

NA=not available.

they developed PVE. Because comorbidity is presumably less prevalent in such a population, this may have contributed to the relatively lower mortality rates.

Secondly, and more important, is the unexpectedly good survival rates of the medically managed patients. Thus, by finding a lower and relatively acceptable mortality in the medical group (14.28%), our study interestingly shows that certain PVE-affected patients can be efficiently treated and cured with antibiotics alone. Patients most likely to benefit from this strategy, according to Truninger¹ and Akowuah⁹ who are among the few authors cautiously and selectively endorsing this type of approach, would be those remaining clinically stable or showing an improvement under antibiotics. Certain echocardiographic features such as the absence of abscesses or the absence of prosthetic dysfunction could also predict the success of such a therapeutic approach, as was the case in our series. PVE caused by the less virulent organisms such as the *Streptococcus* spp can also be successfully treated with antibiotics alone.

Moreover, a systematic recourse to surgery during PVE is not as imperative, and should be subjected to a more rigorous selection. Thus, Habib et al.³ identified patients with complicated PVE and those with *Staphylococcus* PVE as the best candidates for the surgical approach and strongly recommended it during the early phases of management.

Although, as previously reported,^{1,8} *Staphylococcus* spp were the predominantly (30.4%) incriminated organisms, interestingly, neither overmortality nor over recourse to surgery have been recorded in this particular subgroup of the present study. Besides, among the three patients of the conservative strategy arm, two were cured with no longer-term endocarditis or need for surgery, suggesting a possible effectiveness of an exclusively medical strategy in this particular setting. These results, in clear contrast to published data,^{3,12,14} are nevertheless to be taken with caution. The limited number of cases of *Staphylococcus* PVE in our series (7 cases) make it unwise to take firm conclusions. It is of note, though, that a recent series by Hill et al.¹⁵ reports similar findings and suggests that some patients with uncomplicated *S. aureus* PVE can be treated successfully without cardiac surgery.

Limitations of the study

Our study presents several limitations. Firstly, its retrospective uncontrolled design is inevitably prone to bias in the selection of patients for a particular approach. Indeed, our general policy was to initially treat patients with antibiotics alone, and to offer surgery in case of complications, in such a way that solely medically treated patients may globally be considered as less severely affected. Secondly, it was conducted in one tertiary care institution; thus, there will always be a concern for referral bias. Thirdly, the study included a relatively restricted number of patients (similar, though, to previous studies) not conferring the

sufficient statistical power to draw firm conclusions, particularly regarding the optimal therapeutic strategy which still needs to be formally defined. Only larger prospective randomised studies, even though very challenging, can bring definitive answers.

Conclusion

PVE remains a serious and dreaded complication after valvular replacements associated with a heavy early mortality. Although a strategy combining medical and surgical treatment is often recommended, our study interestingly showed that an effectively led medical strategy can be curative. Recourse to early surgery was mainly dictated by a precarious haemodynamic status and generally associated with a very unfavourable prognosis. ■

References

- 1 Truninger K, Attenhofer Jost CH, Seifert B, Vogt PR, Follath F, Schaffner A, et al. Long term follow up of prosthetic valve endocarditis: what characteristics identify patients who were treated successfully with antibiotics alone? *Heart* 1999; **82**:714-20.
- 2 Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med* 1996; **335**:407-16.
- 3 Habib G, Tribouilloy C, Thuny F, Giorgi R, Brahimi A, Amazouz M, et al. Prosthetic valve endocarditis: who needs surgery? A multicentre study of 104 cases. *Heart* 2005; **91**:954-9.
- 4 Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994; **96**:200-9.
- 5 Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; **30**:633-8.
- 6 ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol* 2006; **48**: e1-148.
- 7 Calderwood SB, Swinski LA, Karchmer AW, Waternaux CM, Buckley MJ. Prosthetic valve endocarditis. Analysis of factors affecting outcome of therapy. *J Thorac Cardiovasc Surg* 1986; **92**:776-83.
- 8 Yu VL, Fang GD, Keys TF, Harris AA, Gentry LO, Fuchs PC, et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. *Ann Thorac Surg* 1994; **58**:1073-7.
- 9 Akowuah EF, Davies W, Oliver S, Stephens J, Riaz I, Zaidi P, et al. Prosthetic valve endocarditis: early and late outcome following medical or surgical treatment. *Heart* 2003; **89**:269-72.
- 10 Vlessis AA, Hovaguimian H, Jaggars J, Ahmad A, Starr A. Infective endocarditis: ten-year review of medical and surgical therapy. *Ann Thorac Surg* 1996; **61**:1217-22.
- 11 Tornos P, Almirante B, Olona M, Permanyer G, González T, Carballo J et al. Clinical outcome and long term prognosis of late prosthetic valve endocarditis: a 20-year experience. *Clin Infect Dis* 1997; **24**:381-6.
- 12 Kuyvenhoven JP, van Rijk-Zwikker GL, Hermans J, Thompson J, Huysmans HA. Prosthetic valve endocarditis: analysis of risk factors for mortality. *Eur J Cardiothorac Surg* 1994; **8**:420-4.
- 13 Schulz R, Werner GS, Fuchs JB, Andreas S, Prange H, Ruschewski et al. Clinical outcome and echocardiographic findings of native and prosthetic valve endocarditis in the 1990's. *Eur Heart J* 1996; **17**:281-8.
- 14 Sohail MR, Martin KR, Wilson WR, Baddour LM, Harmsen WS, Steckelberg JM. Medical Versus Surgical Management of *Staphylococcus aureus* Prosthetic Valve Endocarditis. *Am J Med* 2006; **119**:147-54.
- 15 Hill EE, Herregods MC, Vanderschueren S, Claus P, Peetermans WE, Herijgers P. Management of prosthetic valve infective endocarditis. *Am J Cardiol* 2008; **101**:1174-8.