Mycotic Aneurysm, Subarachnoid Hemorrhage, and Indications for Cerebral Angiography in Infective Endocarditis

Antonio V. Salgado, MD, Anthony J. Furlan, MD, and Thomas F. Keys, MD

We compared the clinical course of 68 patients with infective endocarditis and mycotic aneurysm and 147 patients with infective endocarditis but no mycotic aneurysm. Among the patients with mycotic aneurysm, 57% had subarachnoid hemorrhage without warning. Forty-three percent had a neurologic prodrome 2 days to 18 months (median 17 days) prior to discovery of the mycotic aneurysm. A focal deficit consistent with embolism was the most common prodrome (23%). However, there was no significant difference in the frequency of neurologic symptoms between patients with and without mycotic aneurysm. During an average follow-up of 40 months, there were no instances of subarachnoid hemorrhage/mycotic aneurysm among 121 patients discharged after a full course of antibiotic therapy. Therefore, the risk of rupture of an unsuspected mycotic aneurysm following a full course of antibiotics is low. When a prodrome does precede a mycotic aneurysm, it most often is a focal deficit consistent with embolism. We favor angiography in all patients with infective endocarditis who experience a focal deficit with good recovery. The timing and other indications for angiography in infective endocarditis are discussed. (Stroke 1987;18:1057–1060)

Ruptured mycotic aneurysms account for approximately 5% of the neurologic complications of infective endocarditis. Rarely, a ruptured mycotic aneurysm can be the first manifestation of infective endocarditis. This catastrophic event is associated with an 80% mortality rate.

Clinical predictors of mycotic aneurysm, especially neurologic prodromes prior to rupture, are ill-defined since most series contain few patients or include patients with infective aneurysms not due to infective endocarditis. Similarly, there is no consensus regarding the indications for and timing of cerebral angiography in patients with infective endocarditis. Recommendations range from "early" angiography to serial angiograms every 7 days in patients with a variety of neurologic symptoms. This issue is also of concern among patients being considered for acute or long-term anticoagulation therapy since anticoagulation might be hazardous in the presence of a mycotic aneurysm. Although contraindicated in most patients with infective endocarditis, acute anticoagulation therapy is still considered for patients with prosthetic valve endocarditis and for selected patients with native valve endocarditis and recurrent embolic events. Also unanswered is the long-term risk of subarachnoid hemorrhage (SAH) in patients discharged from the hospital after a course of antibiotic therapy for infective endocarditis. Many of these patients are discharged on long-term anticoagulant therapy, and some reports suggest that an unsuspected mycotic aneurysm may rupture months after the acute infectious episode.

With these issues in mind we designed a study to address 3 questions: 1) are there any neurologic or clinical predictors associated with an increased risk of mycotic aneurysm in infective endocarditis, 2) what is the long-term risk of intracranial hemorrhage (ICH) from unsuspected mycotic aneurysm in patients treated for infective endocarditis, and 3) what are the indications for cerebral angiography in patients with infective endocarditis?

Subjects and Methods

The records of 150 consecutive patients admitted to the Cleveland Clinic since 1974 with the diagnosis of infective endocarditis were reviewed. Diagnosis required the presence of positive blood cultures, a new regurgitant heart murmur, predisposing heart disease, or, in the presence of negative blood cultures, fever and a new regurgitant heart murmur. Neurologic complaints and complications were recorded. Among this group there were 3 patients with documented mycotic aneurysm. Sixty-five cases of mycotic aneurysm documented by angiography, at the time of surgery, or by autopsy in the setting of infective endocarditis were found in the English-language literature since 1957. Hence, a total of 68 cases of documented mycotic aneurysms in the setting of infective endocarditis were available for review.

Follow-up information regarding the development of new neurologic complications was obtained in 122 patients discharged from the Cleveland Clinic after completing antibiotic therapy. Follow-up was accomplished by review of available records and direct telephone interviews.
Results

Mycotic Aneurysm Profile

Of the 68 cases with mycotic aneurysm, 37 were women and 31 were men. Their mean age was 31.4 (range 4–67) years. A history of cardiac disease was known in 35 cases (51.5%); in 16 cases, there was no history of cardiac disease, and in 17 any history of cardiac disease was not mentioned. Six patients had a history of intravenous drug abuse. The mitral valve was involved in 52% of the 48 cases in which information regarding valve involvement was available. The most common bacteria were Streptococcus viridans and Staphylococcus aureus. All but 1 case presented with native valve endocarditis.

A history of systemic prodromal symptoms (malaise, fever, weight loss) antedated the onset of neurologic symptoms from 1 week to 16 months in 59 cases (86.8%). In these 59 cases, the mycotic aneurysm eventually ruptured in 43 and remained intact in 16.

A neurologic prodrome prior to the rupture or angiographic discovery of a mycotic aneurysm was present in 29 cases (42.6%). The most common prodrome was a focal deficit indicating embolic infarction (16 cases) (Table 1). The time between the first neurologic complaint and the discovery or rupture of the mycotic aneurysm ranged from 2 days to 18 months (median 17 days). In 17 cases, a lumbar puncture performed prior to the discovery of mycotic aneurysm revealed a polymorphonuclear pleocytosis. In only 1 case was a microorganism (S. aureus) isolated from the cerebrospinal fluid.

Cleveland Clinic Infectious Endocarditis Series

Among 147 patients with infective endocarditis (i.e., excluding the 3 with mycotic aneurysm) 114 patients were men and 33 were women, with a median age of 52.0 years. Forty-six patients (31.3%) had prosthetic valve endocarditis and 98 (66.6%) native valve endocarditis. Two patients had infected intraventricular foramina and 1 infected pacemaker leads.

Neurologic complications occurred in 55 patients (37.4%) and were frequently present in combination. The initial neurologic symptom consisted of a focal deficit in 28 (19.0%), change in mental status in 16 (10.9%), headache in 10 (6.8%), and seizures in 1 (0.7%). Neurologic complaints occurred in 43.4% of the 46 patients with prosthetic valve endocarditis and 34.6% of the 98 patients with native valve endocarditis. Cerebrospinal fluid analysis was obtained in 12 cases; in 7 there was a polymorphonuclear pleocytosis, and 2 of these grew S. aureus. Data comparing cases of infective endocarditis with and without mycotic aneurysm are given in Table 1.

Long-Term Follow-Up

Twenty-five patients died while in the hospital; autopsy was performed in 12. Only 1 revealed an ICH involving the occipital region, but careful vessel examination showed no evidence of aneurysm.

One hundred twenty-five patients were discharged from the hospital after having received at least 4 weeks of intravenous antibiotic therapy. Three patients were lost to follow-up, and another died of an ICH 12 days after discharge while on warfarin. No angiography was performed before death, and the prothrombin time was

| Table 1. Comparative Data on Infective Endocarditis Patients With and Without Mycotic Aneurysm |
|----------------------------------|-----------------|-----------------|
|                                  | With MA No. | With MA Percent |
|                                  | Without MA No. | Without MA Percent |
| Number                           | 68           | 147             |
| Age (mean)                       | 31.4 yrs     | 52.0 yrs        |
| Sex                              |              |                 |
| Women                            | 54.4         | 22.4            |
| Men                              | 45.6         | 77.6            |
| Underlying cardiac disease       |              |                 |
| Not mentioned                    | 25           | 0               |
| Rheumatic heart disease          | 25           | 21              |
| Congenital heart disease         | 17.5         | 38              |
| None known                       | 23.5         | 41              |
| Other                            | 9.0          | 0               |
| History of IV drug abuse         | 8.8          | 2.0             |
| Type of valve at time of IE      |              |                 |
| Native                           | 98.5         | 68.6            |
| Prosthetic                       | 1.5          | 31.2            |
| Valve involved                   |              |                 |
| Mitral only                      | 52*          | 29.2            |
| Aortic only                      | 33.3*        | 55.1            |
| Most frequent microorganism isolated |        |                 |
| Streptococcus viridans           | 33.8         | 30.6            |
| Group D Streptococcus            | 10.3         | 23.8            |
| Other Streptococcus              | 11.8         | 2.7             |
| Staphylococcus aureus            | 17.6         | 19.9            |
| Staphylococcus coagulase-negative| 1.5          | 10.8            |
| Others†                          | 5.9          | 8.4             |
| Not mentioned                    | 14.7         | 0               |
| Negative blood cultures          | 4.4          | 4.0             |

Incidence and nature of neurologic complications during IE

<table>
<thead>
<tr>
<th></th>
<th>With MA No.</th>
<th>With MA Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAH/ICH</td>
<td>57.4</td>
<td>0</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>23.5</td>
<td>19.0</td>
</tr>
<tr>
<td>Headache</td>
<td>13.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>2.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Seizures</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Change in mental status</td>
<td>1.5</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Cerebrospinal fluid pleocytosis

| (17/39) | 43.6 | (7/12) | 58.3 |

MA, mycotic aneurysm; IE, infective endocarditis; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage.

†In 48 cases in which information was available.

†Gram-negative bacilli, dipheroids, yeast, and lactobacillius.
unduly prolonged. The remaining 121 patients were followed for a mean of 40.1 months. Thirty-seven patients were discharged on warfarin and maintained on long-term anticoagulation for 1 month to 11 years. In the total follow-up group, there were 11 deaths (pneumonia, 4; myocardial infarction, 2; renal failure, septic shock, cerebral infarction, metastatic cancer, liver failure, 1 each). There were no instances of SAH or ruptured aneurysms. Two of our 3 patients with mycotic aneurysm were treated surgically, and 1 had resolution of the mycotic aneurysm by sequential angiography while on intravenous antibiotic treatment. Three patients were followed for a mean of 47.6 (range 21–72) months. One developed focal seizures 6 months after discharge, and the other 2 had no subsequent complications.

Discussion

The natural history of infective endocarditis has undergone several important changes over the last 30 years. Recent trends include increased age at onset, decreased proportion of patients with rheumatic heart disease, and increased infections with Group D Streptococcus. In a previous report of prosthetic valve infective endocarditis, aortic prostheses were more likely to become infected than mitral prostheses. It is unclear whether the relative excess of aortic valve endocarditis in our series also reflects a changing trend compared with local referral patterns. Despite these changes, the frequency and the types of neurologic complications in our population were similar to those of earlier series.

Nonneurologic parameters such as site of valve involvement and type of organism appear to be unreliable predictors of mycotic aneurysm risk. Although it is stated that mycotic aneurysm occurs more often with low-virulence organisms, other studies suggest a greater risk with virulent organisms such as S. aureus. Some of these discrepancies may reflect changing treatment regimens that could prevent mycotic aneurysm from developing with low-virulence infection while permitting patients with virulent infection to survive long enough to develop mycotic aneurysm. Morbidity and mortality associated with experimental mycotic aneurysm are related to organism virulence. Of note, these experiments suggest that mycotic aneurysm usually forms within 48 hours of embolization, which corresponds with the earliest documented interval between a neurologic prodrome and the development of mycotic aneurysm.

Comparing the neurologic complications in our series of cases without versus cases with mycotic aneurysm shows no significant differences between the two groups. We could not define a neurologic profile that distinguished between patients with and without mycotic aneurysm. However, the true incidence of mycotic aneurysm in infective endocarditis, and thus the predictive value of neurologic symptoms, remains uncertain since cerebral angiography is not routinely performed and since aneurysms may heal with antibiotic treatment.

In a previous large series, 9 of 16 patients with mycotic aneurysm were said to have been adequately treated prior to aneurysmal rupture. These cases were not included in the present analysis due to lack of clinical information. However, our review revealed that only 2 of 68 cases with mycotic aneurysm eventually ruptured after a full course of parenteral antibiotic treatment. The low risk of neurologic complications after treatment was further evidenced in our follow-up study, in which only 1 case developed ICH while on warfarin after completing antibiotic treatment. Therefore, the risk of rupture of an unsuspected mycotic aneurysm following a full course of antibiotic therapy is probably lower than previously suggested.

The inability to define a clear-cut neurologic or medical prodrome prior to development of a mycotic aneurysm poses a difficult clinical dilemma regarding the indications for cerebral angiography in infective endocarditis. In our opinion, waiting for a catastrophic SAH to occur is not satisfactory. When a prodrome does occur prior to mycotic aneurysm, it most often is a focal deficit consistent with embolism. Since ruptured mycotic aneurysm is associated with a high mortality and since the risk of cerebral angiography is low in most institutions, we favor four-vessel angiography in all patients with infective endocarditis who experience a focal deficit with good recovery during the acute phase of the illness. Since the time course for development of mycotic aneurysm following embolism is uncertain, we recommend that angiography initially be done within 2 weeks of the focal event but not before 48 hours. If negative, a second angiogram should be done on completion of antibiotic therapy only if long-term anticoagulation is planned. Cerebral angiography is also indicated in patients with headache and red blood cells in the cerebrospinal fluid, and should be considered in any patient with nonfocal neurologic symptoms before initiating anticoagulation therapy. In >50% of patients with mycotic aneurysms there is no identifiable prodrome. However, in patients without neurologic symptoms who have successfully completed a course of parenteral antibiotic therapy, the long-term risk of SAH is very low. In such cases, long-term anticoagulation can be safely initiated without cerebral angiography.

References

unduly prolonged. The remaining 121 patients were followed for a mean of 40.1 months. Thirty-seven patients were discharged on warfarin and maintained on long-term anticoagulation for 1 month to 11 years. In the total follow-up group, there were 11 deaths (pneumonia, 4; myocardial infarction, 2; renal failure, 2; septic shock, cerebral infarction, metastatic cancer, liver failure, 1 each). There were no instances of SAH or ruptured aneurysms. Two of our 3 patients with mycotic aneurysm were treated surgically, and 1 had resolution of the mycotic aneurysm by sequential angiography while on intravenous antibiotic treatment. These 3 patients were followed for a mean of 47.6 (range 21–72) months. One developed focal seizures 6 months after discharge, and the other 2 had no subsequent complications.

Discussion

The natural history of infective endocarditis has undergone several important changes over the last 30 years. Recent trends include increased age at onset, decreased proportion of patients with rheumatic heart disease, and increased infections with Group D Streptococcus.\textsuperscript{35–38} In a previous report of prosthetic valve infective endocarditis, aortic prostheses were more likely to become infected than mitral prostheses.\textsuperscript{3} It is unclear whether the relative excess of aortic valve endocarditis in our series also reflects a changing trend compared with local referral patterns. Despite these changes, the frequency and the types of neurologic complications in our population were similar to those of earlier series.\textsuperscript{1,18,39}

Nonneurologic parameters such as site of valve involvement and type of organism appear to be unreliable predictors of mycotic aneurysm risk. Although it is stated that mycotic aneurysm occurs more often with low-virulence organisms,\textsuperscript{40} other studies suggest a greater risk with virulent organisms such as \textit{S. aureus}.\textsuperscript{1,41,42} Some of these discrepancies may reflect changing treatment regimens that could prevent mycotic aneurysm from developing with low-virulence infection while permitting patients with virulent infection to survive long enough to develop mycotic aneurysm.\textsuperscript{1} Morbidity and mortality associated with experimental mycotic aneurysm are related to organism virulence.\textsuperscript{41} Of note, these experiments suggest that mycotic aneurysm usually forms within 48 hours of embolization,\textsuperscript{41,42} which corresponds with the earliest documented interval between a neurologic prodrome and the development of mycotic aneurysm.

Comparing the neurologic complications in our series of cases without versus cases with mycotic aneurysm shows no significant differences between the two groups. We could not define a neurologic profile that distinguished between patients with and without mycotic aneurysm. However, the true incidence of mycotic aneurysm in infective endocarditis, and thus the predictive value of neurologic symptoms, remains uncertain since cerebral angiography is not routinely performed and since aneurysms may heal with antibiotic treatment.\textsuperscript{1}

In a previous large series, 9 of 16 patients with mycotic aneurysm were said to have been adequately treated prior to aneurysmal rupture. These cases were not included in the present analysis due to lack of clinical information. However, our review revealed that only 2 of 68 cases with mycotic aneurysm eventually ruptured after a full course of parenteral antibiotic treatment.\textsuperscript{5,31} The low risk of neurologic complications after treatment was further evidenced in our follow-up study, in which only 1 case developed ICH while on warfarin after completing antibiotic treatment. Therefore, the risk of rupture of an unsuspected mycotic aneurysm following a full course of antibiotic therapy is probably lower than previously suggested.

The inability to define a clear-cut neurologic or medical prodrome prior to development of a mycotic aneurysm poses a difficult clinical dilemma regarding the indications for cerebral angiography in infective endocarditis. In our opinion, waiting for a catastrophic SAH to occur is not satisfactory. When a prodrome does occur prior to mycotic aneurysm, it most often is a focal deficit consistent with embolism. Since ruptured mycotic aneurysm is associated with a high mortality and since the risk of cerebral angiography is low in most institutions, we favor four-vessel angiography in all patients with infective endocarditis who experience a focal deficit with good recovery during the acute phase of the illness. Since the time course for development of mycotic aneurysm following embolism is uncertain, we recommend that angiography initially be done within 2 weeks of the focal event but not before 48 hours. If negative, a second angiogram should be done on completion of antibiotic therapy only if long-term anticoagulation is planned. Cerebral angiography is also indicated in patients with headache and red blood cells in the cerebrospinal fluid, and should be considered in any patient with nonfocal neurologic symptoms before initiating anticoagulation therapy. In >50% of patients with mycotic aneurysms there is no identifiable prodrome. However, in patients without neurologic symptoms who have successfully completed a course of parenteral antibiotic therapy, the long-term risk of SAH is very low. In such cases, long-term anticoagulation can be safely initiated without cerebral angiography.

References


**KEY WORDS** • endocarditis • angiography • mycotic aneurysm
Mycotic aneurysm, subarachnoid hemorrhage, and indications for cerebral angiography in infective endocarditis.

A V Salgado, A J Furlan and T F Keys

*Stroke*. 1987;18:1057-1060
doi: 10.1161/01.STR.18.6.1057

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/18/6/1057

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/