Acute Ischemic Stroke Patterns in Infective and Nonbacterial Thrombotic Endocarditis
A Diffusion-Weighted Magnetic Resonance Imaging Study

Aneesh B. Singhal, MD; Mehmet A. Topcuoglu, MD; Ferdinando S. Buonanno, MD

Background and Purpose—Although infective endocarditis (IE) and nonbacterial thrombotic endocarditis (NBTE) are associated with cardioembolic stroke, differences in the nature of these conditions may result in differences in associated stroke patterns. We compared patterns of acute and recurrent ischemic stroke in IE and NBTE, using diffusion-weighted MRI (DWI).

Methods—Using ICD-9 diagnostic codes and medical record review, we identified 362 patients (387 episodes) with IE and 14 patients with NBTE. Thirty-five patients (with 27 episodes of IE, 9 NBTE) who underwent 36 initial and 29 follow-up DWI scans were selected for this study. DWI lesion size, number, and location were compared between groups and correlated with stroke syndromes and endocarditis features.

Results—DWI was abnormal in all but 2 patients. Four acute stroke patterns were identified: (1) single lesion, (2) territorial infarction, (3) disseminated punctate lesions, and (4) numerous small (<10 mm) and medium (10 to 30 mm) or large (>30 mm) lesions in multiple territories. All patients with NBTE exhibited pattern 4, whereas those with IE exhibited patterns 1, 2, 3, and 4 (6, 2, 8 and 9 episodes, respectively). Seventy-five percent of patients with pattern 3 exhibited the clinical syndrome of embolic encephalopathy. Vegetation size, valve, and organisms had no correlation with stroke patterns.

Conclusion—DWI has utility in differentiating between IE and NBTE. Patients with NBTE uniformly have multiple, widely distributed, small and large strokes, whereas patients with IE exhibit a panoply of stroke patterns. (Stroke. 2002; 33:1267-1273.)

Key Words: brain infarction • diffusion • endocarditis • infection • magnetic resonance imaging • neoplasm • stroke, embolic

Ischemic stroke is the most common neurological complication of endocarditis.1–4 It occurs in approximately 20% of patients with infective endocarditis (IE) and in more than a third of patients with nonbacterial thrombotic endocarditis (NBTE).1–4 Stroke is often one of the presenting symptoms of endocarditis and can be the only manifestation. Brain MRI findings in IE have been described and include multiple ischemic or hemorrhagic strokes, brain abscesses, and mycotic aneurysms.5,6 We are aware of only 2 case reports of brain MRI findings in NBTE, including 1 from our institution; both patients had multiple, widely distributed ischemic strokes.7,8 Patients with IE often undergo serial neuroimaging to assess for developing mycotic aneurysms, new strokes, and hemorrhagic strokes and to evaluate the efficacy of antibiotic treatment. Given the prevalence of endocarditis-associated stroke, and the value of MRI in managing these patients,6 it is important to determine the topography of acute and recurrent strokes associated with IE and NBTE.

Diffusion-weighted MRI (DWI) is a relatively new imaging technique that has several advantages over conventional MRI.9–11 Using DWI, it is possible to detect ischemic lesions within minutes after symptom onset.12 DWI can detect very small ischemic lesions because it has a high signal-to-noise ratio;13 it can be used to differentiate between acute and chronic lesions because ischemic lesions appear hyperintense within minutes after symptoms onset but lose their signal intensity after a few days or weeks.14,15 Thus, DWI can provide knowledge of the temporal and spatial nature of stroke, and this ability is helpful in determining stroke subtype and pathophysiology.16–22 Patients with lacunar syndromes are considered likely to have small-vessel disease if DWI shows a single hyperintense lesion in the relevant location. Conversely, the presence of multiple lesions, in more than 1 arterial territory, suggests emboli from a proximal source like the heart or the aortic arch. At present, it is not known whether the topography of embolic stroke can be influenced by the source of emboli or the nature of the underlying disease.

In this study, we analyzed initial and subsequent DWI scans in patients with IE and NBTE. The purpose of the study

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1267
was to compare the topography of acute and recurrent stroke in 2 conditions known to cause cardioembolic stroke.

Subjects and Methods
Using ICD-9 diagnostic codes 421 and 424.9, we identified 519 patients with 572 episodes of endocarditis admitted to the Massachusetts General Hospital after 1993, the year DWI entered clinical practice at this institution. We reviewed medical records and retrospectively confirmed the diagnosis of NBTE in 14 patients and IE in 362 patients who, in the aggregate, suffered 387 episodes of endocarditis. A diagnosis of IE was confirmed if the patient had pathologically verified IE or met Duke clinical criteria for “definite” or “possible” endocarditis. A diagnosis of NBTE was confirmed if the diagnosis was made on autopsy or if the patient had a triad of (1) a disease process known to be associated with NBTE, (2) vegetations on echocardiogram, and (3) the presence of embolic phenomena. The medical history, neurological examination findings, and relevant laboratory and radiological data were recorded for all patients.

Thirty-five patients who underwent DWI were selected for this study (26 with IE and 9 with NBTE). One patient underwent DWI during each of 2 episodes of staphylococcal endocarditis; each episode was recorded separately for the purposes of this study and thus a total of 27 episodes of IE were analyzed. Among patients with NBTE, valvular vegetations were identified by transesophageal echocardiogram in 5 patients, by transthoracic echocardiogram alone in 3 patients, and by autopsy in 1 patient. Twenty-six of the 27 episodes of IE were evaluated by transesophageal echocardiogram, and vegetations were documented in 24 episodes.

Clinical syndromes were classified according to the Oxfordshire Community Stroke Project criteria as total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS). In addition, patients who had discrete focal neurological deficits localized to both the anterior and posterior circulations were classified as “combined syndromes.” Patients with acute mental status changes attributable to embolic stroke, but without documented focal neurological deficits, were classified as “embolic encephalopathy.”

To study the topographical characteristics of the presenting stroke, we analyzed initial DWI films; to study patterns of recurrence and/or evolution of stroke, we reviewed subsequent DWI scans in all patients in whom it was performed. The presence, size, number, and location of all hyperintense lesions (ischemic strokes) were noted. Lesions were considered small if the largest axial diameter was <10 mm, medium if 10 to 30 mm, and large if >30 mm. Lesions were considered multiple if they were noncontiguous on contiguous slices. We made note of the involved arterial territory (anterior cerebral artery, middle cerebral artery [MCA], posterior cerebral artery [PCA], vertebrobasilar territory, borderzone) and arterial circulation (unilateral carotid, bilateral carotid, vertebrobasilar, combined). To study the topographical characteristics of the presenting stroke, we analyzed initial DWI films; to study patterns of recurrence and/or evolution of stroke, we reviewed subsequent DWI scans in all patients in whom it was performed. The presence, size, number, and location of all hyperintense lesions (ischemic strokes) were noted. Lesions were considered small if the largest axial diameter was <10 mm, medium if 10 to 30 mm, and large if >30 mm. Lesions were considered multiple if they were noncontiguous on contiguous slices. We made note of the involved arterial territory (anterior cerebral artery, middle cerebral artery [MCA], posterior cerebral artery [PCA], vertebrobasilar territory, borderzone) and arterial circulation (unilateral carotid, bilateral carotid, vertebrobasilar, combined).

Statistical Analysis
Two-sample t tests and Fisher exact tests were used as appropriate. A value of P<0.05 was considered statistically significant.

Results
DWI was performed in 9 patients with NBTE and in 26 patients with 27 episodes of IE. Based on Duke criteria, there were 26 episodes of “definite” and 1 episode of “possible” endocarditis. Four patients had late-onset bioprosthetic valve IE, including the patient with 2 episodes of endocarditis. All patients with NBTE had adenocarcinomas (3 lung, 2 pancreas, 2 ovary, 1 liver, 1 colon). Seven patients with NBTE had metastatic cancer; however, none had brain metastases on MRI. Nine (35%) patients with IE and 6 (67%) with NBTE developed stroke before the diagnosis of endocarditis was established (P=0.079); approximately half of these patients had no other endocarditis-related symptoms such as fever or malaise. The distribution of atherosclerotic risk factors (hypertension, diabetes, hypercholesterolemia, smoking) was similar between groups. Five patients with IE had a previous history of stroke, and 6 had atrial fibrillation. Demographic data and stroke characteristics are outlined in Table 1.

Initial DWI
All patients underwent initial DWI within 1 week after the onset of neurological symptoms, except for 1 patient with NBTE and 3 with IE whose initial DWI were performed between 1 and 2 weeks. The 2 most common indications were evaluation of stroke and encephalopathy; other indications included evaluation of seizures and detection of asymptomatic cerebral emboli or mycotic aneurysms (Table 2). Initial DWI was normal in 2 episodes of IE (both were associated with transient stroke-like symptoms). Initial DWI in all other episodes showed hypertensive lesions, suggesting acute ischemic stroke. Single lesions (5 MCA, 1 PCA) were present on 6 scans, all performed in patients with IE (Figure 1). Multiple DWI lesions were present in all patients with NBTE (Figure 2) and in 19 (70%) episodes of IE (Figure 1). All patients with NBTE had at least 1 medium or large lesion and several smaller lesions, which were distributed in more than 1 arterial territory. In general, patients with IE had fewer and smaller-sized lesions. Seven of 9 patients with NBTE had lesions in the anterior and posterior circulation; in contrast, all

### Table 1. Patient Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>IE (n=27)</th>
<th>NBTE (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>53.4</td>
<td>64.3†</td>
</tr>
<tr>
<td>Male (%)</td>
<td>13 (48)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Valve involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native/prosthetic</td>
<td>25/2</td>
<td>9/0</td>
</tr>
<tr>
<td>Mitral/aortic/both</td>
<td>12/7/5</td>
<td>6/2/1</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor/sensory</td>
<td>14 (52)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Language</td>
<td>3 (11)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>3 (11)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Visual</td>
<td>2 (7)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Seizures</td>
<td>4 (15)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>16 (59)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Peripheral embolism</td>
<td>2 (7)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Stroke syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACS</td>
<td>12 (44)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>POCS</td>
<td>2 (7)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>LACS</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Combined/EE</td>
<td>12 (44)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>4 (15)</td>
<td>5 (56)‡</td>
</tr>
</tbody>
</table>

IE indicates infective endocarditis; NBTE, nonbacterial thrombotic endocarditis; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome; EE, embolic encephalopathy. Numbers in parentheses indicate percentages.

*P=0.008.
†P=0.015.
‡P=0.009.
lesions were distributed exclusively in the anterior circulation in the 14 episodes of IE associated with lesions on DWI (P=0.054). The MCA territory was involved in all patients, (H11005 in the 14 episodes of IE associated with lesions on DWI lesions were distributed exclusively in the anterior circulation in the 14 episodes of IE associated with lesions on DWI (P=0.054). The MCA territory was involved in all patients, alone or in conjunction with other territories, except the 1 patient with IE who had a single large PCA stroke. Cerebellar lesions were frequent, being present in 67% of patients with NBTE and 41% of patients with IE. In contrast, brain stem lesions were uncommon, being present in only 3 patients who had multiple additional strokes. Smaller lesions were often located in the arterial borderzones.

Five patients with IE and 2 with NBTE had hemorrhagic infarcts that manifested as punctate hypointensities (“stippling”) within the hyperintense ischemic lesions. In addition to ischemic strokes, 2 patients with IE (including 1 with a mycotic aneurysm) had intracranial hemorrhages in the MCA territory, which appeared hypointense on DWI.

We classified the DWI lesions into 4 patterns: (1) single lesion, suggesting a solitary embolus; (2) multiple closely spaced lesions in a single arterial territory—“territorial infarction”; (3) multiple punctate disseminated lesions; and (4) multiple small and medium or large disseminated lesions. Patterns 3 and 4 suggested multiple emboli occurring within a short time frame or fragmentation of a single embolus within the heart or aorta. All NBTE scans exhibited pattern 4 (Figure 2), which was present in 9 of 27 scans with IE (P=0.012). Patterns 1 (6 scans), 2 (2 scans), and 3 (8 scans) were observed only in IE patients (see Table 2). Six of 8 patients (75%) with pattern 3 exhibited “embolic encephalopathy” (P=0.013); however, other stroke syndromes did not correlate with DWI patterns. The size of the valvular vegetations (recorded in 19 patients with IE and 6 with NBTE) had no correlation to the size, number, or pattern of strokes.

Because a difference in stroke patterns could provide clues to distinguish between IE and NBTE in patients suspected to have endocarditis, we separately analyzed the 6 patients with NBTE and 9 with IE who developed stroke before they were diagnosed with endocarditis. Again, all with NBTE had pattern 4, whereas those with IE displayed a panoply of lesion patterns.

Follow-Up DWI Findings
Among patients with NBTE, 1 underwent a second DWI for evaluation of new hemiplegia after 6 days. The DWI showed new lesions (one large, multiple small) throughout the brain, suggesting ongoing emboli (Table 2). Three patients with NBTE had no new neurological symptoms but underwent 5 follow-up scans to rule out additional, clinically silent strokes within 1 month after the initial DWI. One of these scans showed a new stroke—a small cortical hyperintensity (Table 2). Because all patients with NBTE had pattern 4 at onset, these new lesions did not result in a change in the classification of their stroke pattern.

In the IE group, 4 patients underwent repeat DWI for evaluation of new neurological symptoms within 1 month after the initial DWI (Table 2). Three of these patients had additional small lesions, resulting in a change in stroke pattern in 2 (normal DWI changed to pattern 3, pattern 1 changed to pattern 2). Nine patients without new neurological symptoms underwent 19 follow-up scans, of which 14 were completed within 1 month after the initial DWI. Only 2 patients (DWI performed 3 days and 7 days after the initial DWI) showed new lesions, which were small and did not result in a change in the classification of the stroke pattern (Figure 3).

Discussion
DWI has become a useful imaging technique for the accurate diagnosis and management of stroke. To our knowledge, ours is the first series in the literature to report the results of DWI in patients with NBTE or IE. We found that patients with NBTE uniformly had multiple, disseminated strokes of varying sizes, with at least 1 medium or large lesion (pattern 4). Conversely, patients with IE had a variety of ischemic lesions, including single cortical, territorial, disseminated punctate, and disseminated small and large lesions (patterns 1 to 4). These results are consistent with patterns of endocarditis-associated stroke observed in previous studies. A review of the literature shows that NBTE-associated strokes are usually multiple, and the lesion size is heterogeneous. Biller et al27 found that 31 of 33 patients with NBTE had multiple small and large strokes on postmortem examination. Two recently reported patients with NBTE had multiple strokes on brain MRI, compatible with pattern 4 in this study.7,8 Two previous studies, using conventional MRI, showed that IE-associated stroke can have a variety of patterns, from single lesions to multiple small and large lesions in multiple vascular territories.5,6 Our DWI study

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**TABLE 2. DWI Characteristics**

<table>
<thead>
<tr>
<th>Indication</th>
<th>IE (n=27)</th>
<th>NBTE (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial DWI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (44%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>11 (41%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>1 (4%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Exclude silent lesions</td>
<td>3 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lesion number/pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lesion</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Single lesion (pattern 1)</td>
<td>6 (22%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Multiple lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pattern 2</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pattern 3</td>
<td>8 (30%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pattern 4</td>
<td>9 (33%)</td>
<td>9 (100)†</td>
</tr>
<tr>
<td>Follow-up DWI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of new symptoms</td>
<td>4 (15%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Exclude silent lesions</td>
<td>9 (33%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Scans with new lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>3 (11%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (7%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

IE indicates infective endocarditis; NBTE, nonbacterial thrombotic endocarditis; DWI, diffusion-weighted MRI.

*Numbers in parentheses indicate percentages.
†P=0.017.

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Figure 1. Schematic representation of stroke patterns on initial diffusion-weighted MRI (DWI) in patients with infective endocarditis. Age, sex, and stroke syndromes are shown for each patient. TACS indicates total anterior circulation syndrome; PACS, partial anterior circulation syndrome; LACS, lacunar syndrome; POCS, posterior circulation syndrome.
tic clues such as fever or Roth spots (which suggest IE) and metastatic tumors (which suggest marantic endocarditis) may be absent, and blood cultures may remain negative. Our results suggest that DWI can provide additional diagnostic clues: patients with stroke pattern 1, 2, or 3 may be more likely to have IE, whereas patients with pattern 4 strokes can have either IE or NBTE. The diagnosis of NBTE is most often made postmortem; however, DWI may have utility in making antemortem diagnosis because the presence of pattern 4 strokes on DWI should suggest a work-up for NBTE, particularly if blood cultures are negative. Although our patients had acute ischemic lesions, they may or may not have been simultaneous.28 However, it is likely that they occurred within a few days before or after the clinically relevant lesion. We did not analyze apparent diffusion coefficient images, thus we cannot rule out that some of the lesions were a result of a T₂ “shine-through” effect. Because of the retrospective study design, we cannot definitively evaluate the incidence of recurrent strokes. However, analysis of follow-up scans suggests that recurrent strokes are not uncommon, can occur days or weeks after initiation of treatment, and can be clinically silent. Importantly, the only large recurrent stroke occurred in a patient with NBTE. Among patients with IE, recurrent strokes were small, few in number, and did not result in a major change in the classification of stroke patterns.

In our series, all patients with NBTE had adenocarcinomas. NBTE is associated with numerous other conditions,3 and it is conceivable that these nonmalignant conditions do not cause pattern 4 strokes. The large size and number of strokes in IE and especially NBTE may be related to associated conditions like sepsis, disseminated intravascular coagulation, hypercoagulable states and antiphospholipid antibodies.29,30 Although we did not specifically measure lesion load, it seemed to be higher in NBTE than in IE (compare Figures 1 and 2). Because the timing of initial DWI was comparable, it is unlikely that the higher lesion load in NBTE was an artifact of later imaging. Differences in disease duration, vegetation composition, and friability may account for the differences in lesion load between NBTE and IE. Vegetations in NBTE may fragment more easily and cause more widespread strokes because they lack inflammatory reaction and have little cellular organization.3 Previous studies have debated whether larger vegetations are associated with a higher incidence of embolic complications.4,31–35 Our study was not designed to examine this relationship; however, it is important to note that vegetation size did not have an effect on stroke number, size, or pattern.

Embolism is the most common mechanism of endocarditis-associated stroke, and nearly all our patients were documented to have valvular vegetations. Thus, the topography of ischemic lesions in our study probably reflects the general pattern of embolic stroke. Our results support several longstanding concepts of cerebral embolism.28,36 Most patients had multiple bihemispheric lesions, confirming that cardiac emboli are usually disseminated. The MCA territory was involved in all patients. Although most patients had widespread lesions, only 3 had brain stem lesions, and no patient had multiple brain stem lesions. Importantly, no patient had isolated brain stem strokes, suggesting that strokes restricted to the brain stem rarely result from cardioembolic disease. Although our patients presented with a single clinical event, most had several “clinically silent” lesions as has been observed in previous studies of multiple acute strokes.16,18,21

Multiple acute strokes can occur in several conditions, and several studies have attempted to correlate DWI patterns of multiple infarctions with underlying causes and mechanisms.16,18 Patients with carotid stenosis can have multiple, small and large, artery-to-artery emboli; however, strokes are distributed in the ipsilateral hemisphere,22 giving a pattern 2 appearance, quite unlike the widespread distribution of pattern 4 stroke described in this study. Patients with atrial myxoma and cerebral vasculitis commonly have multiple strokes in more than 1 arterial circulation; however, in these conditions, strokes are rarely as numerous or as large in size.

Figure 2. Schematic representation of stroke patterns on initial DWI in patients with nonbacterial thrombotic endocarditis. Age, sex, and stroke syndromes are shown for each patient. Abbreviations as in Figure 1.
Moreover, vasculitic strokes are usually located in deep rather than cortical or borderzone arterial territories. Thus, the major differential diagnosis in patients with multiple bihemispheric or anterior and posterior circulation strokes is cardiac embolism, most commonly atrial fibrillation and aortic arch atheroma. Cardiac ultrasound helps to determine the precise mechanism in such cases. Caplan has emphasized that different types of emboli (for example, emboli originating in arteries versus emboli originating in the heart) may have distinct radiological characteristics and that the nature of embolic material should be considered when directing treatment. Our study, in which stroke patterns 1 to 3 were associated with IE but not NBTE, demonstrates that there is pattern heterogeneity even within cardioembolic strokes. Whether other conditions that cause cardioembolic stroke have distinct stroke patterns remains to be determined.

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References


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