Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study

Franck Thuny¹, Jean-François Avierinos¹, Christophe Tribouilloy², Roch Giorgi³, Jean-Paul Casalta⁴, Loïc Milandre⁵, Amel Brahim², Georges Nadji², Alberto Riberi⁶, Frédéric Collart⁶, Sebastien Renard¹, Didier Raoult⁴, and Gilbert Habib¹*

¹Department of Cardiology, Hôpital de La Timone, Boulevard Jean Moulin, 13005 Marseille, France; ²Department of Cardiology, South Hospital, Amiens, France; ³Department of Statistics, La Timone Hospital, Marseille, France; ⁴Department of Microbiology, La Timone Hospital, Marseille, France; ⁵Department of Neurology, La Timone Hospital, Marseille, France; and ⁶Department of Cardiothoracic Surgery, La Timone Hospital, Marseille, France

Received 29 October 2006; revised 27 January 2006; accepted 7 February 2007; online publish-ahead-of-print 15 March 2007

Aims To analyse the risk of death according to the type of cerebrovascular complications (CVC) during infective endocarditis (IE) and to analyse the determinants of outcome in patients with IE and a CVC.

Methods and results In two referral centres, 496 consecutive patients with definite IE were prospectively included. Cerebral CT scan was performed in 453 patients. During a mean 2.9 year follow-up, 139 (28%) patients died and CVC occurred in 109 (22%) patients. Stroke was an independent predictor of death, although no significant excess mortality was observed in patients with silent CVC or transient ischaemic attack (TIA). Among CVC patients, mortality was predicted by the presence of a mechanical prosthetic valve IE and a low Glasgow Coma Scale. When valvular surgery was performed in patients after CVC, neurologic exacerbation was rare [4 (6.3%) patients] and was observed only in patients with symptomatic stroke. Among CVC patients, survival was better in operated patients when compared with patients treated conservatively despite theoretical indication for surgery (P < 0.0001). However, the latter group had more comorbidities (P = 0.007) and a lower Glasgow Coma Scale (14.6 ± 1 vs. 12 ± 4, P < 0.0001).

Conclusion Patients with silent CVC or TIA have a relatively good prognosis, whereas those with stroke have significant excess mortality particularly in case of mechanical prosthetic valve IE or impaired consciousness. Valvular surgery can be safely performed after silent CVC or TIA and may improve survival in selected patients with stroke.

KEYWORDS Endocarditis; Stroke; Embolism; Surgery; Mortality

Introduction

Brain injuries occur in 20–40%¹–³ of patients during the active course of infective endocarditis (IE) and are mainly the consequence of vegetation embolization or ruptured mycotic aneurysm. Whereas most of these cerebrovascular complications (CVC) are symptomatic, including transient ischaemic attack (TIA), ischaemic stroke, or intracerebral haemorrhage, an increasing number of silent cerebral embolisms is diagnosed by systematic cerebral imaging. Although previous reports demonstrated excess mortality related to symptomatic ischaemic stroke⁴,⁵ or intracerebral haemorrhage,⁴,⁶,⁷ the prognostic impact of silent cerebral embolism or TIA has never been analysed. In addition, the determinants of outcome after a first CVC are unknown and the risk of neurologic exacerbation related to valvular surgery is still debated.⁸–¹⁰

To resolve these issues, we undertook a large multicentre prospective study in two French referral centres, including patients with definite diagnosis of IE by current diagnostic criteria and with systematic screening for neurologic complications. Our objectives were to analyse the risk of death according to the type of CVC, including silent CVC and TIA, and to analyse the determinants of outcome in patients with IE and a CVC.

Methods

Inclusion criteria

From January 1990 to March 2005, all consecutive patients admitted in two French referral centres with a suspected diagnosis of IE were eligible for the study entry (n = 545). The only exclusion criterion was pacemaker IE (n = 49). Written informed consent was obtained from all participating patients, as required by the institutional review board under an approved protocol. Monthly screening of echocardiography and microbiology databases of all patients

* Corresponding author: Tel: +33 4 91 38 75 88. E-mail address: gilbert.habib@free.fr

© The European Society of Cardiology 2007. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
hospitalized for suspected IE was performed by each centre to ensure that a consecutive sample of all definite diagnoses was obtained. Blood cultures, serologic assessment, transthoracic and transoesophageal echocardiography (TEE) were systematically performed within 48 h of admission. Patients with definite IE according to the Duke criteria\(^1\) formed the final prospective cohort (n = 496). No patient initially included was excluded from analyses after initial assessment. Cerebral computed tomography (CT) scan was systematically performed on admission since 1993 (453 patients) and was repeated if clinically indicated. Antibiotic therapy was started immediately after diagnosis.

**Clinical and echocardiographic data**

The following clinical and biological parameters were prospectively collected at diagnosis and during hospitalization: age, sex, underlying heart disease, intravenous drug abuse, HIV infection, diabetes, history of cancer, comorbidity,\(^12\) congestive heart failure (CHF),\(^13\) the Glasgow Coma Scale,\(^14\) serum creatinine, and oral anticoagulant therapy on admission.

Diagnosis of CVC was based on clinical and CT scan data, or both. CVC included stroke, TIA, and silent cerebral embolism. Ischaemic stroke was defined as the persistence for > 24 h of a focal neurologic deficit caused by altered circulation of the cerebral hemispheres, brain stem, or cerebellum with or without CT or MRI scan documentation.\(^15\) TIA was defined as focal neurologic symptoms of sudden occurrence and rapid resolution ( < 24 h) related to altered circulation of the brain.\(^16\) Silent cerebral embolism was detected by cerebral CT scan performed within 48 h of admission. Haemorrhagic strokes included primary intracerebral haemorrhage, haemorrhagic infarction, and subarachnoid haemorrhage, which were diagnosed as previously described.\(^17–19\) Diagnosis of CVC was confirmed during the clinical course by an experienced neurologist who was unaware of the microbiological and echocardiographic findings. In patients with CVC complicating mechanical prosthetic valve IE, oral anticoagulation was discontinued, replaced by heparin, and the activated partial thromboplastin time closely monitored. When surgery was indicated, cerebral CT scan was systematically performed within 24 h before.

TTE and TEE were performed in all cases, as previously reported.\(^20\) Echocardiographic data included presence and maximal length of vegetations. The measurements of vegetation length were performed in various planes, and the maximal length was used. In the presence of multiple vegetations, the largest length was used for analysis. Abscess was defined as a thickened area or mass with a heterogeneous echogetic or echolucent appearance.\(^21\) Valvular regurgitations were assessed semiquantitatively.\(^22,23\)

**Endpoints**

Endpoints were overall mortality, neurologic mortality, and postoperative neurologic exacerbation. Neurologic death was defined as a death which was a direct consequence of the brain lesions induced by the CVC. Postoperative neurologic exacerbation was defined as either postoperative neurologic death or non-fatal postoperative clinical increase of cerebral damages. The follow-up information was obtained from December 2005 to January 2006 by medical records and contacting the patients’ physicians.

**Statistical analysis**

For categorical variables, the relation between a variable and an event was studied by \(\chi^2\) test or Fisher’s exact test (two-tailed) if the expect count in any cell was < 5. Student’s \(t\)-test or Mann-Whitney \(U\) test was used for continuous variables. Continuous variable was expressed as mean ± SD or median. Survival curves were obtained by the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards model was used to calculate adjusted hazards ratio (HR) and their 95% confidence intervals (95% CI). The proportional hazards and the linearity assumptions were assessed using residuals methods, as proposed by Therneau and Grambsch.\(^24\) For all analyses, valvular surgery was considered as a time-dependent covariable and results were systematically adjusted for this covariable.

All statistical tests were two-sided. For the single-variable analysis, \(P\)-values less than 0.05 were considered as statistically significant. When we have considered the impact of the presence and type of CVC on mortality, multivariable analysis was systematically adjusted for the main prognostic factors on the basis of epidemiological knowledge (i.e. age, sex, comorbidity, CHF, Staphylococcus aureus, abscess, vegetation length, prosthetic valve IE, serum creatinine, and valvular surgery). On the other hand, when endpoints of interest were overall mortality or neurologic mortality after CVC, we tested only the few relevant variables known to be important predictors of outcome (i.e. age, comorbidity, mechanical prosthetic valve IE, CHF, S. aureus, and Glasgow Coma Scale). Then, multivariable model was based only on variables significant in the single-variable analysis, with a systematic adjustment for valvular surgery. Furthermore, predictors correlated in single-variable analysis were not considered for the final model. This strategy was used in order to decrease the probability to include predictors by chance. Analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and S-PLUS software (version 6.2, Insightful Corp., Seattle, WA, USA).

**Results**

**Baseline characteristics**

Among the 496 patients with a definite diagnosis of IE on admission, 393 had two major clinical Duke criteria and 103 had one major and three minor criteria. Baseline patient features are reported in Table 1 and microbiological data in Table 2. Mean age was 58 ± 16 years (range 17–90 years), and 222 patients (45%) presented with \(\geq 1\) embolic event.

**Cerebrovascular complications characteristics**

CVCs occurred in 109 patients (22.2%) during the active phase of IE, with the same rate in the native valve vs. prosthetic valve IE (Table 1) \((P = 0.96)\). CVC were more frequent in patients with mitral valve IE (Table 1) \((P = 0.02)\).

A silent cerebral embolism was present in 17/453 patients (3.8%). CVC was evident before antibiotics were started in 78 patients (16%) and occurred during antibiotic therapy in 31 patients (6.3%) after a median time of 4 days (range 1–21) after institution of antibiotics. Of the 50 patients (10%) with ischaemic stroke, seven (14%) had a haemorrhagic infarction. Recurrent ischaemic stroke was observed in only two patients (0.4%). TIA occurred in 30 patients (6%) and primary intracerebral haemorrhage in 12 patients (2.4%). Among the 19 patients with intracerebral haematoma, cerebral angiogram was performed in 13 patients. Mycotic aneurysm was present in seven patients with primary cerebral haemorrhage and in two with a haemorrhagic infarction. Among these patients, aneurysm rupture occurred during antibiotic therapy in three patients, respectively at 2, 18, and 21 days.

The rate of symptomatic cerebral embolisms (TIA and ischaemic strokes) occurring after the beginning of antibiotic therapy (and after the first echo) was significantly higher in patients with vegetation length \(> 10 \text{mm}\) than in those with vegetation length \(\leq 10 \text{mm}\) [8% (20/247) vs. 3.2% (8/249), \(P = 0.03\)].
Impact of the presence and type of cerebrovascular complications on mortality

The median follow-up was 2.9 years (interquartile range 1.4–5.8 years). Of the 496 patients, four were lost to follow-up (one with a silent CVC, one after a TIA, one after an ischaemic stroke, and one without CVC), 59 (12%) died during their hospitalization, and 80 (16%) after dismissal. Six month, 1 year, and 5 year cumulative mortality rates were 22, 25, and 38%, respectively, in the CVC group vs. 16, 19, and 31% in the no-CVC group (HR = 1.8; 95% CI 1.09–2.43; P = 0.02) (Figure 1). Stroke remained predictor of death after adjustment for age, sex, comorbidity, CHF, S. aureus, abscess, vegetation length, prosthetic valve IE, serum creatinine, and valvular surgery (HR = 1.6; 95% CI, 1.02–2.65; P = 0.04).

Determinants of outcome after cerebrovascular complications

Among the 106 followed patients with CVC, 33 patients (31%) died after a median time of 50 days (range 2–1308). Multivariable analysis identified the Glasgow Coma Scale and the treatment without valvular surgery as predictors of overall mortality (Table 3). Thirteen patients (12%) died from neurologic causes after a median time of 16 days.
postoperative neurologic exacerbation. None of them had had silent cerebral embolism or a TIA before surgery.

Among the 46 patients with CVC who were only medically treated (conservative treatment), 27 (59%) had at least one theoretical indication for surgery [persistent >10 mm vegetation (n = 27), CHF (n = 10), abscess (n = 8)], but were not operated on for the following reasons: death before operation (n = 11), large and/or haemorrhagic strokes (n = 8), severe comorbidity (comorbidity index ≥ 2) (n = 4), or favourable outcome under medical treatment (n = 2). These patients presented with an excess mortality rate when compared with the surgical group (Figure 3). However, when compared with patients who underwent surgery, they had more comorbidities (P = 0.007) and a lower Glasgow Coma Scale (mean ± SD, 14.6 ± 1 vs. 12 ± 4, P < 0.0001).

Discussion

The present study shows that, during IE, (1) mortality depends on the type of CVC. Although stroke is a strong predictor of mortality, silent CVC or TIA is not associated with excess mortality; (2) after a first CVC, a low Glasgow Coma Scale and a mechanical prosthetic valve IE predict mortality. Valvular surgery can be safely performed after silent CVC or TIA and may improve survival in selected patients with symptomatic stroke.

Cerebrovascular complications of infective endocarditis

The incidence of neurologic events complicating IE has been analysed by several previous studies. However, most of these publications were retrospective, included heterogeneous samples, with no standardized diagnostic criteria either for endocarditis or for neurologic complications. Moreover, some cerebral embolisms might remain unrecognized because resulting symptoms were silent. To our knowledge, the present study is the first to prospectively include a large sample of patients with only definite diagnosis of IE according to Duke criteria, and to investigate all CVC, including silent cerebral embolisms. The 22% incidence of CVC we observed in our series is consistent with earlier works involving patients with IE. The 10% rate of stroke in our study is lower than historical rates, but consistent with the large recent series of Anderson et al. in which IE and stroke were confirmed by the application of strict definitions. Finally, we found CVC to occur after initiation of antibiotic therapy in only 6.3% patients. This result is in agreement with the study of Heiro et al., who reported that neurologic manifestations occurred in 25% of patients with definite or possible IE and that only 6% occurred after initiation of antibiotics.

Impact of cerebrovascular complications on outcome

Many previous studies showed that neurologic complications are associated with increased mortality during IE. However, most of these series included both CVC and non-specific complications such as encephalopathies, seizures, and headaches. None of these studies specifically investigated the risk of death according to the type of CVC, including silent cerebral embolisms.

Influence of valvular surgery on outcome in patients with cerebrovascular complications

Valvular surgery was performed in 63 of 109 patients with CVC (58%). Patients were operated on at a median time of 9 days (range 0–2146) after a symptomatic CVC. Among patients operated on after a previous CVC, surgery was performed within 72 h in 17% (3/18) after a TIA, in 17% (5/29) after an ischaemic stroke, and in only one patient after a primary cerebral haemorrhage. Therapeutic strategies and outcome according to the type of CVC are summarized in Figure 2.

Operative mortality in patients with CVC was 4.8% (3.3% after silent CVC or TIA, and 6.1% after a stroke). Overall mortality did not differ significantly according to the delay between the occurrence of an ischaemic stroke and surgery (20% before 72 h vs. 12.5% after 72 h, P = 0.75). Four patients (6.3%) with CVC who underwent surgery had

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Predictors of overall and neurologic mortality after cerebrovascular complications by multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>0.80</td>
</tr>
<tr>
<td>Valvular surgery</td>
<td>0.40</td>
</tr>
<tr>
<td>Neurologic mortality</td>
<td></td>
</tr>
<tr>
<td>Mechanical PVE</td>
<td>15.08</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>0.63</td>
</tr>
<tr>
<td>Valvular surgery</td>
<td>0.27</td>
</tr>
</tbody>
</table>

PVE, prosthetic valve endocarditis.

(range 2–96). Neurologic deaths occurred more frequently in patients with more complicated CVC. No neurologic death occurred after a silent CVC or a TIA, and the rate of neurologic mortality was higher in case of a cerebral haemorrhage (32 vs. 8%, P = 0.006). By multivariable analysis, the Glasgow Coma Scale (HR = 0.63; 95% CI 0.53–0.75; P < 0.001) and mechanical valve prosthesis IE (HR = 15.08; 95% CI 2.78–81.82; P = 0.002) remained the only predictors of neurologic mortality after a first CVC (Table 3).

Figure 1 Overall mortality according to the type of cerebrovascular complications.

Figure 2 Neurologic mortality according to the type of cerebrovascular complications.

Figure 3 Impact of valvular surgery on outcome in patients with cerebrovascular complications.
In the present work, we demonstrated that the risk of death differs according to the type of CVC. Patients with only silent CVC or TIA had a better prognosis than patients with other CVC, and none of these patients died from neurologic causes. This result could be explained by the fact that the absence of large brain injuries carries a better prognosis and allows early surgery to be performed with a low operative risk. Conversely, we found that stroke was a strong predictor of mortality independent of the other prognostic factors, and that the first cause of death among patients with stroke was a direct consequence of this neurologic event. This result underlines the critical need to prevent embolic event during IE to avoid dramatic cerebral damages.

We found Glasgow Coma Scale and mechanic valve prosthesis IE to be the only predictors of neurologic mortality after a first CVC. The predictive value of a low Glasgow Coma Scale after a CVC was also observed in the large series of Hasbun et al., in which an abnormal mental status (lethargy, disorientation, and coma) was a strong predictor of 6 month mortality. The Glasgow Coma Scale indirectly reflects the severity of brain injuries. The predictive value of a mechanical prosthetic valve IE on the risk of neurologic death in patients with CVC could be explained by the potential deleterious effect of anticoagulant therapy in these patients. In the series of Tornos et al., an increased risk of intracerebral bleeding was reported in patients with CVC complicating IE who need anticoagulant therapy, particularly in case of S. aureus infection. They recommend stopping anticoagulant therapy in case of S. aureus IE until the septic phase of the disease is overcome, particularly after a stroke.

**Valvular surgery after cerebrovascular complications**

The impact of valvular surgery on outcome in patients with CVC in IE is largely debated because of lack of controlled studies. A major concern is the risk of postoperative neurologic exacerbation when surgery is performed early after the CVC because hypotension and total heparinization during cardiopulmonary bypass can worsen cerebral damages. Piper et al. found the risk of exacerbation to be low when surgery was performed within 72 h (when the blood-brain barrier is not yet altered). Conversely, Eishi et al. found that the risk of exacerbation of the

Figure 2 Therapeutic strategies and mortality according to the type of cerebrovascular complications.

Figure 3 Survival in patients with cerebrovascular complications and one or more indications for valvular surgery according to therapeutic strategy.
CVC was highest when surgery was performed early after the occurrence of the CVC and gradually decreased as the delay between CVC and operation increased. In their series, the exacerbation rate was 43.8% in patients requiring a cardiac operation within 7 days after cerebral infarction, but was only 2.3% in patients operated on after 28 days.

Our series showed that postoperative neurologic exacerbation was infrequent in patients with a CVC and was never observed after a silent cerebral embolism or a TIA. This result is in accordance with the recent series of Ruttmann et al., in which only one of 65 patients with a previous cerebral embolism experienced a secondary cerebral haemorrhage after valvular surgery. In addition, we found that, among CVC patients, survival was better in operated patients when compared with patients treated conservatively despite theoretical indication for surgery. However, the latter group had more comorbidities and a more severe neurologic status.

Finally, since we have previously shown that vegetation length is a strong predictor of new embolic event, the present study strengthens the need for early valvular surgery in case of silent cerebral embolism or TIA with persistent large vegetations.

Limitations
This study was subject to a referral bias because it was performed in referral centres. The early surgery policy of these centres could have reduced the incidence of new CVC. Moreover, a repeat cerebral CT scan was not systematically performed after antibiotic therapy in all patients. Consequently, the exact incidence of new silent CVC may have been underestimated. Opposite to the recent paper of Ruttmann et al., the influence of the CVC localization was not assessed. As we have chosen to prospectively analyse only strong endpoints (overall and neurologic mortality), we did not have any data on the neurologic recovery rate. Because of an uncontrolled design and a low rate of events in patients with CVC undergoing surgery, this study could not clearly determine the safety period between the CVC and the cardiac operation. However, the assessment of the impact of timing of surgery after CVC was not the primary objective of this study. Finally, the Glasgow Coma Scale is probably not the best mean to assess stroke severity, but it is simple, known by all physicians, with a relatively high specificity when stroke is diagnosed.

Conclusion
In patients with IE, mortality and neurologic outcome depend on the type of CVC. Although patients with stroke have a significant excess mortality particularly in case of mechanical prosthetic valve IE or an impaired consciousness, those with silent CVC or TIA have a relatively good prognosis. Even if valvular surgery can exacerbate cerebral damages after CVC, the risk of postoperative neurologic exacerbation seems to be low after a silent CVC, TIA, and non-massive ischaemic stroke. Further studies are needed to definitely determine the safety period to perform surgery after a stroke complicating endocarditis.

Conflict of interest: none declared.

References


