Surgical treatment of paravalvular abscess: long-term results

Tirone E. David*, Tommaso Regesta, Gheorghe Gavra, Susan Armstrong, Manjula D. Maganti

Peter Munk Cardiac Centre at University Health Network, University of Toronto, Toronto, Ont., Canada

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Abstract

Objective: To examine the outcomes of surgery for active infective endocarditis with paravalvular abscess. Methods: Paravalvular abscess was defined as infective necrosis of the valve annulus that required patch reconstruction before implanting a new valve. Of 383 patients with active infective endocarditis who underwent surgical treatment, 135 (35%) had paravalvular abscess. Patients’ mean age was 51 ± 16 years and 68% were men. The infected valve was native in 69 patients and prosthetic in 66. The abscess involved the aortic annulus in 73 patients, the mitral annulus in 27, the aortic and mitral annuluses in 33, and the aortic and tricuspid and/or pulmonary annuluses in 2. Surgery consisted of radical resection of the abscess, reconstruction of the annulus with patches and valve replacement. Mean follow-up was 6.2 ± 5.2 years and complete. Results: There were 21 (15.5%) operative deaths. Preoperative shock and abscess in the aortic and mitral annuluses were independent predictors of operative death. There were 34 (25%) late deaths. Survival at 15 years was 43 ± 6% for all patients, 50 ± 8% for native valve endocarditis and 35 ± 9% for prosthetic (p = 0.41). Age by increments of 5 years and recurrent endocarditis were independent predictors of late death. There were 16 episodes of recurrent endocarditis in 15 patients, and the freedom from recurrent endocarditis was 82 ± 4% at 15 years. Fifteen reoperations were performed in 14 patients. Freedom from reoperation was 72 ± 9% at 15 years. Conclusions: Surgery for active endocarditis with paravalvular abscess was associated with high operative mortality, particularly in patients in shock and abscess of both mitral and aortic annuluses. Long-term survival was adversely affected by age and recurrent bouts of endocarditis.

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Keywords: Heart valve disease; Infective endocarditis; Paravalvular abscess

1. Introduction

In spite of antibiotic therapy approximately one-third of patients with active infective endocarditis require surgery to save the patient’s life and eradicate the infection [1,2]. Depending on how promptly the disease is diagnosed and appropriate antibiotics started, on the virulence of the microorganism, and on whether the infected valve is native or prosthetic, the infection may extend into the valve annulus and surrounding tissues causing abscess, fistulas and false aneurysms [3]. Delaying surgical treatment often increases the probability of complications and operative mortality and morbidity rates. The notion that less virulent microorganism such as Streptococcus viridans always respond to antibiotics alone is erroneous because this bacteria can cause extensive paravalvular abscess [4]. This study is a retrospective review of our experience with surgery for active infective endocarditis with paravalvular abscess.

2. Patients and methods

A review of the cardiac surgery database of Toronto General Hospital disclosed 383 patients who had surgery for active infective endocarditis from 1978 to 2004. Because the database did not contain all pertinent information for this disease, the hospital medical records were also reviewed to confirm the diagnosis, identify the offending microorganism, and review the operative findings and technical details of the procedures performed. By defining paravalvular abscess as infective necrosis of the valve annulus and surrounding tissues that required debridement and patch reconstruction before a valve could be implanted, 135 patients were identified. The preoperative diagnosis of paravalvular abscess was made by transthoracic echocardiography in 81 (60%) patients. In the remaining 54 patients the diagnosis was made at surgery. Indications for surgery were the presence of abscess, cardiogenic and/or septic shock,
Percentages are shown in parentheses.

Timing of surgery:
- Coronary artery disease: 19 (14)
- Previous coronary artery bypass: 13 (10)

2 (3) 3 (5)

Enterococcus faecalis
Other streptococci: 9 (15) 7 (12)
Streptococcus viridans: 15 (26) 4 (7)

3 (5) 19 (32)
Staphylococcus epidermidis

was available in 117 patients and it is shown in Table 2.

orifices. Information regarding the offending microorganism except if they had large vegetations near the coronary artery angiography was performed in most patients older than 50 years and in those with suspected coronary artery disease were performed.

Mean age
Number of patients 135
Mean age ± SD years 51 ± 16
Male gender 92 (68)

Electrocardiogram:
- Sinus rhythm: 97 (72)
- Atrial fibrillation: 28 (21)
- Complete heart block: 10 (7)

Associated diseases:
- Diabetes mellitus: 14 (10)
- Hypertension: 29 (22)
- Chronic obstructive lung disease: 3 (2)
- Renal failure: 16 (12)

Recent TIA/Stroke (<30 days): 32 (24)

New York Heart Association functional class:
- I: 5 (4)
- II: 4 (3)
- III: 7 (5)
- IV: 119 (88)

Cardiogenic/septic shock: 23 (17)
Native valve endocarditis: 69 (51)
Prosthetic valve endocarditis: 66 (49)
Left ventricular ejection fraction <40%: 16 (14)
Previous coronary artery bypass: 13 (10)
Coronary artery disease: 19 (14)

Timing of surgery:
- Same hospitalization: 42 (37)
- Urgent/emergent: 77 (65)

Percentages are shown in parentheses.

congestive heart failure, or persistent sepsis. Table 1 shows the clinical characteristics of the patients. Coronary angiography was performed in most patients older than 50 years and in those with suspected coronary artery disease except if they had large vegetations near the coronary artery orifices. Information regarding the offending microorganism was available in 117 patients and it is shown in Table 2. Staphylococcus aureus was the most common microorganism in native valve endocarditis and staphylococcus epidermidis in prosthetic valve. Only 2 patients were drug addicts.

2.1. Operative procedures

The surgical principle of radical resection of all infected or even suspiciously infected such as edematous tissues was applied to all patients. The complexity of the operations ranged from resection of part of the valve annulus and surrounding tissues with reconstruction with a patch to radical removal of the base of the heart including the entire aortic root, the intervalvular fibrous body, the posterior mitral annulus and part of the interventricular septum and atrial walls. The techniques for these radical procedures have been described in detail in previous publications [5–7].

The abscess involved the aortic annulus in 73 patients, the mitral annulus in 27, the aortic and mitral annuli in 29, aortic, mitral, and tricuspid in 4, the aortic, tricuspid and pulmonary in 1, and the aortic and pulmonary in 1.

Six attending surgeons performed the operations. Table 3 summarizes the operative data.

2.2. Follow-up

Patients were followed prospectively by the referring cardiologists and contacted by our research personnel. Follow-up was complete. The mean follow-up was 6.2 ± 5.2 years and extended from 0 to 22 years.

2.3. Statistical analysis

All data analyses were performed with SAS 8.1 Software (SAS Institute, Cary, NC). Categorical variables are reported as frequencies and all continuous variables are reported as mean ± standard deviation. The Kaplan–Meier method was used to calculate estimates for long-term survival or freedom

Table 1

Clinical characteristics of patients with paravalvular abscess

<table>
<thead>
<tr>
<th></th>
<th>Native valve</th>
<th>Prosthetic valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD years</td>
<td>51 ± 16</td>
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<td>Male gender</td>
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<td>Percentages are shown in parentheses.</td>
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<td>Complete heart block</td>
<td>10 (7)</td>
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<tr>
<td>Associated diseases:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (10)</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>29 (22)</td>
<td></td>
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<tr>
<td>Chronic obstructive lung disease</td>
<td>3 (2)</td>
<td></td>
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<tr>
<td>Renal failure</td>
<td>16 (12)</td>
<td></td>
</tr>
<tr>
<td>Recent TIA/Stroke (&lt;30 days)</td>
<td>32 (24)</td>
<td></td>
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<tr>
<td>New York Heart Association functional class:</td>
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<td></td>
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<tr>
<td>I</td>
<td>5 (4)</td>
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<td>II</td>
<td>4 (3)</td>
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</tr>
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</tr>
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<td></td>
</tr>
<tr>
<td>Timing of surgery:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same hospitalization</td>
<td>42 (37)</td>
<td></td>
</tr>
<tr>
<td>Urgent/emergent</td>
<td>77 (65)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

Offending microorganisms

<table>
<thead>
<tr>
<th>microorganism</th>
<th>Native valve</th>
<th>Prosthetic valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>24 (41)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>3 (5)</td>
<td>19 (32)</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>15 (26)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>9 (15)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>2 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Other bacteria</td>
<td>3 (5)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Culture negative endocarditis</td>
<td>2 (3)</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

Percentages are shown in parentheses.

Table 3

Operative data

<table>
<thead>
<tr>
<th>Main location of abscess</th>
<th>Native valve</th>
<th>Prosthetic valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-coronary aortic sinus</td>
<td>47 (35)</td>
<td></td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>22 (16)</td>
<td></td>
</tr>
<tr>
<td>Interventricular fibrous</td>
<td>42 (31)</td>
<td></td>
</tr>
<tr>
<td>Posterior mitral annulus</td>
<td>22 (16)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary annulus</td>
<td>2 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Patch material used for reconstruction of annulus:
- Fresh autologous pericardium: 54 (40)
- Bovine pericardium: 71 (53)
- Dacron graft: 4 (3)
- Anterior leaflet of MV of aortic homograft: 6 (4)

Heart valve used for replacement:
- Mechanical: 66 (49)
- Bioprosthetic: 55 (41)
- Aortic homograft: 14 (10)

Operative procedures:
- Reconstruction of LVOFT: 101 (75)
- Reconstruction of posterior MA: 22 (16)
- Reconstruction of LVOFT and posterior MA: 7 (5)
- Bentall: 29 (21)
- Replacement of the ascending aorta: 5 (4)
- AVR: 58 (43)
- AVR + MVR: 35 (26)
- AVR + MVR + TV repair: 6 (4)
- AVR + MV repair: 12 (9)
- MVR: 22 (16)
- AVR + PVR: 1
- AVR + TVR + PVR: 1
- Repair of congenital VSD: 6 (4)
- CABG: 23 (17)

Aortic clamping time (mean ± SD min): 117 ± 43
Cardiopulmonary bypass time: 149 ± 57
Days in ICU (mean ± SD): 5.8 ± 8.4
Days in hospital (mean ± SD): 17.7 ± 14.2

Abbreviations: MV = mitral valve; LVOFT = left ventricular outflow tract; MA = mitral annulus; AVR = aortic valve replacement; MVR = mitral valve replacement; TV = tricuspid valve; PVR = pulmonary valve replacement; TVR = tricuspid valve replacement; VSD = ventricular septal defect; CABG = coronary artery bypass.
from morbid events. The difference in longitudinal outcomes between native and prosthetic valves was evaluated by using the log-rank statistic. All preoperative variables with a univariate \( p \)-value of less than 0.25 or those with known biologic significance but failing to meet this critical \( \alpha \) level were submitted to the multivariable model for Cox regression analysis to determine the independent multivariable predictors of operative and late mortality. Variable retention criteria in the model were set at a \( p \)-value of 0.05.

3. Results

There were 21 operative deaths. The causes of death were often multifactorial, but the main reasons were multigorgan failure in 6 patients, low cardiac output syndrome in 4, persistent sepsis in 2, bleeding disorder in 3, technical errors in 4, stroke in 1, and ruptured aortic root in 1. Table 4 shows the operative mortality in various subgroups of patients. The operative mortality did not change during the period of study. Cox regression analysis identified preoperative shock (odds ratio, OR 2.5, 95% confidence interval, CI 1.5—3.6) and abscess in the aortic and mitral annuluses (OR 2.2, 95% CI 1.3—4.0) as predictors of operative death.

Postoperative complications were common: 12 patients required re-exploration of the chest for bleeding and/or tamponade; 7 patients suffered new stroke (5 intra- and 2 postoperative), 29 patients required permanent pacemaker for heart block, and 7 required hemodialysis for new postoperative renal failure. In addition, 3 patients required further valve surgery for valve dehiscence or persistent sepsis.

Thirty-four patients died during the follow-up. The causes of death were cardiac in 25 patients (congestive heart failure in 8, recurrent endocarditis in 8, myocardial infarction in 3, stroke in 2, sudden in 1, bioprosthetic valve failure in 1, paravalvular leak in 1) and non-cardiac in 9 (cancer in 6, renal failure in 1, diabetes in 1 and respiratory failure in 1). Patients’ survival was 43 ± 6% at 15 years (Fig. 1). The survival at 5-, 10-, and 15-year was 74 ± 5%, 62 ± 6%, and 50 ± 8%, respectively, for native valve endocarditis and 68 ± 5%, 52 ± 7%, and 35 ± 9%, respectively, for prosthetic valve endocarditis ( \( p = 0.41 \)). Cox regression analysis identified age by 5-year increment (Hazard ratio, HR = 1.19, 95% CI 1.04—1.35), and recurrent endocarditis (HR = 1.7, 95% CI 1.28—2.9) as predictors of late death.

Recurrent endocarditis occurred 16 times in 15 patients: 3 during the first postoperative year and 13 in subsequent years. The offending microorganisms were the same as in the first infection in 2 instances, different in 13, and culture negative in 1. Four patients were operated on (one patient had 2 reoperations) with no death, and 12 patients were treated with antibiotics alone with 8 deaths. Freedom from recurrent endocarditis was 82 ± 4% at 15 years (Fig. 2). No predictors of recurrent endocarditis could be identified.

There were 15 reoperations in 14 patients: 5 for valve and/or patch dehiscence, 3 for primary tissue failure, 5 (4 patients) for recurrent endocarditis, and 2 for mitral regurgitation. Freedom from reoperation was 72 ± 9% at 15 years (Fig. 3).

Other valve-related complications were primary tissue failure of bioprosthetic valves in 4 (3 were reoperated on), valve and/or patch dehiscence in 7 (5 were reoperated on), and 10 thromboembolic events.

At the latest follow-up contact, 66 patients were alive and free from reoperation: 46 (70%) were in New York Heart Association functional class I, 15 (23%) in class II, and 5 (7%) in class III.
4. Discussion

The diagnosis of paravalvular abscess in patients with active infective endocarditis is often made by transesophageal echocardiography [8]. Thus, this diagnostic tool should be part of the work-up of patients with active infective endocarditis. The preoperative diagnosis of paravalvular abscess was made in only 60% in our series because some patients did not have preoperative transesophageal echocardiography or were operated on before its development in mid-1980. It is important for the surgeon to know that a paravalvular abscess is present because the operative procedure is more complicated and also associated with higher mortality and morbidity than in simple valve replacement or repair for active infective endocarditis [9].

It has been shown that endocarditis caused by *Staphylococcus aureus* and other virulent microorganisms on valves in the left side of the heart are best treated with early surgery [1,9,10]. In a large merged database on native valve endocarditis the overall mortality was higher in patients with *Staphylococcus aureus* endocarditis than in those with other bacteria (20% vs 12%, p = 0.001), but surprisingly, fewer patients infected with *Staphylococcus aureus* had surgery (26% vs 39%, p = 0.001) [10]. In our series of paravalvular abscess, *Staphylococcus aureus* was the most common offending microorganism in native valve and *Staphylococcus epidermidis* in prosthetic valve endocarditis. However, the offending microorganism had no effect on operative mortality. It is noteworthy that less virulent bacteria such as *Streptococcus viridans* is also capable of causing paravalvular abscess, particularly when not properly treated.

The operative mortality in our series of paravalvular abscess was 15.5%. Preoperative cardiogenic and/or septic shock and abscess in the aortic and mitral annuluses were independent predictors of operative mortality. Mortality rates for surgery for paravalvular abscess vary from 3.7% to 31% in other reports [11—15]. These differences in mortality rates are multi-factorial and the experience of the surgical group is certainly pivotal. Most surgeons believe that aortic valve homograft is the best valve for patients with aortic root abscess, and that it actually reduces operative mortality when compared with reconstruction with synthetic material [13,14]. Other surgeons argue that prosthetic material provide comparable if not better clinical outcomes than homograft [4,16]. We do not believe aortic valve homograft is a substitute for radical debridement and implantation of the new valve on healthy and strong tissues [4]. Persistent or early recurrent endocarditis is probably more related to the surgeons’ recognition of, and ability to extirpate all infected tissues, than the type of valve used for replacement [4]. However, we believe that aortic valve homograft is ideally suited for reconstruction of the aortic root because it is easier to handle than synthetic materials and the anterior leaflet of the mitral valve of the aortic homograft can be used to patch defects created by the resection of the abscess.

Although there is a lot of information on outcomes of surgery for aortic root abscesses [11—16], there is little on mitral annulus abscess or in patients with combined mitral and aortic valve abscesses [17,18]. Resection of abscess in the posterior mitral annulus or in the intervalvular fibrous body or both can be a formidable operative procedure, which is associated with high operative mortality, but we believe that it is the only way to eradicate the infection and it provides satisfactory long-term results [6,7]. In the present study, 27 patients had isolated mitral annulus abscess, and 33 had aortic and mitral annuli abscesses. We believe that fresh autologous pericardium is the best material to reconstruct areas of the mitral and tricuspid annuli that are subtended by cardiac muscle. In a few cases that we have reoperated on these patients, the autologous pericardium had healed into the cardiac muscle, creating a strong fibrous layer that secured the prosthetic valve. And at the reoperation we did not have to reconstruct the mitral annulus again. Fresh autologous pericardium may not be the best material to patch areas such as the intervalvular fibrous body between the mitral and aortic valves or large segments of the non-coronary aortic sinus and aortic annulus. For those areas glutaraldehyde fixed pericardium or Dacron fabric are more appropriate because they are stronger and less likely to calcify and fracture in the future [19].

The outcomes of prosthetic valve endocarditis are worse than that of native valve endocarditis [9]. The operative mortality is higher than in native valve endocarditis and the long-term survival is not as good [9]. In our series of paravalvular abscess, the operative mortality was higher and the long-term survival shorter for patients with prosthetic valves than in those with native valves but the differences did not reach statistical significance likely due to small sample sizes of the subgroups.

Despite of high operative mortality and morbidity with surgery for paravalvular abscess, the long-term survival was satisfactory considering how sick the patients were prior to surgery and the complexity of the operative procedures. The 10- and 15-year survival in this series was 57% as 43%, the freedom from reoperation was 84% and 72%, and the freedom from recurrent endocarditis was 85% and 82%, respectively. It is important to consider that more than one-half of all patients needed more than just aortic root surgery.

Yankah et al. from the German Heart Center recently described their experience with 161 patients with aortic root abscess treated exclusively with aortic valve homograft [11]. Thirty-six patients also had involvement of the mitral valve. They reported an operative mortality was 9.3% for elective/urgent and 14.3% for emergency cases. The aortic valve homograft was explanted in 11 patients because of residual/
recurrent infection, in 2 for structural deterioration, and in 17 for non-structural deterioration. The freedom from reoperation was 72.7% at 10 and 15 years. The survival at 5-, 10- and 15-year was unchanged at 70.4%, that is, there were no deaths after the fifth postoperative year, a remarkable finding [11]. The freedom from recurrent endocarditis at 5-, 10-, and 15-year was also unchanged at 90.1% [11]. Sabik et al. from Cleveland Clinic analyzed their experience with 103 consecutive patients with prosthetic aortic valve endocarditis treated exclusively with aortic valve homograft [20]. Aortic root abscess was present in 78% of patients. The operative mortality was only 3.9% but the 5- and 10-year survival was reduced at 73% and 56%, respectively [20]. The instantaneous risk of recurrent endocarditis peaked at 9 months and the freedom from recurrent endocarditis at 5 and 10 years was 95%. It is difficult to compare clinical outcomes of complex operations such as surgical treatment of endocarditis with paravalvular abscess from different institutions. However, based on the reports by Yankah et al. [11] and Sabik et al. [20], it is likely that the risk of recurrent endocarditis is reduced by the use of aortic valve homograft in these patients, but the long-term survival is influenced by numerous factors and the type of valve is certainly not the most important one.

In conclusion, surgery for paravalvular abscess continues to be associated with high mortality and morbidity. Radical resection of the abscess is essential. The general consensus is that aortic valve homograft is the ideal conduit for aortic root resection of the abscess but it is not a substitute of radical extirpation of the that aortic valve homograft is the ideal conduit for aortic root resection of the abscess is essential. The general consensus is to be associated with high mortality and morbidity. Radical homograft in these patients, but the long-term survival is reduced by the use of aortic valve endocarditis treated exclusively with aortic valve homograft [20]. Aortic root abscess was present in 78% of patients. The operative mortality was only 3.9% but the 5- and 10-year survival was reduced at 73% and 56%, respectively [20]. The instantaneous risk of recurrent endocarditis peaked at 9 months and the freedom from recurrent endocarditis at 5 and 10 years was 95%. It is difficult to compare clinical outcomes of complex operations such as surgical treatment of endocarditis with paravalvular abscess from different institutions. However, based on the reports by Yankah et al. [11] and Sabik et al. [20], it is likely that the risk of recurrent endocarditis is reduced by the use of aortic valve homograft in these patients, but the long-term survival is influenced by numerous factors and the type of valve is certainly not the most important one.

In conclusion, surgery for paravalvular abscess continues to be associated with high mortality and morbidity. Radical resection of the abscess is essential. The general consensus is that aortic valve homograft is the ideal conduit for aortic root resection of the abscess but it is not a substitute of radical extirpation of the abscess and all inflamed tissues. For patients with mitral annulus abscess, fresh autologous pericardium is probably the best patch material, particularly in areas subtended by ventricular muscle.

References


Appendix A. Conference discussion

Dr C. Mestres (Barcelona, Spain): I have to comment on a couple of things, because you concluded that only shock and abscess were independent predictors of operative mortality, and I agree with that. We just published not so long ago a series from a Spanish multicenter trial, or study basically, with about 4200 cases of endocarditis, and we were able to identify a series of 351 patients with an abscess, and out of them, 76 with a fistula. And although the results in the long-term, beyond 5 years up to 10 years, the mortality is about the same, so meaning that there is about a 40 to 45% survival beyond 5 to 10 years, we found that other than shock and abscess, renal failure, prosthetic valve endocarditis and persistent sepsis were prognostic factors for mortality independence. So can you comment on that?

Dr Regesta: In our study only preoperative shock and abscess involving both the mitral and aortic annuluses emerged as predictors of operative mortality by Cox regression analysis. Age and recurrent infective endocarditis were the only two predictors of late death. We examined a large number of variables to determine their role in the clinical outcomes but only those mentioned above were statistically significant by Cox regression analysis. This is probably due to the relatively small sample size.

Dr K. Gigliashvili (Kutaisi, Georgia): My question is about what was the reason of ascending aortic surgery in 4% of your cases?

Dr Regesta: The ascending aorta was replaced because of aneurismal dilation. The aortic root was replaced more often because the abscess had destroyed one or more aortic sinuses.

Dr M. Naliato (Milan, Italy): So let us follow your conclusions. You have told us that sepsis or shock is an independent risk factor. What do you think? In my opinion that it is wisdom to treat the patient, to treat the shock at first, and after then to go to the surgery. What do you think about it?

Dr Regesta: As I mentioned, this study is a retrospective review of prospectively collected data and we could not determine what went on through the surgeon’s mind when the patients were taken to the operating room. Twenty-three patients were in cardiogenic and/or septic shock when...
operated on because of failure of medical therapy. I don’t believe that further medical therapy would be of value if it had already failed.

Dr Naliato: Okay, but shock comes from two sources: one is cardiogenic and the other is from the sepsis.

Dr Regesta: Yes.

Dr Naliato: So sepsis or shock is a very threatening situation and it can cause multiorgan failure. Then from your data and from your conclusion, and I think that it is reality, that at first treating the shock and after then to go forward and to do the operation.

Dr Regesta: Indeed many patients died in multi-organ failure. However, when the operative mortality was examined using multivariate analysis, only preoperative shock and double valve annular abscess emerged as independent predictors of operative death.