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European Journal of Cardio-thoracic Surgery 38 (2010) 528—538

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Surgical treatment for active infective prosthetic valve endocarditis: 22-year single-centre experience☆

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Received 6 October 2009; received in revised form 26 February 2010; accepted 8 March 2010; Available online 23 May 2010

Abstract

Objective: We retrospectively analysed the profile and outcome of surgically treated patients with active infective prosthetic valve endocarditis (PVE) over a period of 22 years. **Methods:** Between May 1986 and December 2008, a total of 1313 patients with active infective endocarditis (AIE) were operated on, 349 (26.6%) of them for PVE. Of these, 77 (22.1%) had to be operated upon due to early PVE (≤60 days, $n = 55$ men, median age: 58 years) and 272 (77.9%) due to late PVE ($n = 200$ men, median age: 63 years). A large proportion of patients were referred to our department with advanced endocarditis and in a condition of cardiac and pulmonary decompensation. A total of 226 (64.8%) patients developed periannular abscess. Operations consisted of 80 aortic valve, 45 mitral valve, 39 double valve and 165 aortic root replacements, 134 of them with a homograft. Perioperative characteristics, probability of survival, freedom from recurrence and predictors for hospital mortality were analysed. Follow-up (maximum: 19.4 years) was completed in 96.3% (total: 1118 patient-years). **Results:** There was high early and late mortality. Overall in-hospital mortality was 28.4% (99/349). The 30-day, 1-, 5- and 10-year survival for the whole PVE study population was 71.4 ± 2.4%, 58.7 ± 2.7%, 44.5 ± 3% and 31.7 ± 3.5% with no significant differences between the early and late PVE patients: 67 ± 5.4%, 55.9 ± 5.8%, 49.4 ± 6.2% and 29.7 ± 7.6%, compared to 72.4 ± 3%, 60 ± 3%, 43.5 ± 3.3% and 31.1 ± 3.8% ($p = 0.93$). Predictors of early mortality were mechanical support (risk ratio (RR): 4.3), emergency operation (RR: 2.1), preoperative high doses of catecholamines (RR: 1.8), mitral valve replacement (RR: 1.5) and age at operation (RR: 1.1). Freedom from re-operation due to recurrent endocarditis at 10 years was 85.8 ± 5.6% for early PVE compared to 92.1 ± 2.3% for late PVE patients ($p = 0.17$). *Staphylococcus aureus* (*S. aureus*) (18.1%) was the most frequent causative micro-organism. **Conclusions:** Surgery for active infective PVE continues to be challenging. It not only carries a high in-hospital mortality but is also associated with a high long-term mortality risk. Early PVE patients were in a more severe condition than late PVE patients. Preoperative status, complications and co-morbidity of PVE patients strongly predict early outcome. Because of the potential risk of late complications, PVE patients need close clinical follow-up.

Keywords: Early mortality; Infective endocarditis; Predictors; Prosthetic valve endocarditis; Surgery

1. Introduction

Infections of prosthetic heart valves continue to be an extremely serious and potentially lethal complication of heart valve surgery. Prosthetic valve endocarditis (PVE) has been estimated to occur with a relatively low but increasing frequency ranging from 0.1% to 2.3% per patient-year and to account for 1—5% of all cases of active infective endocarditis (AIE) [1,2]. Despite advances in diagnosis, medical and surgical therapy over the past few decades, PVE is still associated with a substantial risk of morbidity and overall mortality ranging from 20% to 80% of affected patients [3,4].

PVE is frequently associated with a periannular extension of infection, which has been reported in 56—100% of PVE patients, leading to high rates of heart failure and death [5,6]. It appears to be caused by the bacterial deterioration of local tissue leading to necrosis and paravalvular abscess formation, a destructive process which can progressively and very rapidly lead to total aortic root destruction.

Guidelines based on prospective randomised studies for the best treatment for PVE patients are still lacking [7,8] and therapeutic strategies are a matter of controversial discussion in the literature although surgery is said to be the best treatment option in complicated PVE causing prosthetic dysfunction or heart failure [3,6].

For these reasons, this study was undertaken to review the 22-year experience of the surgical treatment for active infective PVE at the Deutsches Herzzentrum Berlin. The goals of this retrospective study were to

☆ Presented at the 23rd Annual Meeting of the European Association for Cardio-thoracic Surgery, Vienna, Austria, October 18—21, 2009.

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1010-7940/$ — see front matter
doi:10.1016/j.ejcts.2010.03.019

Table 1
Patient population. Demographic and clinical differences between patients with early (≤60 days) and late prosthetic valve endocarditis.

Patients with AIE Period 05/86 to 12/2008	Early PVE, *n* = 77 (22.1%)	Late PVE, *n* = 272 (77.9%)	*p*-value	Total (% of study population)
Gender				
Men	55 (71.4%)	200 (73.5%)	0.714	255 (73.1%)
Women	22 (28.6%)	72 (26.5%)		94 (26.9%)
Total	77	272		349
Age in years				–
Median	58.0	63.0	*0.024*	
Mean	54.4 ± 16.6	59.2 ± 14.9		
Range	3–81	7–87		
Median time First operation – re-operation	47 days	1202 days	–	–
First operation due to AIE	34 (44.2%)	50 (18.4%)	*<0.001*	84 (24.1%)
Prosthesis type at first operation				
Aortic valve	36	179	–	215 (61.6%)
Biological	*19*	*94*		
Mechanical	*17*	*79*	–	49 (14.1%)
Homograft	–	*6*		
			–	60 (17.2%)
Aortic conduit	17	32		
Biological	*3*	*6*	–	25 (7.1%)
Homograft	*6*	*4*		
Mechanical	*8*	*22*		
Mitral valve	20	40		
Biological	*8*	*26*		
Mechanical	*12*	*14*		
Aortic and mitral valve	4	21		
Biological	*4*	*11*		
Mechanical	–	*10*		
Microbiological epidemiology				
Staphylococci				
S. aureus	33 (42.9%)	90 (33.1%)	0.113	123 (35.2%)
S. coag. neg.	*18 (23.4%)*	*45 (16.6%)*	0.169	63 (18.1%)
S. epidermidis	*4 (5.2%)*	*16 (5.9%)*	–	
MRSA	*7 (9.1%)*	*14 (5.1%)*	–	54 (15.5%)
S. general	*2 (2.6%)*	*3 (1.1%)*	–	
	2 (2.6%)	*12 (4.4%)*	–	37 (10.6%)
Streptococci				
Str. general	9 (11.7%)	45 (16.6%)	0.208	56 (16.0%)
Str. viridans	*6 (7.8%)*	*29 (10.7%)*	–	
Str. β-hemolys.	*1 (1.3%)*	*13 (4.8%)*	–	61 (17.4%)
Str. epidermidis	*1 (1.3%)*	*3 (1.1%)*	–	
	1(1.3%)	–	–	
Enterococcus	6 (7.8%)	31 (11.4%)	–	
Pseudomonas	1 (1.3%)	2 (0.7%)	–	
Candida	–	3 (1.1%)	–	
Culture negative	15 (19.5%)	41 (15.1%)	–	
Others	3 (3.9%)	9 (3.3%)	–	
Unknown	10 (12.9%)	51 (18.7%)	–	
Operation performed as				
Elective	6 (7.8%)	49 (18.0%)	*0.030*	55 (15.8%)
Urgent	52 (67.5%)	171 (62.9%)		223 (63.9%)
Emergency	19 (24.7%)	52 (19.1%)		71 (20.3%)
Preoperative status				
Cardiac shock	12 (15.6%)	23 (8.5%)	0.066	35 (10.1%)
High-dose catecholamines	24 (31.2%)	55 (20.2%)	*0.043*	79 (22.6%)
Pulmonary oedema	19 (24.7%)	62 (22.8%)	0.730	81 (23.2%)
Intubation	18 (23.4%)	37 (13.6%)	*0.038*	55 (15.7%)
Septic shock	10 (13.0%)	27 (9.9%)	0.441	37 (10.6%)
Sepsis	19 (24.7%)	43 (15.8%)	0.194	62 (9.1%)
Renal insufficiency	35 (45.5%)	95 (34.9%)	0.092	130 (37.2%)
Dialysis	13 (16.9%)	23 (8.5%)	*0.032*	36 (10.3%)
Persistent fever	40 (51.9%)	90 (33.1%)	*0.010*	130 (37.2%)
Diabetes	15 (19.5%)	61 (22.4%)	0.580	76 (21.8%)
COPD	6 (7.8%)	29 (10.7%)	0.459	35 (10.1%)
Hypertension	35 (45.5%)	120 (44.1%)	0.835	155 (44.4%)
Drug abuse i.v.	3 (3.9%)	13 (4.8%)	0.744	16 (4.6%)
Alcohol abuse	2 (2.6%)	16 (5.9%)	0.250	18 (5.1%)
Septic embolisation	14 (18.2%)	61 (22.4%)	0.423	75 (21.5%)
Quantity	11 (14.2%)	41 (15.1%)	0.406	52 (14.9%)

Table 1 (*Continued*)

Patients with AIE Period 05/86 to 12/2008	Early PVE, *n* = 77 (22.1%)	Late PVE, *n* = 272 (77.9%)	*p*-value	Total (% of study population)
One	3 (3.9%)	20 (7.4%)	–	23 (6.6%)
Multiple	9 (11.7%)	39 (14.3%)	–	48 (13.8%)
Localisation	1 (1.3%)	1 (0.4%)	0.551	2 (0.6%)
Brain	2 (2.6%)	23 (8.5%)	0.339	25 (7.1%)
Lung	–	7 (2.6%)	0.078	7 (2.0%)
Spleen	–	2 (0.7%)	0.155	2 (0.6%)
Kidney	1 (1.3%)	4 (1.5%)	0.450	5 (1.4%)
Eye	2 (2.6%)	1 (0.4%)	0.911	3 (0.8%)
Leg	3 (3.9%)	8 (2.9%)	0.061	11 (3.1%)
Arm			0.672	
Skin				
Abscess formation	52 (67.5%)	174 (63.9%)	0.564	226 (64.8%)
Aortic	44 (57.1%)	158 (58.1%)	0.930	202 (57.9%)
Mitral	6 (7.8%)	10 (3.6%)	0.168	16 (4.6%)
Aortic + mitral	2 (2.6%)	6 (2.2%)	–	8 (2.3%)
Extent of abscess formation	17 (22.1%)	43 (15.8%)	0.242	60 (17.2%)
Localised abscess formation	35 (45.4%)	131 (48.1%)	*0.024*	166 (47.6%)
Aortic-ventricular dehiscence	4 (5.2%)	3 (1.1%)	0.266	7 (2.0%)
VSD fistula	8 (10.4%)	18 (6.6%)		26 (7.5%)
Intra-operative death	4 (5.2%)	16 (5.95)	0.819	20 (5.7%)
Mechanical support	18 (23.4%)	66 (24.3%)	0.872	84 (24.1%)
IABP	17 (22.1%)	54 (19.9%)	0.669	71 (20.3%)
Preoperative	–	*2*	–	–
Intra-operative	*14*	*40*	–	–
Early postoperative	*3*	*12*	–	–
ECMO	–	6 (2.2%)	0.189	6 (1.7%)
Intra-operative		*4*	–	
Early postoperative	1 (1.3%)	*2*	–	7 (2.1%)
	–			–
Assist device	*1*	6(2.2%)	0.616	–
Biventricular	*1*	*4*	–	–
Left ventricular	–	*2*	–	–
Intra-operative		*4*	–	
Early postoperative		*2*	–	
Follow-up in years			0.803	
Completed	96.1%	96.7%		
Median	1.17	1.32		
Range	0–15.1	0–19.4		
Patient-years	245.7	872.0		

AIE: active infective endocarditis; AVR: aortic valve replacement; CABG: coronary artery bypass graft; MVR: mitral valve replacement; PVE: prosthetic valve endocarditis.

(1) characterise the demographic and clinical differences between patients with early (≤60 days) and late PVE;
(2) compare early and long-term survival of these patients especially with regard to their preoperative status;
(3) determine the incidence and survival of second re-operation due to endocarditis recurrence and, finally,
(4) identify independent risk factors for early mortality by the application of uni- and multivariate analysis.

2. Patients and methods

2.1. Patient population

Between May 1986 and December 2008, a total of 1313 patients with AIE were operated on at the Deutsches Herzzentrum Berlin, 964 (73.4%) of them for native valve endocarditis (NVE) and 349 (26.6%) for PVE. An overview of the patient population is given in Table 1.

Of the consecutive series of 349 PVE patients, 77 (22.1%) had to be operated upon due to early PVE (≤60 days, *n* = 55 men, median age: 58 years) and 272 (77.9%) patients due to late PVE (*n* = 200 men, median age: 63 years). The median time from first valve operation to re-operation was 47 days for the early PVE and 1202 days for the late PVE group.

In the late PVE group, there were 61 patients operated on between 60 days and 1 year after the first valve operation (median time: 190 days, range: 84–364 days) and 211 patients >1 year after the first procedure (median time: 4.9 years, range: 367 days to 27.8 years).

A total of 44 (57.1%) patients from the early PVE group and 169 (62.1%) patients from the late PVE group had the first operation at our institution; the other patients were referred from other centres.

2.2. Indications for surgery

An overview of the main operative indications during the acute phase of PVE is given in Table 2. In general, patients had several indications for surgery during antibiotic treatment for PVE. The majority had to be operated on due to progressive heart failure, suspected vegetations, recurrent septic embolism, therapy-resistant infections or prosthetic malfunction. In the early PVE group, the leading indication was progressive heart failure (in 74% of the patients) which

Table 2
Summary of main indications for surgery.

Indication	Early PVE (n = 77)	Late PVE (n = 272)
Progressive heart failure	57 (74.0%)	163 (76.8%)
+Vegetations	22 (28.6%)	100 (36.8%)
+Recurrent septic embolism	11 (14.3%)	50 (18.4%)
+Therapy-resistant septic infection	24 (31.2%)	59 (21.6%)
+Prosthetic malfunction	9 (11.7%)	90 (33.1%)
+Prosthetic destruction	9 (11.7%)	37 (13.6%)
Vegetations	9 (11.7%)	13 (4.8%)
+Prosthetic malfunction	–	8 (2.9%)
+Prosthetic destruction	–	3 (1.1%)
Recurrent septic embolism	5 (6.5%)	14 (5.1%)
Therapy-resistant septic infection	4 (5.2%)	12 (4.4%)
+Vegetations	1 (1.3%)	4 (1.4%)
+Prosthetic malfunction	2 (2.6%)	4 (1.4%)
+Prosthetic destruction	2 (2.6%)	1 (0.3%)
Prosthetic malfunction	2 (2.6%)	24 (8.8%)

was followed by suspected vegetations (11.5%), whereas, in the late PVE group, leading indications were progressive heart failure (76.8%) followed by prosthetic malfunction (8.8%).

2.3. Operations performed

Table 3 presents the operations performed and lists the prostheses used.

For both groups, the prevalent operative procedure was aortic root replacement (ARR), which was performed in 41 patients (53.3%) in the early, and in 124 patients (45.6%) in the late, PVE group. Additionally, in the early group, 22 patients (28.5%) underwent mitral valve replacement (MVR), 10 (12.9%) aortic valve replacement (AVR) and four (5.3%) double valve replacement. In the late PVE group, besides the patients undergoing ARR, 70 patients (25.7%) underwent AVR, 43 (15.8%) MVR and 35 (12.9%) combined AVR and MVR.

Table 3
Operation performed in patients with early (≤60 days) and late prosthetic valve endocarditis.

Operation	Early PVE (n = 77)	Late PVE (n = 272)	p-value
AVR	10 (12.9%)	70 (25.7%)	*0.019*
Bioprosthesis	8	51	
Homograft	1	9	0.351
Mechanical prosthesis	1	10	
			0.007
Aortic root replacement	41 (53.3%)	124 (45.6%)	
Homograft	34	100	0.059
Biological	7	23	
Mechanical	–	1	*0.040*
MVR	22 (28.5%)	43 (15.8%)	
Bioprosthesis	14	29	
Mechanical prosthesis	8	14	
AVR + MVR	4 (5.3%)	35 (12.9%)	
Bioprosthesis	3	11	
Aortic homograft + bioprosthesis	1	10	
Mechanical prosthesis	–	11	
Others	–	3	
Concomitant CABG	2 (2.6%)	27 (9.9%)	

AVR: aortic valve replacement; MVR: mitral valve replacement; PVE: prosthetic valve endocarditis; CABG: coronary artery bypass graft.

2.4. Follow-up

Follow-up was completed by telephone contact with the patients, by analysing standardised mail questionnaires sent to the patients, by consulting the population registry and by contacting peripheral hospitals. Postoperatively, all patients were seen at least once a year in our outpatient department.

In the early PVE group, three patients were lost to follow-up and it was completed in 96.1% of all cases with 246 patient-years (range: 0–15.1 years, median: 1.17 years). In the late PVE group, nine patients were lost to follow-up and it was completed in 96.7% of all cases with 872 patient-years (range: 0–19.4 years, median: 1.32 years).

2.5. Definition of active infective PVE

According to the updated Duke's criteria and the recently published ESC-guidelines of 2009 [8,9], active infective PVE is defined on the basis of vegetations or abscess as seen in the echocardiogram and accompanied by positive blood cultures or intra-operatively harvested valve cultures, on the basis of clinical evidence of persistent sepsis or recurrent septic embolism or on the basis of the intra-operative diagnosis. Early PVE was defined as the diagnosis of PVE within 60 days of prosthetic valve implantation [2].

2.6. Statistical analysis

The statistical analysis was performed using SPSS 12.0.1 for Windows. For quantitative data, medians and ranges or means and standard deviations were calculated. Qualitative data are reported as relative frequencies and percentages. For comparison of different patient groups, Pearson's chi-square test and, for continuous data, the Student's t-test was used. Analysis of survival and freedom from end points was performed according to the method of Kaplan–Meier. Standard errors for Kaplan–Meier estimates were calculated by the Greenwood formula. Comparison of survival in different patient groups was performed using weighted log-rank tests. Predictors for survival time were identified by Cox regression. First, a univariable approach evaluating all possible risk factors was used, followed by a multivariable Cox regression in a forward/backward selection procedure. Aikaike's information criterion (AIC) was used to assess the goodness of fit. The assumption of proportional hazard was checked. All the statistical analyses were performed by an independent statistician.

3. Results

3.1. Demographic and clinical differences between early (≤60 days) and late PVE patients

Early PVE patients were significantly younger (p = 0.024).

By analysing the preoperative status, it was found that a large proportion of patients were referred to our department with advanced endocarditis and in a condition of cardiac and pulmonary decompensation. In comparison, early PVE patients needed, preoperatively, high doses of catecholamines (≥0.25 μg kg^{-1} body weight) significantly more often

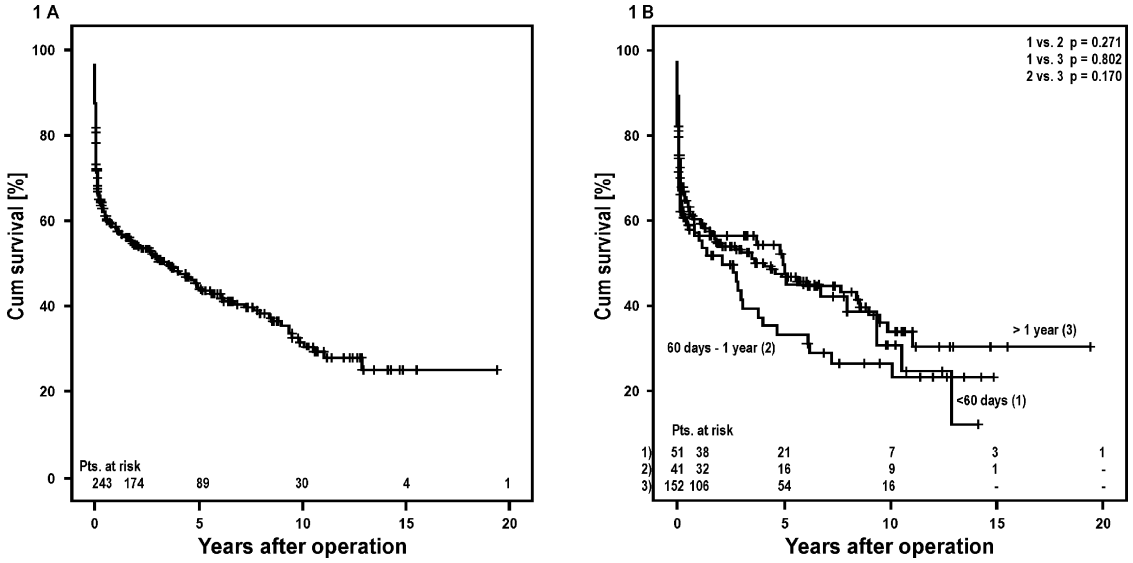

Fig. 1. Overall survival (a). Survival rates of the early (<60 days, curve 1) compared to the late PVE patients, who were subdivided into those who were operated on between 60 days and 1 year (curve 2) and more than 1 year (curve 3) (b).

($p = 0.043$) and had a tendency towards development of cardiac shock ($p = 0.066$). They were referred to our hospital significantly more often with intubation ($p = 0.038$) than late PVE patients.

In terms of the urgency of operation, both groups showed a high percentage of patients undergoing an emergency or urgent procedure but the proportion was significantly greater in early PVE patients than in the late PVE group ($p = 0.030$).

On admission, early PVE patients significantly more often showed not only renal insufficiency leading to dialysis ($p = 0.032$) but also persistent fever despite antibiotic treatment ($p = 0.010$) than late PVE patients.

By analysing the causes of the first operation, it was found that early PVE patients had been significantly more often operated upon due to active infective endocarditis ($p \leq 0.001$) than late PVE patients.

The comparison of the operations performed showed that homograft aortic root replacement was the most common operation in both groups (Table 3). Further, the distribution differed between the groups with MVR performed significantly more often in the early PVE group ($p = 0.007$). In the late PVE patients, we found significantly more frequent AVRs ($p = 0.019$) and concomitant coronary artery bypass grafting surgery (CABG; $p = 0.040$).

Abscess formation was found in 64.7% of the study population. There were no significant differences either in the number of patients or in the abscess localisation and extent of abscess formation between the two groups, but there was a significant difference in the incidence of abscess causing a ventricular septal defect which was seen more often in early PVE patients ($p = 0.024$).

In the prevalence of preoperative septic embolisation, which was seen in 21.5% of all patients, there was no difference between the groups, but analysis of the location showed spleen embolism to have a higher tendency in the late PVE patients ($p = 0.07$).

With regard to the subgroups of patients who had been operated on due to AIE at their first intervention, 11 out of 34 (32.3%) of early PVE patients had persistence of the same micro-organism (*Staphylococcus aureus* (*S. aureus*) $n = 6$, *Streptococcus* (*Strep.*) $n = 3$ and others $n = 2$). In the late PVE group, this was the case in four out of 50 (8%; *Enterococcus* $n = 2$, *S. epidermidis* $n = 1$ and *Strep. viridans* $n = 1$).

3.2. Overall survival, early (≤30 days) and late mortality

Analysis of the overall survival curve for all PVE patients shows high early and late mortality rates (Fig. 1a). The 30-day, 1-, 5- and 10-year survival for the whole PVE study population was $71.4 \pm 2.4\%$, $58.7 \pm 2.7\%$, $44.5 \pm 3\%$ and $31.7 \pm 3.5\%$, respectively, with no significant difference between the early and the late PVE patients: $67 \pm 5.4\%$, $55.9 \pm 5.8\%$, $49.4 \pm 6.2\%$ and $29.7 \pm 7.6\%$, compared to $72.4 \pm 3\%$, $60 \pm 3\%$, $43.5 \pm 3.3\%$ and $31.1 \pm 3.8\%$, respectively ($p = 0.93$). Fig. 1b shows the survival rates of the early (<60 days, curve 1), compared to the late, PVE patients, who were subdivided into those who were operated on between 60 days and 1 year ($n = 61$, curve 2) and >1 year ($n = 211$, curve 3) after the first valve operation. There was no significant difference among the three groups.

In the early PVE group ($n = 77$), there were 25 early deaths (≤30 days) resulting in an early mortality rate of 32.4%. Of these, four were intra-operative deaths due to myocardial failure or septic shock (5.2%), one patient died from haemorrhagic shock in the first postoperative week (1.3%), six patients due to myocardial failure (7.8%) and one patient each from cerebral bleeding (1.3%), pulmonary failure (1.3%) or other causes (1.3%), respectively. The other 11 patients died due to septic multi-organ failure (14.2%), which at a frequency of 44.0% (11/25 patients) presents the main cause of early death in this collective.

In comparison, in the late PVE group ($n = 272$), there were 74 early deaths (≤30 days) resulting in an early mortality rate of 27.2%. There were 16 (5.8%) intra-operative deaths, 10 due to myocardial failure and six due to septic multi-organ failure in patients operated on as a last-resort treatment.

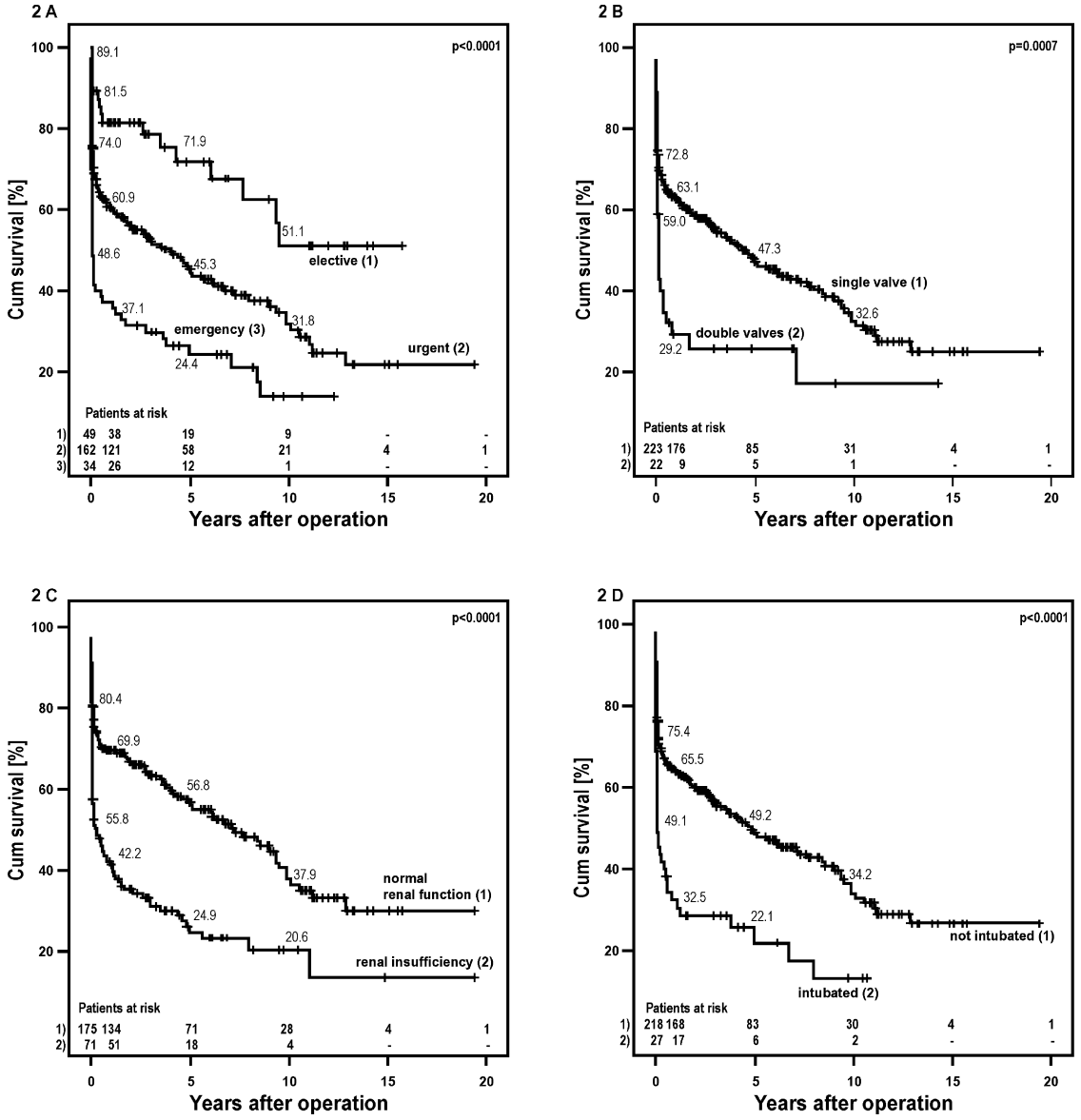

Fig. 2. Survival rates with highly significant differences in various subgroups of PVE patients. Priority of operation (a), single vs double valve replacement (b), preoperative normal renal function vs renal insufficiency (c) and preoperative mechanical ventilation (d).

The causes of the other 58 early deaths showed a similar pattern as in the early PVE group. As in the early PVE group, 33 patients died due to septic multi-organ failure (12.1%) which, with a rate of 44.6% (33/74 patients), is the main cause for early death also in this collective.

Poor outcome was seen after post- or intra-operative mechanical support, which was necessary in 24.1% ($n = 84$ patients) of the study population due to primary cardiac failure (Table 1). The 30-day and 1-year survival of these patients, compared to those without the need of support, were $29 \pm 5.2\%$ and $16.9 \pm 4.3\%$ versus $83.8 \pm 2.2\%$ and $71.3 \pm 2.8\%$, respectively ($p < 0.0001$).

We found high mortality rate but no significant difference in 30-day, 1-, 5- and 10-year survival between patients with and without abscess formation: $68.4 \pm 3.1\%$, $57.8 \pm 3.3\%$, $43.9 \pm 3.5\%$ and $27.3 \pm 4\%$, compared to $76.4 \pm 3.8\%$, $62.2 \pm 4.4\%$, $46.6 \pm 5\%$ and $39.9 \pm 5.7\%$ ($p = 0.10$).

Comparison of late mortality (30 days to 1 year) showed similar high rates in both groups with septic multi-organ failure being the main cause of late death in 20 out of 41 patients (48.7%).

3.3. Survival in various subgroups with regard to their preoperative status

Fig. 2a–d shows the survival rates with highly significant differences in various subgroups of PVE patients.

Analysis showed that patients who underwent operation as an urgent or emergency procedure (Fig. 2a), patients requiring double valve replacement (Fig. 2b) and those with preoperative renal insufficiency (Fig. 2c) or who arrived at our hospital intubated (Fig. 2d) were at higher risk of death.

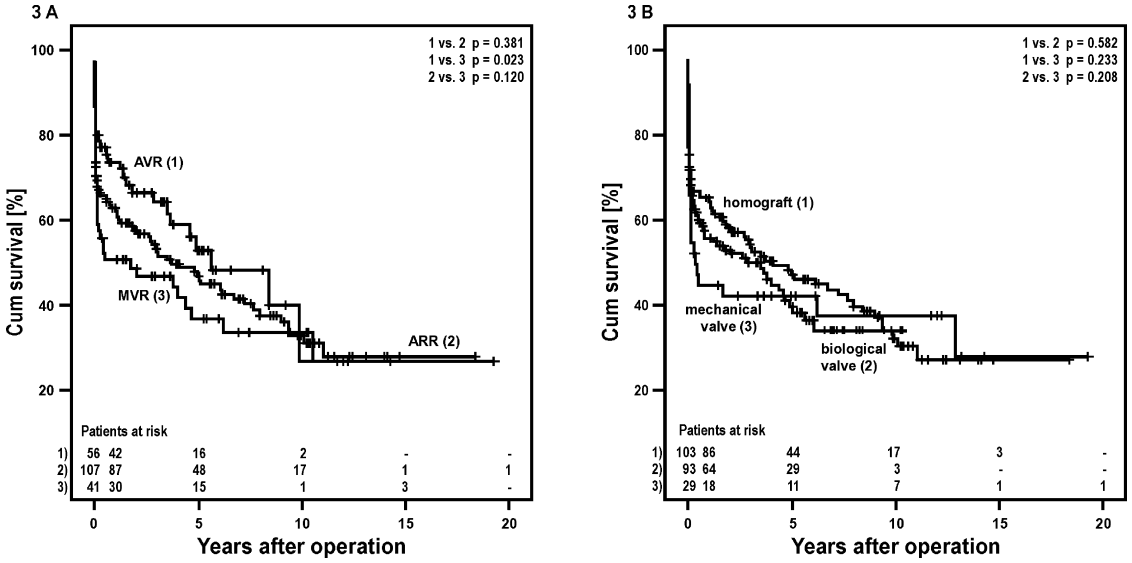

Fig. 3. Survival with regard to location of valve implantation (a) and prosthesis type used (b).

3.4. Survival with regard to location of valve implantation and prosthesis type used

Fig. 3a shows that the survival was significantly different after AVR compared to MVR: the 30-day, 1- and 5-year survival for the AVR group was 80 ± 4.8%, 73.7 ± 5.3% and 53 ± 7.2% compared to 67.2 ± 6.0%, 50.7 ± 6.4% and 36.9 ± 6.7% for the MVR group ($p = 0.023$). The survival curve of PVE patients undergoing homograft ARR runs parallel and there were no significant differences compared to the AVR and MVR curves, with the following 30-day, 1-, 5- and 10-year survival rates: 71.7 ± 3.7%, 65.2 ± 4%, 48.5 ± 4.5% and 32.4 ± 4.9%.

Fig. 3b shows that survival was independent of the prosthesis type used. Comparison of the survival rates of PVE patients after the implantation of biological or mechanical prostheses showed no significant differences between the groups. The 30-day, 1-, 5- and 10-year survival for the biological prostheses group was 70.1 ± 4%, 55.9 ± 4.4%, 39.6 ± 4.8% and 34.2 ± 5.1% compared to 65.9 ± 7.2%, 44.8 ± 7.6%, 42.2 ± 7.6% and 37.5 ± 8.1% for the mechanical prostheses, which were used predominantly in the first decade of the study period ($p = 0.20$).

3.5. Freedom from re-operation due to re-infection

A total of 18 out of 349 patients (5.2%) developed repeat re-infection leading to second re-operation in six early and 12 late PVE patients, resulting in a 30-day, 1-, 5- and 10-year freedom from re-operation due to re-infection of 100%, 88.8 ± 4.7%, 85.8 ± 5.6% and 85.8 ± 5.6% for the early PVE group compared to 99.5 ± 0.5%, 95.3 ± 1.6%, 92.1 ± 2.3% and 92.1 ± 2.3% for the late PVE patients (0.17; Fig. 4). Of these 18 patients, 11 patients (61.1%) preoperatively showed aortic root-abscess formation.

Of the six cases of repeat re-infection in the early PVE group (7.8%), there were three early (≤60 days, 3.9%) and two late re-infections (60 days to 1 year, 2.6%) and one *de novo* infection 2.6 years (1.3%) after the first re-operation.

On second re-operation in two patients each, a mechanical valve, a bioprosthesis and an aortic homograft were used. There was no intra-operative or cardiac-related death. Two of the six patients (33.3%) died within 60 days of the surgery.

The 12 repeat re-infections of the late PVE group (4.4%) comprised two early re-infections (≤60 days, 0.8%), five late re-infections (1.8%) and five *de novo* infections at a median of 1.5 years (1.1–3.9 years) after the first re-operation (1.8%).

On second re-operation, two patients received mechanical valves, five a bioprosthesis and five an aortic homograft. There was no intra-operative death. Four out of the 12 patients (33.3%) died within 60 days of the surgery.

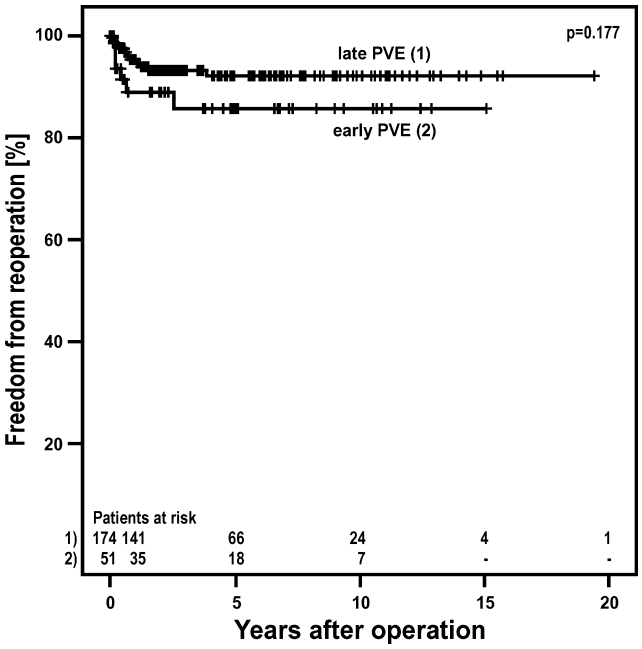

Fig. 4. Freedom from re-operation due to re-infection in early and late PVE.

Table 4
Risk factors for early mortality (≤30 days) in the univariate and multivariate Cox regression analysis in prosthetic active infective endocarditis.

Univariate Cox regression	Risk ratio	95% CI	*p*-value
Risk factors			
Mechanical support	5.10	3.73–6.95	≤0.001
Preop. septic shock	3.90	2.66–5.72	≤0.001
Mitral valve abscess	2.92	1.81–4.63	≤0.001
Emergency operation	2.68	1.63–4.41	≤0.001
Preop. catecholamines	2.65	1.96–3.58	≤0.001
Preop. dialysis	2.50	1.71–3.67	≤0.001
Preop. pulmonary oedema	2.47	1.83–3.33	≤0.001
Preop. ventilation	2.23	1.59–3.14	≤0.001
Preop. renal insufficiency	2.21	1.67–2.93	≤0.001
Double valve replacement	1.95	1.31–2.90	0.001
Concomitant CABG	1.80	1.13–2.86	0.013
Preop. cardiac shock	1.61	1.06–2.45	0.026
COPD	1.61	1.05–2.48	0.030
Diabetes	1.54	1.12–2.12	0.007
Staphylococcal infection	1.45	1.09–1.92	0.009
Mitral valve replacement	1.42	1.06–1.91	0.018
Age at operation per year	1.01	1.00–1.03	0.003

Multivariate Cox regression	Risk ratio	95% CI	*p*-value
Risk factors			
Mechanical support	4.3	3.1–5.9	≤0.001
Emergency operation	2.1	1.3–3.5	0.003
Preop. catecholamines	1.8	1.3–2.5	≤0.001
Mitral valve replacement	1.5	1.2–2.1	0.004
Age at operation	1.1	1.1–1.2	≤0.001

CI: confidence interval; preop.: preoperative.

3.6. Predictors for early mortality (≤30 days) in uni- and multivariate analysis

The risk factors for early mortality (≤30 days) in the uni- and multivariable logistic regression analysis with risk ratio (RR), 95% confidence interval (CI) and *p*-values are given in Table 4. It is shown that the preoperative status is highly predictive for the outcome. Patients with advanced PVE arriving at our clinic in a condition of cardiac, pulmonary or renal insufficiency were at higher risk.

In multivariable analysis, mechanical support (RR: 4.3), emergency operation (RR: 2.1), preoperative high doses of catecholamines (RR: 1.8), MVR (RR: 1.5) and age at operation per year (RR: 1.1, CI: 1.1–1.2, $p < 0.001$) were found to be independent risk factors for early mortality.

4. Discussion

Our study presents 22-year single-centre results in a group of high-risk patients with active infective early and late PVE undergoing surgery and compares the outcome of these patients. The results of our study confirm previous reports that documented the poor outcome of PVE patients [6,10] and demonstrate that PVE is associated not only with a high in-hospital mortality rate but also with a high long-term mortality risk. It is shown that the preoperative status is highly predictive for the outcome. Our results concur with those from a recently published multicentre study by Habib et al., in which the authors could demonstrate that complicated PVE was associated with a bad outcome and recommend early surgery for these patients [3]. Additionally, our study confirms previous reports that documented the association of periannular abscess complications with increased mortality and the need of surgery in almost all patients [5,11] underlined by recently published data by David and colleagues [12]. They demonstrated that surgery for active endocarditis with paravalvular abscess was associated with high operative mortality, particularly in patients in shock and with abscess formation on both mitral and aortic annuli. For the risk stratification and survival in our study, it has to be taken into consideration that our hospital is a referral surgical centre receiving patients who have already been treated medically elsewhere and we had no input regarding the medical management. They were referred for surgery only after medical therapy failed with a complicated clinical course of PVE and no patient, even with a high associated morbidity, was refused for surgery. Analysis of early mortality in our study with regard to the preoperative status showed that a large proportion of patients were referred to our department with advanced endocarditis and in a condition of cardiac and pulmonary decompensation. Survival curves adjusted for these variables showed statistically significant differences for these patients (Fig. 2a–d). In our study, the main causes of the 99 (28.3%) early deaths (<30 days) were septic multi-organ failure in 44 (44.4%) and myocardial failure in 27 (27.2%) patients besides the 20 (20.2%) patients who died intra-operatively and in whom operation was performed as an *ultima ratio* therapy. Additionally, early survival of patients requiring post- or intra-operative mechanical support differed significantly and was extremely poor compared to that of patients without the need of support (29.0% vs 83.8%). These results suggest that early outcome could have been improved if patients had been operated upon before their PVE had been complicated, for example, by heart failure or septic shock [12,13]. Such data were confirmed by the results of our uni- and multivariable analysis of risk factors for early mortality (≤30 days).

Several studies tried to identify prognostic factors in PVE but their results are conflicting due to heterogeneity of the study population. Habib et al. identified severe heart failure, staphylococcal infection and complicated PVE as markers of both in-hospital and late mortality and they clearly showed in their study that severe heart failure and *S. aureus* infection were the only independent predictors of in-hospital death. In addition, other markers such as co-morbidity and early PVE were identified as independent prognostic markers of late death. The authors concluded that a subset of patients with PVE, that is, patients with early staphylococcal PVE and patients with complicated PVE, must be managed aggressively [3].

In comparison, data from the International Collaboration on Endocarditis showed that in-hospital death, which occurred in 22.8% of the study patients, was predicted by older age, health-care-associated infection, *S. aureus* infection and complications of PVE, including heart failure, stroke, intra-cardiac abscess and persistent bacteraemia. The authors concluded, amongst others, that complications of PVE strongly predict in-hospital mortality, which remains high despite prompt diagnosis and the frequent use of surgical intervention [6].

A significant number of hospital survivors died during mid- and long-term follow-up. Our study showed similar high late

mortality rates for the early and late PVE group with septic multi-organ failure being the main cause of late death. The 10-year survival in our study was only 31%, also similar to that reported by the Toronto and Stanford University [12,14] showing that these patients need close clinical follow-up because of the potential risk of late complications.

In our study, 22.1% of cases of PVE occurred within the first 60 days after valve replacement. Although our study showed a higher mortality in patients with early PVE (33%) compared to those with late PVE (27.6%), there were no statistically significant differences, which concurs with some, but conflicts with other, published studies [12,15,16]. The reasons for these conflicting results include the small number of patients in some studies, the heterogeneity of study populations with differences in the number of medically and surgically treated patients, the lack of uniform definition of PVE and the retrospective nature of all of these studies which make endocarditis studies often not comparable with each other. However, it has to be pointed out that early PVE patients were in a more severe condition than late PVE patients and that early PVE was more often caused by recurrence than by *de novo* re-infection.

In the literature, there is a good deal of information on surgery for aortic root abscess [17—20], but only few reports on mitral annulus abscess or on patients with combined MV and AV abscesses [21,22]. The results of our study confirm previous reports that documented the poor outcome after MVR. The only way to eradicate the infection and provide satisfactory long-term results is resection of abscess in the posterior mitral annulus and in the inter-valvular fibrous body which is an operative procedure associated with high operative mortality [23,24].

The best type of prosthesis for implantation in patients with native and prosthetic AIE is a matter of controversial discussion in the literature. Many have treated this problem with prosthetic root replacement using either mechanical or tissue valves.

However, the few studies that compare mechanical and biological prostheses are limited in terms of the numbers of patients and the study populations are mostly not comparable with each other. In the study by Moon et al. of patients with native and prosthetic endocarditis, the operative mortality, survival rate and the rate of freedom from re-operation were independent of whether a mechanical or a biological valve was implanted [14]. Leyh et al. found the 1- and 5-year survival rates in patients with acute AV prosthetic endocarditis who received an ARR to be independent of whether a homograft or a composite prosthesis was used. None of these patients ($n = 24$) had to be re-operated on because of re-infection [25].

In this study, there were 134 out of 349 (38.4%) patients undergoing homograft ARR, which is the standard procedure in patients with aortic root abscess in our institution.

Because of the complexity of the operation and the controversial discussion of the risk of recurrent endocarditis for mechanical prostheses and bioprostheses reported in the literature [14,25], the superiority of the homograft in the treatment of AIE has been questioned.

Additionally, it has to be mentioned that the influence of the age of the recipient on the long-term durability of the homograft has been reported previously by numerous studies, showing that younger patient age is the most important predictor of structural valve deterioration [26,27].

We believe that, in severe destructive endocarditis with aorto-ventricular dehiscence caused by abscess, the aortic homograft is ideally suited for reconstruction of the aortic root. Repair of the structural defects created by the resection of the abscess can be achieved by making use of the muscular cuff of the soft annulus and of the anterior mitral leaflet adhering to the aortic homograft. Additionally, the low early re-infection rate and the excellent long-term freedom from re-infection reported in previous publications without any significant differences between native and prosthetic endocarditis patients document the outstanding role of the homograft in the treatment and eradication of AIE [17,20,22].

4.1. Study limitations

The present study has limitations. It is retrospective and there is a natural bias in the clinical assessment of the two patient groups. It reports results from a single institution and surgical referral centre which may have caused a selection bias towards more severe or complicated cases, thus limiting direct generalisation of the results. Additionally, we cannot provide data on the duration of medical therapy. Despite these limitations, the present study represents a unique attempt to analyse a single-centre experience over a period of up to 22 years in the surgical treatment of severe PVE.

5. Conclusions

Surgery for active infective PVE continues to be challenging. It not only carries a high in-hospital mortality but is also associated with a high long-term mortality risk.

Early PVE patients were in a more severe condition than late PVE patients.

Preoperative status, complications and co-morbidity of PVE patients strongly predict early outcome. Because of the potential risk of late complications, PVE patients need close clinical follow-up.

Acknowledgements

We thank Mrs A. Benhennour for bibliographic assistance, Mrs K. Weber for photographic work and Mrs A. Gale for editorial assistance.

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Appendix A. Conference discussion

Dr M. Sousa Uva (*Lisbon, Portugal*): This is a retrospective review of a series of 349 patients with active prosthetic valve endocarditis, 22% of whom with early and 78% with late; it is an impressive series during a 22-year period. I have some observations and then a couple of questions.

The first observation, almost two-thirds of patients had periannular abscess with no difference — and that was a little bit surprising for me — between early and late prosthetic valve endocarditis and almost half had aorto-ventricular dehiscence. These were severely ill patients, particularly those with early prosthetic valve endocarditis, with a significantly more severe clinical presentation than those with late, as would be expected. For example, in the early group, 25% required emergency surgery. I think roughly half were treated with aortic homografts, and I think you are a centre with a big experience in aortic homografts. And the 30-day mortality was highest, as would be expected, 32% and 27%, respectively, in the early and the late groups, and it was particularly high in those patients that required mechanical support. It was 81% mortality in this subset of groups. And finally, at five years, only 44% of the patients were still alive. So not only was the early mortality high, which would be expected, but a little bit surprising is that mortality continued to be steady; more than half of the patients at five years were dead. So I have four questions.

Do you have any information regarding the duration of antibiotic therapy before surgery? Although these patients were referred from other centres, this must be difficult to answer.

Dr Musci: We often don't know the duration and type of preoperative antibiotic treatment, and we have therefore created a close follow-up with the cardiologists so that we can influence the treatment. Every patient received three antibiotics. That is the first answer to your question. We were also surprised at the high incidence of abscess formation in the late groups. And this shows that the patients are treated with antibiotics for too long. In the median time they were treated for about 8 weeks in the late group until they came to our hospital with a complication like abscess formation.

Dr Sousa Uva: Is this a manual retrospective data analysis of individual clinical records, did you go and see each clinical record, or is it based on analysis of a prospective clinical database?

Dr Musci: It is a combination of an analysis of a prospective clinical database and retrospective clinical records of all patients. We created our own endocarditis database five years ago. All patients who are seen and operated on in our hospital are followed up. But there is a natural bias because we only

see patients who are referred to our centre for operation. So we don't see the patients who don't come to our clinic. That is also one of the natural biases of this study.

Dr Sousa Uva: The third question is, based on the very poor results that you have in some patient subsets, particularly those requiring mechanical support, do you still follow the policy of offering surgery for everybody without turning down any patient? Is there any indication for no surgery in your experience?

Dr Musci: In our institution we don't have any indication not to operate on patients. We operate, and that is known by all the cardiologists in Berlin, on every patient. So that is the reason for the poor outcome of the patients, especially those patients who can't be weaned from cardiopulmonary bypass. So you saw that 90% of patients needing intra-operative support like ECMO died. But we operate on every patient. We don't refuse any patient an operation.

Dr Sousa Uva: And finally, the last question. This is an experience extending over 22 years. Did you look at time-related trends? In other words, was there any difference in demographics and results in the first versus the second decade of your experience?

Dr Musci: The only difference was a different micro-organism. We saw a shift towards more resistant micro-organisms like Staph aureus and other very resistant micro-organisms of the HACEK group.

Dr L. Torracca (*Milan, Italy*): I have a question. What is your protocol in terms of duration of antibiotic therapy before surgery? Is there any protocol in your institute, out of emergency, obviously?

Dr Musci: No, we don't have any protocol because we see only patients for operation. But we have a postoperative protocol. We recommend 6 weeks of at least three different antibiotics after these operations.

Dr J. Tsai (*Pingtung, Taiwan*): Dr Musci, we spoke many times about infective endocarditis. Your outcome is related to early operation. But I have a question. How early, how early, because always the infective endocarditis patient is in the hands of the cardiologist. Would you kindly give us how early, please?

Dr Musci: The European Society of Cardiology has guidelines saying that the patients have to be operated on when they develop complications. But we see the patients they have already developed severe complications like annular abscess formation or heart failure or septic embolisation and these patients often die. So we try to operate before they have any complications, but we are not successful in this strategy. We are trying to change the opinion of our referring cardiologists in Berlin. And now we are developing a close relationship, but we are still not successful with this. So an excellent patient would be a patient who has no abscess formation and vegetation treated for only one or two or three days, not longer, but we don't see these patients. So our conclusion is to operate as soon as possible.