Endocarditis in the elderly: clinical, echocardiographic, and prognostic features

Giovanni Di Salvoa,b, Franck Thunya, Valerie Rosenbergc, Valeria Pergolaa,b, Olivier Belliardc, Geneviève Derumeauxd, Ariel Cohenc, Diana Iarussib, Roch Giorgie, Jean-Paul Casaltaf, Pio Casob, Gilbert Habibab*

aService de Cardiologie B, la Timone Hospital, Marseille, France
bInstitute of Cardiology, second University of Naples, Italy
cService de Cardiologie, Saint-Antoine Hospital, Paris, France
dService de Cardiologie, Charles Nicolle Hospital, Rouen, France
eDepartment of Statistics, la Timone Hospital, Marseille, France
fDepartment of infectious diseases, la Timone Hospital, Marseille, France

Received 26 January 2003; received in revised form 5 May 2003; accepted 21 May 2003

Aims Infective endocarditis (IE) is more and more frequent in elderly persons and it has been associated with various clinical, bacteriological, and prognostic features. The aim of the study was to define the clinical, echographic, and prognostic characteristics of IE in a large population of elderly patients from four European centres (three French, one Italian).

Methods and results Three hundred and fifteen consecutive patients with definite IE underwent clinical evaluation, echocardiography, blood cultures, and follow-up. Patients were separated into three groups: group A: 117 patients aged <50 years, group B: 111 patients aged >50 and <70 years, group C: 87 patients aged >70 years.

Elderly patients (group C) presented more frequently than other groups with digestive or urinary portal of entry, pacemaker endocarditis, and anaemia. S bovis endocarditis was less frequent and S aureus endocarditis more frequent in younger (group A) patients than in other groups. No difference was observed among groups concerning echocardiographic data as well as the incidence and localization of embolic events.

Elderly patients were operated on as frequently as younger patients and their operative risk was similar in other groups (11%, 3%, and 5% in groups C, B, and A, respectively, P=ns). Overall mortality in elderly patients was low (17%) but significantly higher than in younger patients (10% in group A, 7% in group B, P=0.02). By multivariate analysis, the only risk factors for in-hospital mortality were age (P=0.003), prosthetic valve (P=0.002), and cerebral embolism (P=0.006). Conversely, surgical management was associated with a lower in hospital mortality (P=0.03).

Conclusions In this largest series of elderly patients with IE, IE in elderly carries specific features when compared with younger patients, although the echographic characteristics and embolic risk are similar. The overall mortality rate in elderly patients is higher than in younger, but the mortality in operated patients is low and similar than that of younger patients

© 2003 Published by Elsevier Ltd on behalf of The European Society of Cardiology.

KEYWORDS
Endocarditis; Echocardiography; Surgery; Elderly

* Corresponding author: Dr G. Habib, Hopital la Timone, Service de Cardiologie B, Boulevard Jean Moulin, 13005 Marseille, France.
Tel.: +0491387588; fax : +0491474377
E-mail address : gilbert.habib@ap-hm.fr (G. Habib).
Introduction

The incidence of infective endocarditis (IE) does not appear to have declined in recent years, ranging from 10 to 50 cases/million inhabitants a year and the increased life span in the industrialized world, make elderly people an increasing proportion of patients with IE.1,2

Previous reports showed that IE in advanced age was associated with a more severe prognosis1,2 and with a high occurrence of complications.3 This more severe clinical course has been related to less severe initial symptoms and delayed diagnosis in elderly people3,4 and to the greatest incidence of more aggressive pathogens in this population.2,3 Conversely, other authors found no difference in clinical presentation and outcome of endocarditis between elderly and younger patients.1,3,5,6

The causes for these conflicting results are multiple, including the use of transthoracic (TEE) vs transesophageal echocardiography (TEE),4,5 various diagnostic criteria,3,4 inclusion of patients with prosthetic4 valves or not,5,6 and the relatively small number of elderly patients included in some studies.

The aim of our study was to compare clinical, echocardiographic and prognostic features of patients older than 70 with those of younger patients, including prosthetic valve endocarditis, in a large sample of patients with IE definite by Duke criteria,7 using multiplane TEE.

Materials and methods

Patients

Among patients referred to our centres for suspected IE between September 1993 and January 2002, three hundred and fifteen consecutive patients (228 men and 87 women, mean age 56±17 years, age range 17–88 years) fulfilled the diagnosis for definite IE using Duke criteria7 and formed our study population. Patients have been recruited in four European centers (55%, 27%, 9%, and 9% from Marseille, Paris, Naples, and Rouen, respectively). Patients mean age was 57±15, 57±18, 50±18, and 61±15 years, respectively. Surgically treated patients were 57%, 28%, 47%, and 57%, respectively in these centres. Operative techniques were similar between centers.

Of these, 185 patients had a pathologic confirmation by surgery or necropsy. Patients were separated into three groups: group A included 117 (37%) patients younger than 50 years [80 male and 37 female, mean age 37±8 years], group B included 111 (35%) patients aged 50 to 70 years [97 male and 14 female, mean age 60±6 years], and group C included 87 (28%) patients older than 70 years [51 male and 36 female, mean age 77±4 years, of them 23 (29%) patients were over 80 years].

Clinical data

For each group the following explanatory variables were analyzed: fever, new or changing murmur; immunological manifestations (Oster’s nodes, Roth spots); biological markers (anaemia [haemoglobin <10 g/dl], leukocytosis [white blood cell count >10000/μl]; C reactive protein >5 mg/l; renal failure [serum creatinine >2 mg/dl]), delay to diagnosis, defined as delay between the onset of symptoms and correct diagnosis; As the end-points of interest were studied: major complications occurring during acute IE: embolic events (based on clinical signs and data derived from non invasive diagnostic procedures), congestive heart failure (New York Heart Association classes III–IV), need for cardiac surgery, in-hospital mortality, in-hospital mortality after medical treatment and after cardiac surgery.

Blood cultures

All patients had an ‘endocarditis diagnostic kit’ using an automate (Bac tert Becton Dickinson, Spars, Maryland) including standard blood culture (BC) and special samples for isolation of intracellular pathogens, and for various specific antibodies.8 Additional BC was systematically performed if the temperature was >38.5°C and cultures of the leads and of the pacemaker device were systematically obtained in patients with IE on pacemaker leads.

Echocardiographic study

All patients underwent transthoracic as well as transesophageal examinations using commercially available devices, allowing multiplane TEE studies. All echocardiographic studies were performed during the acute phase of IE without any complications. Definition of vegetations, abscesses, major and minor echocardiographic criteria have been detailed elsewhere.7,9 Similarly, the method of assessment of vegetations characteristics, including size and mobility) has been previously described.10

Surgical management

Surgery was performed in 152 patients (48%). The indications for surgery included acute aortic or mitral insufficiency in 29% of patients, severe heart failure in 22%, large persistent vegetation after systemic embolization or associated with significant valvular regurgitation in 26%, and abscess or perivalvular involvement in 23% patients. The surgical procedures were valve replacement in 130 patients (85%), and conservative surgery in 22 (15%) patients. Conservative surgery was performed in 11/117 (9%) group A patients, 9/111 (8%) group B, and 2/87 (2%) group C patients. Of the 152 operated patients, 113 (74%) were operated on while on antibiotic treatment (Group A: 42%, Group B: 41% and Group C: 17%) and 52 (34%) underwent surgery within the first fifteen days after the diagnosis of IE (group A: 43%, group B 41% and group C 16%).

Statistical analysis

All analyses were performed using a commercially available package (SPSS for Windows, Rel 10.0.1999.Chicago: SPSS Inc). The occurrence of the different explanatory variables as well as the end-point of interest (in-hospital mortality, in-hospital mortality after medical treatment, in hospital mortality after cardiac surgery) in the three studied groups were compared using χ² test. Fisher’s exact test (two tails) was used if the expected count in any cell was <5. Continuous variables (delay to diagnosis) were compared using ANOVA and Bonferroni’s post-hoc test. Both overall and pairwise comparisons (group C vs group A+group B) were performed. No adjustment was made for the multiple tests of significance. In addition, a multivariate analysis was performed using a forward stepwise logistic regression using likelihood ratio test, with P values at 0.10 as the threshold for entering or removing variables. The logistic regression model was elaborated from variables identified by univariate analysis and from a priori selected clinically relevant variables (age, prosthetic valve IE, surgery, embolic events, cerebral embolism,
New York Heart Association classes III–IV, renal failure, abscess, *streptococcus bovis* and *staphylococcus aureus*). A *P* value <0.05 was considered statistically significant.

**Results**

**Predisposing cardiac conditions**

The occurrence of predisposing heart disease was similar among groups (Table 1). The localization of native valve endocarditis was mitral, aortic, and tricuspid, in 33%, 39%, and 14%, respectively. Multiple valve endocarditis was observed in 9% of patients. Incidence of prosthetic valve endocarditis was similar between groups, but pacemaker endocarditis was more frequent in group C than in other groups. A digestive presumed portal of entry was more commonly detected in group C (19%) and in group B (16%) than in younger (5%), *P*<0.0001. Similarly, urinary presumed portal of entry was more frequent in group C (13%) than in other groups (group A 2%, group B 6%, *P*<0.005). Conversely, intravenous drug abusers were present exclusively in group A (15%, *P*<0.0001).

** Infective microorganisms**

The most frequent isolated pathogens were *Streptococci* in 45% (Table 2). The proportion of *S. bovis* IE was higher in group B and C than in group A (*P*<0.001), while *S. aureus* was more frequent in young patients.

**Clinical and laboratory data are shown on Table 3**

Clinical features were similar between groups, including incidence of fever, new murmur and splenomegaly. Only Osler’s nodes were less frequently observed in older patients. Other symptoms and biological markers were similar between groups, except anaemia, which occurred more frequently in group B and C than in group A. Conversely, the delay to diagnosis was similar between groups, (group A: median of 20 days; group B: median of
22 days; group C: median of 27 days, \( P=\text{ns} \), as were the incidence and localization of embolic events.

**Echocardiographic data**

Echocardiographic data are presented in Table 4. Vegetations were observed in 227 (72%) patients, abscesses in 53 (17%) patients, new periprosthetic regurgitation in 16 (5%) patients and aneurysm or valvular perforation in 24 (8%) patients. In 20 patients (6%), only a minor echocardiographic criterion was observed (valvular thickening, or nonoscillating mass). No difference was observed between groups concerning echocardiographic data (Table 4).

**Therapeutic options and outcome**

Table 5 summarizes the therapeutic options and outcomes in the three patient groups. The overall mortality was clearly higher in elderly (17%) than in younger patients (10% in group A, 7% in group B, \( P=0.02 \)). Surgical treatment was performed slightly less frequently in group C than in other groups, although 41% of elderly patients were operated on. Mortality was relatively high in non-operated elderly patients (21%), but only 11% in elderly patients who could be treated with surgical therapy. The operative risk was similar in elderly than in younger patients in this situation. For the whole population, mortality was lower in operated patients than in patients treated with antibiotic alone (6% vs 15%, respectively, \( P=0.04 \)).

Among the 51 non operated elderly patients, seven (14%) patients had undisputed indication for surgery (severe heart failure, persistent sepsis or multiple embolisms). Of them, five were not considered good candidates for surgery because of very poor general condition and two declined surgery.

In patients with prosthetic valve IE, mortality was significantly higher than in the remaining population (20% vs 9%, \( P=0.01 \)). Conversely, mortality in patients with pacemaker IE (5%) was similar to that of patients with native valve IE (9%).

**Logistic regression analysis**

To determine which factors are important predictors of in-hospital mortality in the whole study population, a logistic regression analysis was performed including age, prosthetic valve IE, abscesses, IVDA, pacemaker IE,
anaemia, leucocytosis, embolic events, cerebral embolism, renal failure, New York Heart Association classes III–IV, surgery, S. aureus IE and S. Bovis IE. Using a stepwise procedure, the following independent risk factors for in-hospital mortality were identified: age, as continuous variable, \((P=0.003)\), prosthetic valve \((P=0.002)\), and cerebral embolism \((P=0.006)\). Conversely, surgical management was associated with a lower in hospital mortality \((P=0.03)\) (Table 6).

**Discussion**

This study is the largest published series on infective endocarditis in elderly patients. The main results are: (1) although IE in elderly is quite similar than in younger patients, it carries some specific clinical and biological features; (2) the prognosis of IE is worse in elderly patients than in younger, age being an independent prognostic factor for in-hospital mortality; (3) surgical treatment is frequently performed in elderly patients with an operative risk similar than in younger patients.

**Predisposing cardiac conditions and portal of entry**

The repartition of predisposing heart disease was similar among groups (Table 1). This result is in accordance with previous studies. Selton-Suty\(^1\) found a particular occurrence of IE on prosthetic devices in elderly patients. In our study however, the incidence of prosthetic valve endocarditis was similar between groups, but pacemaker endocarditis was more frequent in elderly patients, similar to their data.\(^1\) Pacemaker endocarditis has been associated with a more difficult and delayed diagnosis\(^11\) and worse prognosis. The relatively high frequency of pacemaker endocarditis in our series may partly explain the worse prognosis in these patients.

A digestive presumed portal of entry was more commonly detected in elderly patients in our series. This result is in agreement with some series,\(^4\) but differs from others.\(^5,6\) However, this result is in accordance with the high incidence of \(S\) bovis endocarditis in our series. \(S\) bovis is an increasing cause of endocarditis, especially in elderly patients,\(^12\) and has been associated with colonic disease, older age, multiple valve involvement, and high embolic risk.\(^13,14\) The high incidence of \(S\) bovis in our population may be related to the high incidence of colonic lesions in elderly patients. In our series however, \(S\) bovis IE was clearly more frequent in elderly (16\%) than in young patients (group A: 5\%), but was also frequently observed in middle-aged patients (group B: 22\%). Similarly, urinary presumed portal of entry was more frequent in older patients, probably for the high rate of procedures involving the urethra and prostatic bed. Conversely, the higher frequency of \(S\) aureus endocarditis in younger patients is related to the more frequent intravenous drug abuse in this population.

**Clinical and laboratory features of IE in elderly**

In our study, clinical and laboratory features did not differ between elderly and younger patients, except for Osler’s nodes and anaemia. Fever has been reported to be less frequent in elderly,\(^3,4\) but not in more recent series.\(^5,6\) Similarly, a longer delay to diagnosis was observed in some series, but not in other.\(^4\) However, in our series, none of these two features were observed. Anaemia was very common in elderly patients, probably

<table>
<thead>
<tr>
<th>Table 5 Therapeutic options and outcome; number (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
</tr>
<tr>
<td>(n=315)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Operated patients</td>
</tr>
<tr>
<td>In-hospital mortality after medical treatment</td>
</tr>
<tr>
<td>In-hospital mortality after cardiac surgery</td>
</tr>
</tbody>
</table>

\(^a\)P values of the test based on the comparison between the three age groups.

\(^b\)P values of the test based on the comparison of group C vs groups A and B.

<table>
<thead>
<tr>
<th>Table 6 Multivariate analysis: predictors of in-hospital mortality among 315 patients with IE(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Embolic events</td>
</tr>
<tr>
<td>Cerebral embolism</td>
</tr>
<tr>
<td>Prosthetic valve IE</td>
</tr>
<tr>
<td>Abscess</td>
</tr>
<tr>
<td>Absence of surgery</td>
</tr>
<tr>
<td>Streptococcus bovis</td>
</tr>
<tr>
<td>Staphylococcus Aureus</td>
</tr>
<tr>
<td>NYHA III-IV</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Leucocytosis</td>
</tr>
<tr>
<td>&gt;10000/mcl</td>
</tr>
<tr>
<td>Pacemaker IE</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
</tbody>
</table>

\(^a\)Multivariate analysis was performed using a forward stepwise logistic regression using likelihood ratio test.
<table>
<thead>
<tr>
<th>Authors</th>
<th>TTE/TEE</th>
<th>Total (n)</th>
<th>Age of elderly (yr)</th>
<th>Prosthetic IE elderly (%)</th>
<th>EEa elderly (%)</th>
<th>RFb elderly (%)</th>
<th>HFc elderly (%)</th>
<th>Surgery elderly (%)</th>
<th>In-hospital death elderly (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terpenning et al. (3)</td>
<td>TTE</td>
<td>144</td>
<td>&gt;60 years</td>
<td>49</td>
<td>28</td>
<td>46</td>
<td>13</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Werner et al. (4)</td>
<td>TTE/TEE</td>
<td>104</td>
<td>&gt;70 years</td>
<td>20</td>
<td>30</td>
<td>25</td>
<td>na</td>
<td>d</td>
<td>nad</td>
</tr>
<tr>
<td>Selton-Suty et al. (1)</td>
<td>na</td>
<td>114</td>
<td>&gt;70 years</td>
<td>25</td>
<td>36</td>
<td>8</td>
<td>na</td>
<td>d</td>
<td>nad</td>
</tr>
<tr>
<td>Gagliardi et al. (5)</td>
<td>TTE/TEE</td>
<td>108</td>
<td>&gt;65 years</td>
<td>24</td>
<td>25</td>
<td>36</td>
<td>36</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Netzer et al. (6)</td>
<td>na</td>
<td>135</td>
<td>&gt;65 years</td>
<td>24</td>
<td>28</td>
<td>36</td>
<td>45</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Present study</td>
<td>TEE</td>
<td>315</td>
<td>&gt;70 years</td>
<td>87</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>

*EE = embolic events.
*RF = renal failure.
*HF = heart failure.
*na = not available.
related to the high incidence of bowel lesions in these patients, and in accordance with the high proportion of *S. bovis* endocarditis in elderly.

**Echocardiographic data**

Echocardiography plays a key role in the diagnosis and management of infective endocarditis. Transesophageal echocardiography is useful for both the diagnosis of IE and the prediction of embolic risk. Patients with vegetations larger than 15 mm have been associated with an increased embolic risk and a worse prognosis. Werner showed that the detection rate of vegetations by TTE was lower in older patients, and recommend the use of TEE in these patients. In our study, the occurrence of vegetations and other major echocardiographic criteria was similar among young, middle age and elderly patients, demonstrating the high sensitivity of TEE and the importance of performing early TEE in elderly people with suspected IE. The vegetations in elderly have been reported to be smaller and to carry a lower embolic risk. In these latter series however, TEE was not performed in all patients, and the number of embolic events was low. In our study however, TEE was performed in all patients, and the vegetation characteristics were similar between young and older patients. The similar incidence of embolic events we observed in elderly as compared with young patients is in agreement with Terpenning et al., Gagliardi et al. and Netzer et al. This finding is consistent with the comparable presence among elderly and young patients of large and mobile vegetations which carry a high embolic risk.

**In-hospital mortality**

The main result of our series is that in-hospital mortality is higher in elderly patients than in younger. The true influence of age on outcome in endocarditis is still debated. Although older series showed that advanced age was associated with a worse prognosis, more recent series gave conflicting results. Selton-Suty et al. compared 25 old patients with 89 younger (>70 years). Mortality was higher in older patients than in younger (28% vs 13.5%) and age appeared as an independent risk factor for mortality by multivariate analysis. Similarly, Netzer et al. found a higher mortality rate in 53 elderly patients (>65 years) as compared with 82 younger patients (60 years) (25 vs 11%, P<0.04), but this difference was no longer significant after multivariate analysis. Conversely, age did not appear as a prognostic marker in the series of Gagliardi et al. and Werner et al. These conflicting results may be explained by several factors: the definition itself of elderly patient may vary among studies (>60 or 65 years in some series, >70 years in others); the inclusion of or not of patients with prosthetic valve IE may alter the outcome of the elderly patients. Finally, and more important, the number of elderly patients studied was often small, as well as was the number of deaths (Table 7). The latter point may both limit the conclusions of some studies, and explain the discrepancies between them.

Our study overcomes all of these limitations. A large number of patients with strict diagnostic criteria were studied, and all of them underwent both clinical evaluation and TEE. All elderly patients with IE were studied without exclusion of prosthetic endocarditis which represents a significant part of IE in elderly. The large number of patients studied in our series allow us to draw two main conclusions concerning treatment and outcome in elderly patients with IE.

First, age clearly predicts a higher mortality in patients with endocarditis. In-hospital death was more frequent in elderly than in younger patients, and multivariate analysis identified age as an independent predictor of mortality, as well as were cerebral embolism and prosthetic endocarditis.

Second, surgical treatment appears as a reasonable option in elderly. Surgical management was associated with good prognosis in our study. For the whole population, the in-hospital mortality was lower in operated patients than in those treated with antibiotic alone; in addition, surgical treatment appeared as an independent factor of good prognosis by multivariate analysis. Other studies found higher in-hospital mortality despite similar surgical management. However, the mortality rate we observed is similar to that observed in other studies in which early surgery was extensively performed.

In our series, although mortality was higher in elderly than in other groups, elderly patients who could be operated on had very good outcome (11% mortality), similar to that of younger patients. Although only seven elderly patients with undisputed indication for surgery were not operated on, we cannot exclude that this relatively low in-hospital mortality could be partially explained by this selection.

**Study limitations**

There are a number of limitations to the current study. First, our study was retrospective and was performed in referral centers, which may introduce a referral bias as regards diagnosis, management of patients, delay before diagnosis, performance of blood cultures before antibiotic treatment and use of surgery. Second, the inclusion of intravenous drug abusers and prosthetic valve endocarditis may have influenced our results. However, no case of IVDA was observed in elderly patients, and prosthetic endocarditis was equally frequent in the three groups. Third, although our study suggested a benefit for early surgery in elderly patients, this point was not specifically addressed by our study. We can only conclude that in our large sample, surgical management was associated with a low mortality risk. The true benefit of early operation to reduce mortality in these patients need follow up studies. Finally, we believe that some discrepancies between studies may not be explained by methodological differences only, but perhaps more important by the differences in the endocarditis population itself; the epidemiological spectrum of endocarditis is changing with time, and may be different among different countries; for example, the proportion of *S. bovis* endocarditis is high in France, but not in United States, even in an elderly population. The cause for
these differences between countries is not clear but may account for apparently discordant data in the elderly.

Clinical implications

Our study demonstrates that although IE in the elderly is quite similar than in younger patients, it carries some specific clinical and biological features, including higher incidence of pacemaker infection, anaemia and digestive or urinary portal of entry. Vegetation characteristics, as defined by TEE, are similar in the elderly than in the younger patient, as is the embolic risk. Advanced age is associated with a higher in-hospital mortality rate as compared to younger patients, but selected elderly patients who could be treated by surgical therapy present with a low mortality, similar to that of younger patients.

References