Mechanisms of Intracranial Hemorrhage in Infective Endocarditis

Robert G. Hart, MD, Kathleen Kagan-Hallet, MD, and Susan E. Joerns, MD

Analysis of 17 patients with infective endocarditis and intracranial hemorrhage yielded several different mechanisms of bleeding. Nine of 15 (60%) symptomatic intracranial hemorrhages occurred within 48 hours of admission and 3 more (20%) after hospital discharge. In 7 patients with Staphylococcus aureus endocarditis, symptomatic intracranial hemorrhage occurred within 48 hours of admission and resulted from septic arteritis in all 3 examined pathologically. Secondary hemorrhagic transformation (hemorrhagic infarction) was asymptomatic in 2 nonanticoagulated patients but was associated with clinical worsening in 2 anticoagulated patients. Anticoagulation potentially contributed to intracranial hemorrhage in 4 of the 17 patients (24%). Proven mycotic aneurysms were present in only 2 patients (12%), 1 of whom presented with massive, fatal intracranial hemorrhage. Mycotic aneurysms amenable to surgery are uncommon and underlie only a fraction of intracranial hemorrhages in infective endocarditis. (Stroke 1987;18:1048–1056)

Intracranial hemorrhage (ICH) occurs in about 5% of patients with infective endocarditis.1 4 These hemorrhages are usually attributed to ruptured mycotic aneurysms, even when no aneurysm is demonstrable.1 As mycotic aneurysms are sometimes obliterated by the hemorrhages that they produce, their arteriographic and even pathologic demonstration is not always possible.2 5 6 However, ICH in infective endocarditis can also result from septic erosion of the arterial wall with rupture but without a well-delineated aneurysm.7 Surgical intervention in this situation is usually not feasible, as the necrotic fusiform segment cannot be repaired but requires resection with or without pedicle/bypass grafting.8 9 Additionally, hemorrhagic transformation of ischemic brain infarcts can result in ICH, which is often massive in anticoagulated patients.10 12 These different pathomechanisms of ICH have distinct management implications. Seventeen patients with infective endocarditis and ICH were studied to define the frequency and clinical features of different mechanisms of hemorrhage.

Subjects and Methods
Consecutive patients with active infective endocarditis during 1978–1986 were retrospectively studied from review of inpatient medical records at 6 hospitals. The diagnosis of infective endocarditis required the presence of fever, persistently positive blood cultures, predisposing heart disease or a new diastolic murmur, and absence of other, extracardiac sources of bacteremia. ICH was defined as an increased, noncalcific density on noncontrast computed tomography (CT) or as xanthochromic spinal fluid with >500 red cells/mm³. All patients with infective endocarditis who had focal neurologic abnormalities and most patients with presumed nonfocal “toxic” encephalopathies underwent CT, allowing reliable detection of symptomatic ICH.

Results
ICH occurred in 17 patients, 8% of those with infective endocarditis. ICH was present at the time of hospital admission in 41% (7 of 17) and occurred within 48 hours of admission in an additional 12% (2 of 17). Ages ranged from 21 to 74 years (mean 44). Six patients were intravenous drug abusers. Staphylococcus aureus was the infecting organism in 53%, S. epidermidis in 12%, and Streptococcus spp. in only 18%. Five patients (29%) were anticoagulated or had bleeding diathesis at the time of ICH. The overall mortality was 59% (10 of 17); death was a direct result of ICH in 35% (6 of 17). For purposes of analysis, patients were divided into 3 groups based on the type of ICH and infecting organism (Table 1). Brief, annotated case histories are provided.

Patient 1. A 59-year-old alcoholic woman with malaise and fever for 4 days had abrupt onset of left hemiparesis that occurred the day of admission (Day 1). She was febrile with systolic and diastolic cardiac murmurs; 6 blood cultures grew S. aureus. Initial CT was normal, and spinal fluid was clear. On Day 2, she suddenly became comatose; CT revealed subarachnoid hemorrhage and a right frontoparietal infarct with parietal hemorrhage (Figure 1). Coagulation studies and platelet count were normal. On Day 3, she was pronounced brain dead. Autopsy revealed S. aureus endocarditis of both the aortic and mitral valves with multiple vegetations, subarachnoid and intraparenchymal brain hemorrhage, and a large right brain infarct. No evidence of systemic embolism was found. The right middle cerebral artery (MCA) adjacent to the hemorrhage was occluded by a septic embolus with inflammatory erosion of the arterial wall (Figure 2).
**Patient 2.** A 37-year-old alcohol and intravenous drug abuser with 4 days of fever was admitted for confusion and left hemiparesis. The clinical findings were suggestive of aortic valve endocarditis. Four blood cultures subsequently grew *S. aureus*, and CT showed temporal lobe hemorrhage (Figure 1). Admission prothrombin time (PT) was $1.5 \times$ control, and platelet count was 22,000/mm$^3$ (attributed to sepsis); he had ingested aspirin just before admission. Over the next 24 hours, he became progressively obtunded with signs of transtentorial herniation; repeat CT showed an enlarging hematoma. Autopsy confirmed acute endocarditis of the aortic valve with vegetations and a massive ICH with herniation. Multiple acute embolic infarcts were present in the spleen, kidneys, and intestine. Adjacent to the hematoma, a medium-sized artery was completely necrotic with Gram-positive cocci enmeshed in fibrin within the vessel lumen.

**Patient 3.** A 38-year-old intravenous drug abuser with 10 days of malaise and nausea and 3 days of severe headache and confusion was febrile on admis-
Table 1. Intracranial Hemorrhage in Infective Endocarditis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Organism</th>
<th>Duration of symptoms</th>
<th>Antecedent ischemia</th>
<th>Day of hemorrhage</th>
<th>Site of hemorrhage</th>
<th>Arteriography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/59/F</td>
<td>35</td>
<td>M</td>
<td><em>Staphylococcus aureus</em></td>
<td>4 days</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Temporal lobe</td>
<td>—</td>
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<tr>
<td>2/37/Mt</td>
<td>67</td>
<td>M</td>
<td><em>S. aureus</em></td>
<td>4 days</td>
<td>None</td>
<td>Day 1</td>
<td>Temporal lobe</td>
<td>—</td>
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<tr>
<td>3/38/M</td>
<td>25</td>
<td>M</td>
<td><em>S. aureus</em></td>
<td>10 days</td>
<td>None</td>
<td>Day 1</td>
<td>Temporal lobe</td>
<td>—</td>
</tr>
<tr>
<td>4/68/M</td>
<td>70</td>
<td>M</td>
<td><em>S. aureus</em></td>
<td>1 day</td>
<td>None</td>
<td>Day 1</td>
<td>Temporal lobe</td>
<td>—</td>
</tr>
<tr>
<td>5/31/M</td>
<td>57</td>
<td>M</td>
<td><em>S. aureus</em></td>
<td>7 days</td>
<td>None</td>
<td>Day 1</td>
<td>Occipital lobe</td>
<td>No mycotic</td>
</tr>
<tr>
<td>6/57/F</td>
<td>45</td>
<td>F</td>
<td><em>S. aureus</em></td>
<td>2 days</td>
<td>None</td>
<td>Day 2</td>
<td>Parietal lobe</td>
<td>No mycotic</td>
</tr>
<tr>
<td>7/52/F</td>
<td>56</td>
<td>F</td>
<td><em>S. aureus</em></td>
<td>2 days</td>
<td>None</td>
<td>Day 1</td>
<td>Parietal lobe</td>
<td>—</td>
</tr>
</tbody>
</table>

Primary hemorrhage — other than *S. aureus*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Organism</th>
<th>Duration of symptoms</th>
<th>Antecedent ischemia</th>
<th>Day of hemorrhage</th>
<th>Site of hemorrhage</th>
<th>Arteriography</th>
</tr>
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<tbody>
<tr>
<td>8/33/M</td>
<td>52</td>
<td>M</td>
<td>Culture negative</td>
<td>3½ wks</td>
<td>7 wks</td>
<td>7½ wks</td>
<td>Hemispheric</td>
<td>—</td>
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<tr>
<td>9/26/M</td>
<td>35</td>
<td>M</td>
<td><em>Streptococcus viridans</em></td>
<td>4 wks</td>
<td>Day 1</td>
<td>Temporal lobe</td>
<td>No mycotic</td>
<td></td>
</tr>
<tr>
<td>10/21/M</td>
<td>62</td>
<td>M</td>
<td><em>Streptococcus sanguis</em></td>
<td>Uncertain</td>
<td>None</td>
<td>Day 1</td>
<td>Hemispheric</td>
<td>—</td>
</tr>
<tr>
<td>11/30/M</td>
<td>70</td>
<td>M</td>
<td>Diphteroids</td>
<td>2 days</td>
<td>None</td>
<td>14 mos</td>
<td>Frontal lobe</td>
<td>(+) Mycotic</td>
</tr>
<tr>
<td>12/55/Ft</td>
<td>55</td>
<td>F</td>
<td><em>S. epidermidis</em></td>
<td>2 wks</td>
<td>None</td>
<td>4 mos</td>
<td>Frontal lobe</td>
<td>—</td>
</tr>
<tr>
<td>13/62/Mt</td>
<td>62</td>
<td>M</td>
<td><em>S. epidermidis</em></td>
<td>2 wks</td>
<td>None</td>
<td>Day 9</td>
<td>Hemispheric</td>
<td>No mycotic</td>
</tr>
</tbody>
</table>

Hemorrhagic infarction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Organism</th>
<th>Duration of symptoms</th>
<th>Antecedent ischemia</th>
<th>Day of hemorrhage</th>
<th>Site of hemorrhage</th>
<th>Arteriography</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/27/Mt</td>
<td>45</td>
<td>M</td>
<td><em>Actinobacillus</em></td>
<td>7 days</td>
<td>Day 2</td>
<td>Day 4</td>
<td>Occipital lobe</td>
<td>—</td>
</tr>
<tr>
<td>15/48/Mt</td>
<td>58</td>
<td>M</td>
<td><em>Streptococcus bovis</em></td>
<td>6 wks</td>
<td>Day 1</td>
<td>Day 18</td>
<td>Hemispheric</td>
<td>—</td>
</tr>
<tr>
<td>16/25/M</td>
<td>60</td>
<td>M</td>
<td><em>S. aureus</em></td>
<td>4 days</td>
<td>Day 1</td>
<td>Days 1–4</td>
<td>Hemispheric</td>
<td>—</td>
</tr>
<tr>
<td>17/74/M</td>
<td>74</td>
<td>M</td>
<td><em>S. aureus</em></td>
<td>2 days</td>
<td>Day 1</td>
<td>Days 1–7</td>
<td>Hemispheric</td>
<td>—</td>
</tr>
</tbody>
</table>

F, female; M, male; 2°, secondary to; ICH, intracranial hemorrhage; CNS, central nervous system.

*Time interval in relation to Day 1, day of hospital admission.

†Contralateral brain ischemia.

Patient 4. A 68-year-old man with metastatic prostate adenocarcinoma and an aortic valve bioprosthesi

sion, and 4 blood cultures grew *S. aureus*. Coagulation studies were normal; platelet count was 80,000/mm³. CT showed a right temporal lobe hematoma (Figure 1). He died 2 weeks later of cardiac complications. Autopsy revealed acute endocarditis of mitral and aortic valves, a myocardial abscess, recent infarcts of the spleen, kidneys, and heart, and a right temporal lobe hemorrhage. Inflammatory changes were present in the walls of arteries adjacent to the hematoma; no aneurysmal dilatation was found.

Patient 5. A 31-year-old intravenous drug abuser with fever and malaise for 1 week and with additional headache had right-sided weakness the day of admission. He had a new diastolic murmur, and all blood cultures grew *S. aureus*. CT showed a left occipital lobe hemorrhage (Figure 1). Coagulation studies and platelet count were normal. Cerebral arteriography revealed no mycotic aneurysm. A craniotomy was performed to evacuate the hematoma. The patient had good neurologic recovery and underwent aortic valve replacement 6 weeks later. There has been no further ICH in the subsequent 5 years.

Patient 6. A 57-year-old diabetic woman was admitted after 2 days of chills, fever, and nausea. Multiple blood cultures grew *S. aureus*. On Day 2, she became obtunded; CT showed a left parieto-occipital hemorrhage. Coagulation studies and platelet count were normal. Arteriography revealed no mycotic aneurysms. Craniotomy was performed to remove the hematoma. She underwent mitral and aortic valve replacement 4 weeks later; acute endocarditis with large vegetations were pathologically confirmed. There has been no further ICH in the subsequent 5 years.

Patient 7. A 52-year-old female intravenous drug abuser suffered 2 days of fever and progressive obtu

sation. She was febrile and deeply stuporous, with decerebrate responses to noxious stimulation. She had conjunctival petechiae and a prominent cardiac murmur. Four blood cultures grew *S. aureus*. 

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Table 1. (continued)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Outcome</th>
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<tr>
<td>Arteritis</td>
<td>Death 2° ICH</td>
</tr>
<tr>
<td>Arteritis</td>
<td>Death 2° ICH</td>
</tr>
<tr>
<td>Arteritis</td>
<td>Cardiac death</td>
</tr>
<tr>
<td>—</td>
<td>Death, probably CNS</td>
</tr>
<tr>
<td>—</td>
<td>Craniotomy, survived</td>
</tr>
<tr>
<td>—</td>
<td>Craniotomy, survived</td>
</tr>
<tr>
<td>—</td>
<td>Death 2° sepsis</td>
</tr>
<tr>
<td>Arteritis</td>
<td>Death 2° ICH</td>
</tr>
<tr>
<td>( + ) Myotic</td>
<td>Survived</td>
</tr>
<tr>
<td>—</td>
<td>Survived</td>
</tr>
<tr>
<td>—</td>
<td>Craniotomy, survived</td>
</tr>
<tr>
<td>—</td>
<td>Death 2° ICH</td>
</tr>
<tr>
<td>—</td>
<td>Death 2° ICH</td>
</tr>
<tr>
<td>No myotic</td>
<td>Cardiac death</td>
</tr>
<tr>
<td>—</td>
<td>Asymptomatic ICH, survived</td>
</tr>
<tr>
<td>—</td>
<td>Asymptomatic ICH, survived</td>
</tr>
</tbody>
</table>

Coagulation studies and platelet count were normal. CT showed 2 discrete hemorrhages in the left parietal lobe and right basal ganglia, as well as a hemorrhagic infarct of the right parieto-occipital region (Figure 1). She developed hypotension and disseminated intravascular coagulation and died within 48 hours of admission. Autopsy was not performed.

Comment on Patients 1–7

These 7 patients shared a similar clinical course of *S. aureus* endocarditis with onset of ICH during uncontrolled infection, before or within 48 hours of the initiation of antibiotic therapy. *S. aureus* was the infecting organism in 78% (7 of 9) of cases with early ICH (within 48 hours of hospital admission). Conversely, all patients with *S. aureus* and symptomatic ICH experienced hemorrhage within 48 hours of hospital admission.

Recognized ipsilateral embolism preceded ICH in only 1 patient (Patient 1), whereas embolic infarcts in different brain areas on CT coexisted with ICH in 2 other patients (Patients 4 and 7). In 2 patients with ICH who were obtunded or confused on admission (Patients 2 and 3), the possibility of ipsilateral ischemic events preceding ICH cannot be discounted given incomplete historical information, and both had widespread systemic emboli at autopsy. In 2 patients (Patients 1 and 2), the pathologic lesion underlying the ICH was shown to be septic erosion of the arterial wall without aneurysmal dilatation (Figure 2). In another patient (Patient 3), the exact site of inflammatory arterial rupture was not discovered at autopsy, but no mycotic aneurysm was present. In 2 additional patients (Patients 5 and 6), arteriography shortly after ICH did not reveal mycotic aneurysms, and there was no further ICH. Patient 4 died 2 weeks after ICH; death was immediately preceded by focal seizures, but neither CT nor autopsy was available to assess for recurrent hemorrhage as the precipitating event.

Patient 8. A 33-year-old healthy man presented to his physician for 2 weeks of fever, chills, and malaise and was empirically treated with erythromycin. Ten days later, he again developed malaise and confusion. Splinter hemorrhages were present on both palms. CT showed a small right parietal cortical infarct; an echocardiogram was interpreted as showing a vegetation on the mitral valve. Multiple blood cultures were sterile. He was treated for 5 weeks with i.v. antibiotics for presumed infective endocarditis. Two weeks after finishing antibiotic therapy (2½ months since the start of clinical illness), he suddenly became aphasic, and CT showed a small left parietal infarct. Echocardiography again showed a presumed 1.0-cm mitral vegetation. Blood cultures were sterile, and antibiotics were withheld. Four days later, while awaiting valve replacement surgery, he suddenly developed coma; CT showed a large left brain hemorrhage (Figure 3). He rapidly developed transtentorial herniation and died; autopsy showed vegetative endocarditis on a myxomatous mitral valve (no bacteria) and brain hemorrhage with herniation. Adjacent to the hematoma, a large branch of the MCA was infiltrated with acute pyogenic arteritis (Figure 4).

Comment on Patient 8

After apparent bacteriologic cure of infective endocarditis, an embolic brain infarct was shortly followed by pyogenic arteritis with massive ICH. The mitral valve showed healing endocarditis without active infection. The large vegetation suggested by echocardiography shortly before death was not seen at autopsy, suggesting it had embolized. Alternatively, misinterpretation of the echocardiograms could have resulted from unrecognized myxomatous changes mimicking vegetations. In this patient, septic arteritis from an infected embolus occurred after apparent, but not actual, bacteriologic cure.

Patient 9. A 26-year-old intravenous drug abuser with 4 weeks of fever, chills, and malaise developed abrupt nonfluent aphasia and right hemiparesis. Examination revealed splinter hemorrhages and a mitral regurgitant murmur. Multiple blood cultures grew *Streptococcus viridans*. The initial CT was done 2 days after stroke onset, revealing a left posterior temporal—occipital lobar hemorrhage. Coagulation studies and platelet count were normal. Arteriography performed 8 days later showed changes of an avascular mass but no aneurysm. He recovered uneventfully following 6 weeks of antibiotics. There has been no further ICH in the subsequent 7 years.
Comment on Patient 9

The mechanism of ICH is uncertain. The hemorrhagic lesion appeared quite dense on CT, favoring primary hemorrhage rather than secondary hemorrhagic infarct in this nonanticoagulated patient, although the 36-hour interval between the stroke and the initial CT was sufficient time for hemorrhagic transformation. Arteriography did not reveal an aneurysm. ICH occurred early, during uncontrolled infection, and may represent septic arteritis associated with a nonvirulent organism.

Patient 10. A 21-year-old man suddenly collapsed, remaining comatose. CT showed a large left hemispheric brain hemorrhage with intraventricular extension (Figure 3); he died of transtentorial herniation shortly thereafter. He had been ill for an uncertain period of time, complaining of fever, recurrent headache, and a 9-kg weight loss. Multiple premortem blood cultures grew *Streptococcus sanguis*. Autopsy showed a bicuspid aortic valve with active endocarditis with vegetations. An aneurysm was found adjacent to a large hematoma, with acute inflammatory changes but...
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no definite bacteria seen. Septic embolic infarcts of the spleen, pancreas, and myocardium were present.

Patient 11. A 30-year-old man had 2 days of prominent headache, fever, and malaise. Neurologic examination was normal. Extensive evaluation for fever of unknown origin included spinal fluid findings of aseptic meningitis, a diastolic heart murmur, a mitral valve vegetation on echocardiography, and diptheroid species in 2 of 8 blood cultures. Two months before admission, he had an abscessed tooth removed. Multiple other investigations were unrevealing; he was treated with antibiotics for possible infective endocarditis. Occasional headaches persisted. Fourteen months later, he had a sudden severe headache and neck stiffness. CT showed a lobar hematoma (Figure 3). Arteriography revealed an aneurysm in a peripheral branch of the MCA, adjacent to the hemorrhage (Figure 5). The aneurysm was surgically repaired. Multiple blood cultures and culture of the resected aneurysm were sterile. Repeat arteriography 8 months later was normal.

Comment on Patients 10 and 11

Of 15 patients with symptomatic ICH, there were only 2 (13%) in whom ruptured mycotic aneurysms were documented. However, arteriographic (n = 5) or autopsy (n = 6) data were available in only 11 patients. The organisms were nonvirulent, and ICH occurred several weeks after the initial symptoms (although exact duration of illness in Patient 10 was unclear). ICH was the presenting feature in 1 patient and occurred months after bacteriologic cure in the other. Antecedent clinical brain embolism did not occur in either patient.

Patient 12. A 55-year-old woman with a bioprosthetic mitral valve had fever and dyspnea for 2 weeks. Examination showed fever, splenomegaly, and palmar petechiae. Sixteen blood cultures all grew S. epidermidis. Coagulation studies and platelet count were normal. She had sudden left lower extremity pain with diminished arterial pulses on Day 9 and a sudden left hemiparesis on Day 16, both attributed to embolism. Cranial CT showed a small right parietal hypodensity consistent with an acute infarct. Abdominal CT revealed splenic and renal infarcts. Anticoagulation was initiated, the neurologic deficit resolved, and the remainder of the hospital course was uncomplicated. She was discharged on chronic anticoagulation. Four months later, she had abrupt right hemiparesis, headache, and confusion. PT was 3.5 × control; blood cultures were sterile. CT showed a left frontal lobe hemorrhage (Figure 3), which was surgically evacuated. She made a good recovery; there has been no further ICH in the subsequent 2 years.

Comment on Patient 12

No arteriography was done. ICH was associated with excessive anticoagulation, which was assumed to be the proximate cause.

Patient 13. A 62-year-old man with a bioprosthetic mitral valve and chronic atrial fibrillation was receiving chronic oral anticoagulation. He presented with 2 weeks of malaise and fever; 6 blood cultures grew S. epidermidis. Antimicrobial agents were started. Admission PT was 1.5 × control, and oral anticoagulation was continued. On Day 9, he was afebrile and doing well when he suddenly developed left hemiparesis. CT showed a hemorrhage in the white matter of the
right hemisphere (Figure 3). PT was 1.8 x control. Arteriography showed changes of an avascular mass but no aneurysm. The hematoma was surgically evacuated, but he remained hemiplegic, dying of secondary pulmonary complications resulting from his neurologic deficit. No autopsy was performed.

Comment on Patient 13
The mechanism of ICH is uncertain. No mycotic aneurysm was revealed by arteriography, and no antecedent ischemic event suggested secondary hemorrhagic transformation in a setting of anticoagulation. ICH occurred after 8 days of antibiotics and was associated with an organism that is usually nonviral.

Patient 14. A 27-year-old man with a mechanical aortic valve had fever, headache, and malaise for 1 week. He was receiving chronic oral anticoagulation (admission PT was 1.4 x control) and chronic penicillin prophylaxis. On admission, blood cultures grew Actinobacillus, i.v. antibiotics were begun, and oral anticoagulation was replaced with i.v. heparin. On Day 2, he had abrupt weakness and numbness of his left side; partial thromboplastin time (PTT) was 1.3 x control. Initial CT was normal, and heparin was discontinued. Twenty-four hours after stroke onset, repeat CT showed hypodensity involving the midposterior portion of the right hemisphere, consistent with acute infarct. Heparin infusion was restarted without a bolus loading dose. Six hours later, he complained of headache, had a convulsion, and evolved signs of herniation. PT was 1.6 x control, PTT was 1.4 x control, and platelet count was normal. CT showed hemorrhage into the infarct with intraventricular extension. He was brain dead the next day. Autopsy showed acute prosthetic valve endocarditis with perivalvular abscess; permission for postmortem brain examination was denied.

Patient 15. A 48-year-old man with a mechanical prosthetic mitral valve suffered 6 weeks of fever followed by sudden left hemiparesis, concomitant right hand weakness, and severe dysarthria on the day of admission. Initial CT was normal, and he was receiving chronic oral anticoagulation; admission PT was 2.1 x control. Anticoagulation was continued, and by Day 7, his neurologic deficits had largely resolved. Multiple blood cultures grew Streptococcus bovis; antimicrobial therapy was started on Day 7. On Day 17, he became transiently obtunded but with no focal findings. The next day, he became suddenly stuporous, aphasic, and right hemiplegia. CT showed a large left parietal hemorrhage with surrounding hypodensity, consistent with either edema or infarction (Figure 3). PT was again 2.1 x control. He slowly improved neurologically but died 2 weeks later during cardiac valve replacement surgery. Autopsy revealed acute endocarditis with multiple vegetations and a large hemorrhage surrounded by a rim of infarction and with intraventricular extension of bleeding. There was no evidence of septic arteritis or aneurysmal changes. Splenic and renal infarcts were present.

Comment on Patients 14 and 15
In Patients 14 and 15, ICH was presumably secondary to hemorrhagic transformation of an initial infarct during anticoagulation. In Patient 14, the secondary hemorrhage precipitated transtentorial herniation. In Patient 15, ICH occurring 11 days after initiation of antibiotic therapy was assumed to be due to a ruptured mycotic aneurysm. It is not entirely certain, even at postmortem, whether ICH resulted from a mycotic aneurysm that was obliterated at rupture or from hemorrhagic transformation of a recent embolic infarct in this anticoagulated patient. 

Patient 16. A 25-year-old intravenous drug abuser had 4 days of fever, chills, and malaise followed by abrupt right-sided paralysis the day of admission. He was febrile with a prominent systolic heart murmur. He was globally aphasic with right hemiplegia. Initial CT (within 6 hours of stroke) showed multiple small areas of hypodensity in both hemispheres. Multiple blood cultures grew S. aureus; echocardiography revealed a mitral valve vegetation. Coagulation studies and platelet count were normal. During the initial 4 days of antibiotics, neurologic deficits improved slightly; repeat CT showed a large MCA distribution infarct with central hemorrhagic transformation (Figure 6). Hemorrhage was not apparent on CT repeated on Day 10. He suddenly deteriorated on Day 17; a
fourth CT showed hypodense areas consistent with new infarcts (Figure 6).

**Patient 17.** A 74-year-old man with a mechanical prosthetic aortic valve had abrupt left-sided weakness following 2 days of fever. On admission, there was a severe left hemiparesis, anosognosia, and left hemianopsia. PT was 1.2× control on admission; oral anticoagulants were discontinued. Six blood cultures grew *S. aureus*. Admission CT (within 6 hours of stroke) was normal. Neurologic deficits slowly improved. Repeat CT after 1 week showed a large area of hypodensity occupying most of the right parietal lobe with minimal patchy areas of increased density within the infarct. On Day 19, anticoagulation was restarted. Subsequent course was uneventful with no ICH in the succeeding 8 months.

**Comment on Patients 16 and 17**

Diagnosis of hemorrhagic infarction was based on serial CTs demonstrating hemorrhagic transformation of an initially nonhemorrhagic infarct. In these 2 patients, hemorrhagic transformation occurred within large infarcts and was not associated with clinical worsening.

**Discussion**

ICH complicating infective endocarditis is the result of a spectrum of arterial injury ranging from acute, pyogenic necrosis to large, aseptic aneurysms that may rupture weeks to months after bacteriologic cure. While the term "mycotic aneurysm" has usually been applied to both processes, the difference is not merely semantic. The extremes of this continuum appear to represent different clinical syndromes with distinct therapeutic implications.

Septic emboli appear to be a necessary substrate for ICH, although clinically recognized ipsilateral embolism precedes ICH in only 40% of cases. Sustained bacteremia in tricuspid valve endocarditis, even with virulent organisms, does not result in ICH, supporting the necessity of embolic fragments. The offending infected emboli may escape clinical recognition by being small, by incompletely obstructing flow, or by preventing infarction by collateral circulation. Clearly, lack of antecedent clinical brain embolism does not eliminate the risk of ICH, as most hemor- rhages occurred without recognized, antecedent embolism. Ipsilateral or contralateral brain ischemia preceded symptomatic ICH in only 5 (33%) of our 15 symptomatic patients.

Symptomatic ICH associated with *S. aureus* occurred within 48 hours of admission. This propensity for early hemorrhages in *S. aureus* endocarditis has been noted by others. Although ICH usually occurs early during the bacteremic phase, patients with *S. aureus* endocarditis can later develop mycotic aneurysms. The lobar location of ICH on CT is distinctive and should suggest infective endocarditis when occurring in relatively young patients with fever (Figure 1). ICH due to septic arteritis usually occurs during uncontrolled infection. Surgical treatment is difficult, requiring sacrifice of the involved artery, sometimes with microvascular pedicle/bypass surgery, as there is not a well-delineated aneurysmal neck that can be readily clipped.

Dilated mycotic aneurysms usually have no evidence of active infection and may be more amenable to surgical therapy. Many, possibly most, mycotic aneurysms heal spontaneously without rupture during antimicrobial treatment. Resolution may take many months. However, late rupture of mycotic aneurysm after otherwise successful treatment of infective endocarditis can occur (Patient 11). It is possible that additional patients in our series developed late rupture of mycotic aneurysms, as prolonged follow-up was not complete in all patients and such patients may not have been identified if hospitalized at other institutions.

While ICH occurs in about 5% of patients during the acute course of infective endocarditis, proven ruptured mycotic aneurysm is reported in only about 1.7% (range 0.8-2.8%) (Table 2). Of patients with ICH and ruptured mycotic aneurysms, only about one third undergo surgical repair, due to fatal initial hemorrhage or to multiplicity of aneurysms. The fraction of our patients who could have potentially benefited from surgical treatment of mycotic aneurysm under ideal circumstances of detection and prediction of rupture is quite small. Among our 179 patients with infective endocarditis of mitral and/or aortic valves, ICH possibly related to potentially surgically treatable mycotic aneurysm occurred in a maximum of 2.2% during the acute hospital course (Patients 4, 13, 14, and 15). Two of these 4 patients (Patients 4 and 14) were never surgical candidates due to large initial infarcts. Hence, a maximum 1.1% of our patients could have benefitted

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**Table 2. Brain Hemorrhage and Mycotic Aneurysm in Infective Endocarditis**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>% brain hemorrhage</th>
<th>% proven ruptured</th>
<th>% operations ruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current series</td>
<td>209</td>
<td>7</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Pruitt et al</td>
<td>218</td>
<td>6</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Royden-Jones et al</td>
<td>385</td>
<td>3</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>LeCam et al</td>
<td>855</td>
<td>18</td>
<td>4.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Wilson et al</td>
<td>628</td>
<td>—</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>Frazee et al</td>
<td>459</td>
<td>—</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Dreyer and Fields</td>
<td>28§</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Garvey and Neu et al</td>
<td>107</td>
<td>—</td>
<td>2.8</td>
<td>—</td>
</tr>
<tr>
<td>Mean</td>
<td>5</td>
<td>1.7</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

*Recent clinical reports, excluding asymptomatic brain hemorrhage due to hemorrhagic infarction. Brain hemorrhage largely limited to that occurring during the acute course, as few reports provide substantial follow-up. Includes 30 cases of tricuspid valve endocarditis. Selected population primarily derived from referral-based intensive care unit with high mortality and high prevalence of major complications. Selected patients with heroin-associated endocarditis.*
from surgical correction of a potential mycotic aneurysm under ideal circumstances during the acute hospital course. A similar figure for ICH following hospital discharge cannot be generated due to incomplete follow-up of all patients.

Enthusiasm for detection of unruptured mycotic aneurysms is tempered by the uncertain risk of rupture. Anecdotal case reports confirm that many unruptured mycotic aneurysms, including large and enlarging mycotic aneurysms, fully heal following antimicrobial therapy.8.14.15.26 The prevalence of unruptured intracranial mycotic aneurysms in patients with endocarditis is unknown. Among 24 patients without ICH in our series who underwent arteriography or autopsy, no incidental unruptured mycotic aneurysms were discovered, although early deaths and single arteriography may systematically underestimate late-developing mycotic aneurysms.26,27 For the 1–2% of patients who experience ruptured mycotic aneurysm following hospital admission, there is no accurate denominator of the frequency of unruptured aneurysms to determine risk of rupture. Current recommendations concerning the indications for surgery for unruptured mycotic aneurysms are entirely arbitrary.8,26

All 3 patients with symptomatic ICH occurring during hospitalization for endocarditis, but >48 hours after admission, were receiving anticoagulants because of mechanical prosthetic valves. None was excessively anticoagulated; 2 had experienced prior ischemic strokes.

We postulate that brain emboli complicating infective endocarditis result in ICH by at least 3 different mechanisms: 1) sterile emboli can cause infarcts that undergo secondary hemorrhagic transformation that is usually mild and asymptomatic in the absence of anticoagulation therapy; 2) septic emboli during uncontrolled infection, particularly with virulent organisms, can cause acute, erosive arteritis with rupture; and 3) septic emboli during effective antimicrobial therapy and/or associated with nonvirulent organisms can injure the arterial wall, leading to subacute development of aneurysms that are often aseptic at the time of rupture. S. aureus is the most common organism underlying symptomatic ICH; these hemorrhages usually occur early, during uncontrolled infection.1,3,13 Mycotic aneurysms amenable to surgery appear to underlie only a fraction of brain hemorrhages in patients with infective endocarditis.

Acknowledgments

We are particularly grateful to Linda Ansbacher, MD (Columbia, Mo.), and Anthony D’Agnostino, MD (Portland, Ore.), for providing pathologic material and Wanda Schaeffer of Good Samaritan Hospital (Portland, Ore.) for obtaining case records.

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Key Words • infective endocarditis • mycotic aneurysm • intracranial hemorrhage • hemorrhagic infarction
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Stroke. 1987;18:1048-1056
doi: 10.1161/01.STR.18.6.1048

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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