Original Contributions

Stroke in Infective Endocarditis

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We reviewed 212 consecutive episodes of infective endocarditis in 203 patients at six hospitals between 1978 and 1986 and found that 21% were complicated by stroke. Of 133 episodes involving native mitral and/or aortic valves, brain ischemia occurred in 19%, brain hemorrhage in 7%, and non-central nervous system emboli in 11%; vegetations were identified in 56% of 113 adequate echocardiograms and did not correlate with risk of embolism. In native-valve endocarditis, most (74%) ischemic strokes had occurred by the time of presentation and an additional 13% occurred ≤48 hours after diagnosis; the incidence of brain ischemia was 13% on presentation, 3% during the first 48 hours of hospitalization, and 2%-5% during the remainder of the acute course. Stroke recurred at a rate of 0.5%/day, often heralding relapse/uncontrolled infection. Only 9% of ischemic infarcts were large (all in patients with Staphylococcus aureus infection), while 8% were small and subcortical. Brain hemorrhage occurred primarily at the time of presentation, particularly in intravenous drug abusers, and was associated with uncontrolled S. aureus infection with pyogenic arteritis. Ischemic and hemorrhagic stroke continue to be frequent and important in patients with infective endocarditis and are clustered during uncontrolled infection. Patients with infective endocarditis and ischemic stroke on presentation seldom had recurrent emboli after the infection was controlled; anticoagulants and surgery are not warranted to prevent recurrent stroke in these patients. Symptomatic mycotic aneurysms are quite uncommon. (Stroke 1990;21:695-700)

Subjects and Methods

We retrospectively reviewed the records of all patients with infective endocarditis at six hospitals: three university-affiliated teaching hospitals (Medical Center Hospital in San Antonio, Texas during 1980–1986, University of Missouri Hospital in Columbia during 1978–1985, and Oregon Health Sciences University Hospital in Portland during 1980–1985), two large, private nonprofit urban hospitals during 1980–1985 (Good Samaritan Hospital in Portland and Santa Rosa Hospital in San Antonio), and one university-affiliated Veterans Administration hospital (Audie L. Murphy Veterans Hospital in San Antonio) during 1978–1986. Two university-affiliated teaching hospitals and both private hospitals (65% of patients) provide primary through tertiary care to a population of mixed socioeconomic status in urban areas of 100,000–1,000,000 people. One university-affiliated hospital (Medical Center Hospital) and the Veterans Administration hospital serve primarily indigent patients. Consecutive patients with endocarditis were identified by a computer search of discharge diagnosis codes (International Classification of Diseases–ninth revision codes 421.0, 421.9, and 424.0) supplemented by a review of infectious disease logbooks. Inclusion criteria were 1) a febrile illness with persistently positive blood cultures, predisposing heart disease or a new regurgitant murmur,
and no identified extracardiac source of infection; 2) for culture-negative endocarditis, a febrile illness with either pathologic confirmation or a new regurgitant murmur combined with oculocutaneous manifestations; or 3) for tricuspid valve endocarditis, persistently positive blood cultures without an extracardiac source of infection and either a characteristic murmur of tricuspid regurgitation, echocardiographic evidence of an abnormal tricuspid valve, or multiple pulmonary infiltrates suggestive of emboli. These criteria resulted in exclusion of many intravenous drug abusers with isolated staphylococcal bacteremia.

Of 377 charts reviewed, 212 (56%) episodes of endocarditis occurring in 203 patients met these inclusion criteria; this fraction was similar at all six hospitals. Excluded episodes were primarily those in patients with bacteremia and/or sepsis with possible endocarditis who were treated presumptively but had other extracardiac potential sources of infection. Pathologic confirmation of endocarditis (surgical or postmortem) was available for 82 episodes (39%). Echocardiographic results were not used to determine inclusion (except in tricuspid valve endocarditis). Of seven episodes (3%) of culture-negative endocarditis, five were confirmed as having endocarditis by surgery or at autopsy. The two patients suspected of having simultaneous mitral/aortic and tricuspid valve endocarditis were analyzed with the patients having mitral/aortic valve endocarditis.

Stroke was defined as a focal neurologic deficit of abrupt onset lasting >24 hours, whereas transient ischemic attacks (TIAs) were defined as focal neurologic deficits lasting <24 hours. The diagnosis of a subcortical infarct required compatible clinical neurologic deficits (excluding cortical signs) plus CT visualization of a purely subcortical lesion. The diagnosis of a cortical infarct required cortical signs (e.g., aphasia, hemianopsia) or CT visualization of a cortical lesion. Supratentorial infarcts that did not meet these criteria were deemed to be of uncertain location. Brainstem/cerebellar infarcts were classified based on the characteristic neurologic syndromes. Three strokes that followed prosthetic valve implantation were not included. Systemic embolism did not include the oculocutaneous manifestations and were restricted to episodes of clinical embolism. The diagnosis of renal embolism required arteriographic or radioisotope scan confirmation. Only episodes of clinical embolism (no occult emboli discovered at autopsy) were considered. Echocardiographic data were those of the original clinical reading; the diagnosis of vegetations on echocardiograms did not include those described as "possibly present" or those with only thickening of the involved valve. Detailed analysis of patients with prosthetic valve endocarditis appears elsewhere, as part of a larger series. Statistical comparisons were performed using standard $\chi^2$ tables.

**Results**

Demographic features of the patients with infective endocarditis varied importantly between types of hospitals (Table 1). At university-affiliated teaching hospitals patients with endocarditis were younger (mean age 38 compared with 51 years) and more often intravenous drug abusers (38% compared with 15%) than at private and Veterans Administration hospitals. Among 59 episodes involving the mitral valve, mitral valve prolapse occurred in 16 (27%) and mitral anulus calcification occurred in six (10%). Among 61 episodes of aortic valve endocarditis, bicuspid aortic valve (nine, 15%) and calcific aortic stenosis (seven, 11%) were the major structural lesions.

Among 133 episodes of endocarditis involving native mitral and/or aortic valves, ischemic stroke/TIA occurred in 19% (25) and non–central nervous system (CNS) systemic emboli occurred in 11% (15) (Table 2); ischemic stroke and/or brain hemorrhage occurred in 23% (31; both occurred in three episodes). Overall, 69% (37) of the 54 episodes of clinical embolism in episodes of native-valve endocarditis (including multiple emboli) were to the brain. Among episodes of native-valve endocarditis, ischemic stroke ($p=0.06$), brain hemorrhage ($p=0.01$), and death ($p=0.001$) were more frequent with *Staphylococcus aureus* infection than with all other infections (Table 3). Although small numbers limit the power of our comparisons, no important differences in the rates of stroke or systemic embolism were found when comparing valve sites with the same infecting organism (Table 4).
Among 133 episodes of native-valve left-sided endocarditis, echocardiograms were obtained and were technically adequate to assess for valvular vegetations in 85% (113); most echocardiograms (81%) were both M-mode and two-dimensional echocardiograms, while the remaining 21 (performed during the earlier years) were only M-mode. Vegetations were seen on 45% (14 of 31 initial echocardiograms in episodes of *Staphylococcus aureus* endocarditis and on 57% (35) of 61 initial echocardiograms in episodes of *Streptococcus* sp. endocarditis. Ischemic stroke had occurred in 21% (11) of the 53 episodes in which vegetations were present on the initial echocardiogram compared with in 20% (12) of the 60 episodes without vegetations. Late emboli (those occurring >48 hours after admission) occurred in 15% (eight) of the 53 episodes with vegetations on the initial echocardiogram and in 7% (four) of the 60 without vegetations (p>0.05).

Among the 133 episodes of native-valve endocarditis, CT was carried out in 92% of the 38 episodes with focal or multifocal neurologic deficits, allowing reliable classification of the stroke as ischemic or hemorrhagic. Ischemic stroke/TIA occurred in 25 episodes in 25 patients (mean age 50 years, 68% men); of the 37 ischemic events, three (8%) were TIA (all amaurosis fugax) and the remainder were strokes. By combined CT and clinical criteria, 62% (23) of the 37 ischemic events involved the cortex or cerebellar hemisphere, 16% (six) were exclusively subcortical, 11% (four) involved the retina (three were amaurosis fugax, one was a central retinal artery occlusion), and the remaining 11% (four) were of uncertain location. Three infarcts (8%) involved the occipital cortex; three others (8%) had the typical CT and clinical features of small subcortical infarcts in the distribution of a single penetrating artery (e.g., they were lacunes). Excluding the four retinal ischemic events, most infarcts were small (19 of 33, 58%) or of moderate size (11 of 33, 33%); all three (9%) large hemispheric infarcts occurred in patients with *Staphylococcus aureus* infection. Among 18 ischemic events in patients with *Staphylococcus aureus* endocarditis, 10 (56%) were moderate-sized or large infarcts, seven (39%) were small, and one episode (5%) was amaurosis fugax.

Time of the onset of CNS ischemia could not be determined in two patients with native-valve endocarditis; of the remaining 23 patients, onsets occurred at the time of presentation in 74% (17) and within 48 hours after diagnosis in 13% (three). Of the 37 episodes of initial CNS and non-CNS clinical embolism in episodes of native-valve endocarditis, 76–84% (28–31) occurred within 48 hours of presentation (the range reflects the uncertain timing of three embolisms). Overall, the rate of initial ischemic stroke was 13–14% (17–19 of 133) on presentation, 3–4% (3–5 of 116) during the first 48 hours after...
admission, and 2–5% (2–4 of 83) during the subsequent 4 weeks (the decreasing denominator reflects deaths and valve replacement).

Of the 25 initial CNS ischemic events in episodes of native-valve endocarditis, 56% (14) were single and unifocal, 28% (seven) were multifocal, and 16% (four) were unifocal but associated with concurrent "toxic" encephalopathy. Multifocal ischemia was more often associated with Staphylococcus aureus endocarditis (five of 10, 50%) than with Streptococcus viridans endocarditis (one of nine, 11%) (p > 0.05). Brain hemorrhage with dramatic clinical deterioration and death followed the initial ischemic stroke in two of the 25 episodes (8%); in both episodes the patient had uncontrolled infection (Staph. aureus in one, Strept. viridans in the other) with pyogenic arteritis eroding the arterial wall adjacent to the septic emboli at postmortem examination. For these two patients the interval from the initial ischemic stroke to arterial rupture was 24 hours with Staph. aureus and 4 days with Strept. viridans infection.

Following the initial embolism in native-valve endocarditis, only one of the 37 patients received anticoagulants (subcutaneous heparin 10,000 units/day) although three additional patients had underlying coagulation abnormalities. Embolism recurred in 19% (seven [five had a stroke and two had systemic embolism]) of the patients, in 27% (five) of 18 episodes with vegetations but in only 13% (two) of 15 without vegetations on echocardiograms. The risk of recurrent stroke following initial brain ischemia was 0.5%/day during hospitalization. Active/uncontrolled infection was present in 43% (three) of the seven patients with recurrent embolism. The prevalence of recurrent ischemic stroke during controlled infection was 11% (risk approximately 0.3%/day) in the 36 patients without anticoagulation treatment.

Nine (7%) of the 133 episodes of native-valve endocarditis were complicated by symptomatic intracranial hemorrhage during the acute course. No patient was receiving anticoagulants at the time of hemorrhage, although one patient had coagulation abnormalities attributed to sepsis. Asymptomatic hemorrhagic transformation of an initially ischemic stroke was seen on serial CTs in two additional patients. Intracranial hemorrhage occurred in 17% (six) of 36 patients with Staph. aureus infection of native mitral/aortic valves and in 36% (four) of 11 patients who were intravenous drug users with Staph. aureus infection. Brain hemorrhage was a presenting symptom in six of the nine patients and occurred ≤48 hours after admission in two others. The single late hemorrhage occurred in a patient who had recently completed 6 weeks of antibiotic therapy and who then had an ischemic stroke followed by a fatal brain hemorrhage 4 days later; autopsy showed pyogenic arteritis with rupture of the artery. The intracranial hematomas were lobar hematomas in eight patients (three with intraventricular extension) and primarily subarachnoid in the other. Mortality was 67% (six of nine); four deaths resulted directly from the brain hemorrhage. A dilated mycotic aneurysm was identified in only one patient with Streptococcus sanguis infection who presented with a fatal brain hemorrhage. Acute pyogenic arteritis without aneurysm was found at autopsy in four patients, and three others underwent arteriography, which did not show mycotic aneurysms.

Of 26 episodes in intravenous drug abusers with native-valve endocarditis, 42% (11) were Staph. aureus infection. Among 36 episodes of native mitral and/or aortic valve infection with Staph. aureus, ischemic stroke occurred less frequently (two of 11, 18% and eight of 25, 32%, p > 0.05) and primary brain hemorrhage occurred more frequently (four of 11, 36% and two of 25, 8%, p = 0.04) in drug abusers than in those without drug abuse.

Discussion

The prevalence of stroke complicating infective endocarditis has remained surprisingly constant in recent decades, despite important changes in several clinical aspects of this disorder. Approximately one fifth of patients with native-valve endocarditis have ischemic stroke (19% in this series). In two of 133 episodes (2%) of native-valve endocarditis, ischemic stroke was an isolated presenting feature, with endocarditis unsuspected for several days following hospital admission. Our data define several important features of endocarditis-associated stroke, including the clustering of events during uncontrolled infection, the relatively low risk...
of recurrent and late embolism when infection is controlled, and the infrequency of symptomatic mycotic aneurysms.

Three recent reports have linked vegetations on echocardiography to an increased risk of embolism (mean 3.7 [range 2.2-4.9] times)\(^{19-21}\) while another study failed to confirm this association.\(^{22}\) The lack of a relation between stroke and vegetations in our patients may be partially explained by the trend toward an inverse association between vegetations and \textit{Staph. aureus} endocarditis, with its high risk of early embolism. Recent advances in echocardiographic techniques, including the transesophageal approach, may result in useful clinical correlations.\(^{23-25}\)

Clinical embolism occurred in 28% of the episodes of native mitral and/or aortic valve endocarditis, and 69% of these emboli involved the brain. In recent reports, a mean of 63% (range 50-83%) of all clinical emboli involved the CNS.\(^{8,12,14,19,20}\) Clinical detection of emboli clearly underestimates their true prevalence. In one patient who presented with a unilateral stroke who had early arteriography, four cerebral arteries were obstructed by emboli; three obstructions were unsuspected clinically or by CT. Moderate to large infarcts were five times more frequent with \textit{Staph. aureus} endocarditis than with nonvirulent \textit{Streptococcus} sp. endocarditis. In our study, emboli in \textit{Staph. aureus} endocarditis tended to occur early, to be multiple, to involve the brain, and to carry a poor prognosis. Emboli in patients with nonvirulent \textit{Streptococcus} sp. infection more often occurred late, were usually single, and involved the systemic circulation. Most non-CNS clinical emboli involved the limbs, and 8% of our patients with native mitral and/or aortic valve endocarditis suffered limb emboli, a rate comparable to those in other recent series (3-8%).\(^{12,17,26}\)

Among episodes of \textit{Staph. aureus} endocarditis of native mitral and/or aortic valves, intravenous drug abusers tended to have fewer strokes (18%) than patients who did not abuse drugs (32%). This trend has been noted by others.\(^{27,28}\) Possible reasons for the lower stroke rate in drug abusers include misdiagnosis of tricuspid valve endocarditis, infection with less virulent strains of \textit{Staph. aureus}, and underrecognition of small cerebral emboli in such patients, whose mean age is 22 years younger than that of patients who do not abuse drugs. Ischemic stroke occurred in two of 33 patients with presumed isolated tricuspid valve involvement (6%). Paradoxical embolism via a patent foramen ovale has been previously reported in patients with tricuspid valve endocarditis.\(^{29,30}\) Unrecognized, concurrent involvement of the mitral and/or aortic valves could also underlie such strokes.

Of all emboli, almost two thirds (66%) occurred on presentation and an additional 11% during the subsequent 48 hours. The rate of initial stroke following the first 48 hours of antibiotics was only 2-5%. Clustering of emboli at presentation, during uncontrolled infection, has long been appreciated.\(^{2,8,28,31}\)

Aggregate data suggest that approximately 15% (range 9-18%) of all patients with native mitral and/or aortic valve endocarditis present with brain ischemia.\(^{2,21,33}\) Embolism long after bacteriologic cure occurs, but its frequency cannot be estimated in our study as prolonged follow-up was not available in many survivors. Earlier studies emphasized that most late emboli were major and often lethal,\(^{26}\) but two recent studies with long-term follow-up reported late emboli, with predominantly minor nonfatal strokes, in only 1-2% of survivors.\(^{8,34}\)

We hypothesize that septic emboli, especially in patients with \textit{Staph. aureus} endocarditis, cause most intracranial hemorrhage due to pyogenic arteritis during uncontrolled infection.\(^{35}\) Intracranial hemorrhage occurred in 17% of patients with \textit{Staph. aureus} endocarditis in our series and in 32% (10 of 31) of those with \textit{Staph. aureus} mitral and/or aortic valve endocarditis another report.\(^{33}\) These hemorrhages occur early during the course and are not amenable to surgical prophylaxis, emphasizing the importance of early recognition of endocarditis and urgent antimicrobial treatment. Intracranial hemorrhage is infrequent during and following antibiotic therapy, unless infection relapses. Dilated mycotic aneurysms, often sterile at the time of rupture, occurred in 1.6% (21 of 1,284) of patients in recent series and are associated with streptococcal infection.\(^{8,12,18,32,35,36}\) As many unruptured mycotic aneurysms heal fully with antibiotic therapy while others unpredictably hemorrhage, we can discern at present no rational approach to presymptomatic detection and management of these uncommon lesions.\(^{16,23,37,38}\)

Most (87%) ischemic CNS events in patients with infective endocarditis occur on presentation or shortly thereafter, before control of infection. The risk of recurrent embolism is low when infection is controlled (0.3%/day). Late initial ischemic infarcts during antibiotic therapy (<5%) were small and nonrecurrent. These data do not support the use of anticoagulation for primary or secondary prevention of stroke complicating endocarditis. In patients who have early embolism before control of infection, initial embolism per se does not appear to warrant valve replacement in the absence of other indications.

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References


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