Is Cerebral Angiography Indicated in Infective Endocarditis?

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Background and Purpose: Patients with infective endocarditis may develop intracranial mycotic aneurysms. Whether these patients should undergo cerebral angiography followed by prophylactic surgery if an aneurysm is detected is an unresolved question.

Methods: We estimated the probability of survival 12 weeks after the diagnosis of infective endocarditis on the basis of data available in the literature.

Results: For a 40-year-old female patient with right-sided hemiplegia, the 12-week survival is estimated to be 83.75% without angiography and 83.65% with angiography; the specific mortality of intracranial mycotic aneurysms is relatively small but increases by 40% (from 0.25% to 0.35%) if angiography is performed. The mortality from rupture appears to be the most important factors that affect the analysis.

Conclusions: Cerebral angiography should not be performed routinely in patients with infective endocarditis. Specific subgroups in whom such a policy might be beneficial have not yet been identified.

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KEY WORDS • aneurysm • angiography • endocarditis

Intracranial mycotic aneurysms are uncommon but life-threatening complications of infective endocarditis. One might consider cerebral angiography in patients suffering from infective endocarditis to detect intracranial mycotic aneurysms before a catastrophic rupture occurs, because cerebral angiography is rather accurate and safe, and the risks of a neurosurgical intervention have decreased considerably in the last decades. Some authors advocate angiography and surgical removal of detected mycotic aneurysms only in patients suffering from neurological symptoms. Others recommended complete cerebral angiography even in patients who are neurologically asymptomatic. It is generally recognized that all these statements are more or less arbitrary, because they are based on retrospective and anecdotal evidence.

The management problem of mycotic aneurysms differs from that of saccular aneurysms at the base of the brain in at least two respects. A mycotic aneurysm is only one of the risks in the extensive and life-threatening disease process of infective endocarditis. In addition, mycotic aneurysms tend to disappear when the infective endocarditis is treated adequately with antibiotics. This suggests that there is a risk of rupture only in a limited period of time, with a more or less definable beginning and end.

In this analysis we quantitatively estimate the effects of the performance of cerebral angiography on survival. The available data are explicitly presented, which allows detailed examination of the underlying assumptions. An analysis that makes these assumptions the main target of criticism is an essential first step toward consensus about the indications for cerebral angiography in infective endocarditis.

Subjects and Methods

The analysis will be related to the following example of a patient with clinically definite infective endocarditis. A 40-year-old woman had a left-sided hemiparesis and sensory loss the day before hospital admission. About 6 months before admission she complained of headache, painful joints, and fatigue. One month before she had had a tooth extraction. Examination revealed a systolic heart murmur and fever (temperature, 38.3°C). The erythrocyte sedimentation rate was 65 mm in the first hour, and she had anemia. Blood cultures showed Streptococcus viridans. Computed tomographic scanning of the brain showed a hypodense area corresponding to infarction in the cortical territory of the right middle cerebral artery.

The dilemma is schematically represented by a decision tree in Figure 1. The final outcome is defined as survival 12 weeks after the diagnosis of infective endocarditis is made. In Table 1 we have summarized the probability estimates used for the quantitative estimation of the effects of either strategy ("angiography" versus "no angiography") on 12-week survival. The probabilities reflect as closely as possible the relative frequencies derived from
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no angiography 600%
ruptured aneurysm 1.2%
no rupture 98.8%

patient with infective endocarditis

angiography 83.20%
ruptured aneurysm 25%
no rupture 75%

angiogram positive

surgery 81.40%
surgery 3%
no rupture 97%

angiogram negative

no complications 87.00%
ruptured aneurysm 17%
no rupture 83%

FIGURE 1. Decision tree for angiographic screening for cerebral mycotic aneurysms in infective endocarditis. Square at extreme left of this tree denotes choice of whether to perform cerebral angiography or not (decision node). Circles represent events that may follow this choice (chance node). Probability estimates (p) are added for all branches (see also Table 1). The probability of a positive angiogram is calculated as p(T+)=p(T+|MA)×p(MA)=90%×12%=10.8%, where p(T+|MA) is the sensitivity of cerebral angiography and p(MA) the prevalence of cerebral mycotic aneurysms. The probability of an aneurysm rupture after a negative angiogram is calculated as p(RUPT|T−)=1−[1−p(T+|MA)]×p(RUPT)=1−0.13%=0.13%, where p(RUPT) is the probability of intracranial aneurysm rupture in infective endocarditis. “Balloons” indicate expected 12-week survival probabilities computed by “averaging out” the decision tree. For example, the 12-week survival probability at chance node A is 25%×0%+75%×84%=63% and at chance node B is 1.2%×63%+98.8%×84%=83.75%.

published studies. For some events, however, there is no empirical evidence available, and in that case we used subjective estimates based on related data. We shall examine the effects of varying the probabilities over wide ranges on the results of the analysis.

Mortality From Infective Endocarditis

Overall mortality rates published in recent studies range from 15% to 50%. These differences may be partly attributed to initial patient characteristics and to diagnostic criteria. Based on this last study we estimated the risk of death from infective endocarditis (with the exclusion of mortality from mycotic aneurysms) in our patient to be 16% (95% confidence interval [CI], 3–40%) after 12 weeks.

Prevalence of Mycotic Aneurysms

The prevalence of cerebral mycotic aneurysms in infective endocarditis is uncertain, because cerebral

<table>
<thead>
<tr>
<th>Mycotic aneurysm and rupture</th>
<th>Estimate %</th>
<th>Plausible range %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of intracranial mycotic aneurysms</td>
<td>12</td>
<td>4–26</td>
</tr>
<tr>
<td>Risk of intracranial hemorrhage from rupture of mycotic aneurysm</td>
<td>1.2</td>
<td>0.3–5</td>
</tr>
<tr>
<td>Mortality from rupture</td>
<td>25</td>
<td>5–57</td>
</tr>
<tr>
<td>Cerebral Angiography</td>
<td></td>
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<tr>
<td>Sensitivity</td>
<td>90</td>
<td>75–100</td>
</tr>
<tr>
<td>Mortality from cerebral angiography</td>
<td>0.06</td>
<td>0–1</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical mortality</td>
<td>3</td>
<td>1–8</td>
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angioysis is not routinely performed and mycotic aneurysms are, as a rule, clinically silent before rupture. The estimated prevalence of these aneurysms among infective endocarditis patients varies in recent studies from 0.8% to 12%, with the lower figure derived from clinical studies and the higher from autopsied cases.\textsuperscript{12,13}

The estimation of 12% (95% CI, 4–26%) based on 41 autopsied cases is the best approximation in our view, although it is based on a case series observed between 1939 and 1959,\textsuperscript{13,15} when antimicrobial regimens were less optimal. On the other hand, in the preantibiotic era many patients with infective endocarditis died within a short time, before they could have developed a mycotic aneurysm, and the prevalence of mycotic aneurysms is probably not much lower today.\textsuperscript{14}

Although it has often been suggested that the prevalence of mycotic aneurysms is higher in patients with neurological symptoms, a comparison of infective endocarditis patients with and without a mycotic aneurysm from the series of Salgado and coworkers\textsuperscript{2} shows that the prevalence of neurological symptoms (before a possible rupture) is not different between these groups.

**Risk of Aneurysm Rupture in Infective Endocarditis**

It was shown by Hart et al\textsuperscript{7} that primary intracranial hemorrhage occurred in 13 of 209 consecutive patients with active endocarditis admitted to the hospital during 1978–1986. Ten of these 13 patients had either angiographic or postmortem examination, and in two of the 10 patients a mycotic aneurysm was demonstrated. From these data it can be derived that the risk of an intracranial hemorrhage from aneurysm rupture in infective endocarditis is 1.2% (95% CI, approximately 0.3–5.0%). If this figure is related to the prevalence of intracranial hemorrhage or major neurological deficits. We estimated the interval between diagnosis of infective endocarditis and rupture of a mycotic intracranial aneurysm from the two most recent series of patients with intracranial mycotic aneurysms.\textsuperscript{1,3} The time from diagnosis of infective endocarditis to rupture ranged in one study from 0 to 35 days for 11 patients (median, 12 days) and in the other from 0 to 28 days for seven patients (median, 8 days). Thus, most episodes of rupture seem to occur during a limited period after the initial diagnosis of infective endocarditis. This is supported by the finding on serial angiography that mycotic aneurysms have a tendency to disappear under an adequate regimen of antibiotics.\textsuperscript{1,3,11,12} Based on these data we assumed that a patient with infective endocarditis is at risk for rupture of a cerebral mycotic aneurysm only within the first weeks after infective endocarditis has been diagnosed. We shall therefore consider survival after 12 weeks as the relevant outcome.

We did not take into account the time in which the aneurysm develops in our estimates of the prevalence of mycotic aneurysms at the time of angiography. We simply assumed that all aneurysms are present at the time of angiography and that thereafter no further aneurysms will develop. This implies that we overestimate the prevalence of mycotic aneurysm at the time of angiography to a certain extent, because in reality mycotic aneurysms continue to develop after that time.\textsuperscript{11} The risk of rupture of a mycotic aneurysm in the period after angiography is also underestimated, because our estimate is based on studies that report the risk of rupture before as well as after infective endocarditis has been diagnosed.\textsuperscript{1,3}

**Mortality From Aneurysm Rupture**

A ruptured mycotic aneurysm was reported to result in death in 25% (95% CI, 5–75%) in a recent but small series of 12 patients.\textsuperscript{15} The median age in this series of patients was 30 years (range, 18–57 years).

**Cerebral Angiography**

The risk of death from conventional cerebral angiography is estimated to be 0.06% in an overview of eight prospective studies that report the complication rate of conventional cerebral angiography in patients with mild cerebrovascular disease.\textsuperscript{14} The mean age of the patients in this series was approximately 60 years. We shall use the results of this overview as estimates of the risks of angiography in the 40-year-old patient, because it is unlikely that this risk is lower in a patient suffering from a severe systemic disease such as infective endocarditis, although the patient is younger.\textsuperscript{17}

No explicit data are available regarding the test characteristics of angiography for cerebral aneurysms, whether of mycotic origin or not. It has been stated in a number of publications that 90% of the intracranial mycotic aneurysms are revealed by angiography and that false-positive results never occur.\textsuperscript{3,18–20}

**Surgical Treatment**

The risk of surgery for intracranial mycotic aneurysms is relatively low. Brust et al\textsuperscript{3} report uneventful recovery in all four patients who were operated on for an unruptured aneurysm. In a study on the complications of surgery in 1,000 patients with ruptured, noninfective aneurysms at the base of the brain it is reported that the mortality rate is 6.1% (95% CI, 4.7–7.8%).\textsuperscript{21}

Because mycotic aneurysms occur most often at the cerebral convexity, which implies a less hazardous surgical procedure, it is assumed that the surgical risk is 50% lower. Thus surgical mortality in our patient is estimated to be 3%.

**Time Course**

Few studies provide good evidence about the time course of the occurrence of mycotic aneurysms and associated hemorrhage. This is partly caused by the difficulty in establishing the onset of infective endocarditis. In addition, the angiographic detection of mycotic aneurysms is usually prompted by the occurrence of intracranial hemorrhage or major neurological deficits. We estimated the interval between diagnosis of infective endocarditis and rupture of a mycotic intracranial aneurysm from the two most recent series of patients with intracranial mycotic aneurysms.\textsuperscript{1,3} The time from diagnosis of infective endocarditis to rupture ranged in one study from 0 to 35 days for 11 patients (median, 12 days) and in the other from 0 to 28 days for seven patients (median, 8 days). Thus, most episodes of rupture seem to occur during a limited period after the initial diagnosis of infective endocarditis. This is supported by the finding on serial angiography that mycotic aneurysms have a tendency to disappear under an adequate regimen of antibiotics.\textsuperscript{1,3,11,12} Based on these data we assumed that a patient with infective endocarditis is at risk for rupture of a cerebral mycotic aneurysm only within the first weeks after infective endocarditis has been diagnosed. We shall therefore consider survival after 12 weeks as the relevant outcome.

The 12-week survival probabilities of the two strategies for the 40-year-old patient with neurological symptoms are 83.75% with and 83.65% without cerebral angiography (Figure 1). The difference between the two strategies is quite small, which points toward a "toss-up" situation.\textsuperscript{23} If cerebral angiography and surgery were without any risk, the 12-week survival probability...
after angiography would be 84%, which is the estimated survival rate from infective endocarditis. The decrease in survival probability that can be specifically attributed to aneurysm rupture and to the corresponding diagnostic and therapeutic procedures is 0.25% without angiography and 0.35% with angiography. In other words, the aneurysm-specific mortality increases by 40% if angiography is performed. In absolute terms, it can be concluded from these figures that routinely performing angiography would result in one additional death in 1,042 patients who are similar to the patient used as an example.

This analysis also allows an estimation of the effect of surgery on the 12-week survival if an intracranial mycotic aneurysm has already been demonstrated. If a patient with a demonstrated intracranial mycotic aneurysm is not operated on, the point estimate of the risk of aneurysm-related death is 2.5% (risk of rupture of the mycotic aneurysm is 10%, that of mortality after rupture is 25%). The surgical mortality is estimated to be 3%, however, which indicates that surgical treatment of an already demonstrated intracranial mycotic aneurysm increases the aneurysm-specific mortality.

Uncertainty in the Quantification

We investigated the effect of uncertainty in the numerical assessments on the optimal choice by varying the probabilities one by one over wide ranges, while keeping the other probabilities fixed. The results are presented in Figure 2. For example, if the prevalence of intracranial mycotic aneurysms is estimated to be 26%, instead of the 12% used in our analysis, the risk of rupture given a mycotic aneurysm would be 4.6% (1.2% divided by 26%) instead of 10% (1.2% divided by 12%), because the risk of aneurysm rupture in infective endocarditis is kept fixed at 1.2%. It can be inferred from Figure 2 that the difference in 12-week survival between the two strategies ranges between $-0.1\%$ (angiography preferred) if the prevalence of intracranial mycotic aneurysms is 4%, and $0.4\%$ (angiography not preferred) if the prevalence is 26%. Figure 2 clearly shows that the risk of aneurysm rupture in infective endocarditis and the mortality from rupture emerge as the most critical factors. The extremes of the intervals representing the prevalence of mycotic aneurysms and the mortality from surgery only just cross the zero difference line.

It is obvious that balancing the risks of angiography and surgery on the one hand and the risk of death from a ruptured mycotic aneurysm on the other is the core of the clinical dilemma. To investigate the joint effect of variations in these three factors on the decision, we executed a threshold analysis that provides the values for which both strategies have equal survival probabilities, i.e., the "threshold" (the continuous lines in Figure 3). Above this threshold the strategy "no angiography" results in the highest survival probability, and below this line "angiography" results in the highest survival probability. Figure 3 shows thresholds for the mortality of surgery and of angiography for two different values of mortality related to aneurysm rupture (see text). Threshold lines represent values that give rise to equal survival probabilities for the two strategies. Above the threshold angiography results in the highest survival. Filled circle indicates probability estimates used for the 40-year-old patient in our analysis.
depends on the risk of angiography. If the mortality related to aneurysm rupture is 0.6%, angiography might be beneficial if surgical mortality is below 5.0%.

Timing of Angiography

Until now we have assumed that the angiography is performed at the optimal moment to demonstrate any aneurysm within the 12-week period of the analysis. This assumption leads to a bias in favor of angiography, because we overestimated both the prevalence of mycotic aneurysm at the time of angiography and the risk of aneurysm rupture after angiography. In Figure 4 we present the results of a threshold analysis for the prevalence of mycotic aneurysms at the time of angiography and the risk of aneurysm rupture after angiography. This figure indicates that if the prevalence of mycotic aneurysm at the moment of angiography lies above 4%, the results of the analysis are dominated by the risks of aneurysm rupture after angiography. If angiography is performed early in the course of the disease not all mycotic aneurysms that will eventually develop are detected, but the risk of subsequent aneurysm rupture is nevertheless high. In a later stage more aneurysms will be detected, but the risk of aneurysm rupture will have decreased. So, if cerebral angiography is considered at all, it is better to perform it early in the course of the disease.

Discussion

This analysis examines the question of whether cerebral angiography should be performed in patients who suffer from infective endocarditis. On the basis of the relatively small amount of clinical evidence available from published series, the effects of two competing strategies ("angiography" and "no angiography" at the time infective endocarditis is diagnosed) are estimated quantitatively. It appears that for a 40-year-old female patient with hemispheric deficits the survival probability after 12 weeks is higher without angiography. The absolute difference in survival probability is quite small (83.75% and 83.65%), but in a relative sense, the aneurysm-specific mortality increases by 40% if angiography is performed. It was furthermore shown that, at least on the basis of probability estimates used in our analysis, surgical treatment of a mycotic aneurysm once it has been demonstrated is more harmful than medical treatment only.

In the interpretation of the results of this analysis we have to take into account that several factors favored angiography. We overestimated the risk of aneurysm rupture by neglecting the possibility that a mycotic aneurysm can also rupture before infective endocarditis is diagnosed. Furthermore, it has not been taken into account that surgical treatment is not always feasible, depending on the location of the aneurysm. Despite this bias we find that the benefits of angiography do not outweigh its risks. Finally, the pain and discomfort from undergoing cerebral angiography and surgery have also been excluded from the analysis. Our analysis indicates, therefore, that angiography should not be performed in the 40-year-old patient used as an example.

In our view, this recommendation against angiography holds for the majority of infective endocarditis patients. Angiography might be beneficial only if the risk of aneurysm rupture in infective endocarditis or the mortality from aneurysm rupture is substantially higher than in our 40-year-old patient. Furthermore, it was shown that if cerebral angiography is indicated (in consideration of anticoagulant therapy or with a highly skilled surgical unit available), it is better to perform angiography early after admission to the hospital than later in the course of the disease.

In conclusion, our quantitative estimation of the clinical value of cerebral angiography and surgery for patients with infective endocarditis demonstrates that it is better not to perform cerebral angiography routinely in patients with infective endocarditis. Although some recent studies favor cerebral angiography in patients who have neurological abnormalities not attributable to systemic toxicity, there is at present no evidence that certain subgroups of patients with endocarditis benefit from angiographic detection and surgical treatment of mycotic aneurysms.1-3

References

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