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Early Recurrent Ischemic Stroke Complicating Intravenous Thrombolysis for Stroke
Incidence and Association With Atrial Fibrillation

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Background and Purpose—Mechanisms of early neurologic deterioration after treatment with intravenous, recombinant, tissue-type plasminogen activator (IV rt-PA) include symptomatic intracerebral hemorrhage (SICH) and early recurrent ischemic stroke. We observed a number of cases of acute deterioration due to recurrent ischemic events.

Methods—We undertook a single-center, retrospective analysis of consecutive acute stroke patients treated with IV rt-PA between January 2006 and December 2008 to define the incidence of early neurologic deterioration (≥4-point drop on the National Institutes of Health Stroke Scale within 72 hours) and its mechanism. Deterioration was attributed to SICH when associated with a PH1 or PH2 hemorrhage on postdeterioration computed tomography scans, to recurrent ischemic stroke when there was clinical and radiologic evidence of a new territorial infarction or new vessel occlusion, and otherwise to evolution of the incident stroke.

Results—Of 228 consecutive IV rt-PA–treated patients, 34 (15%) developed early neurologic deterioration, 18 (8%) secondary to incident strokes 10 (4.4%) due to SICH, and 6 (2.6%) due to early recurrent ischemic events, which were significantly associated with atrial fibrillation (present in 5 of 6 patients; 4 paroxysmal, 1 permanent). In 4 patients, sudden clinical deterioration developed during or shortly after IV rt-PA infusion, and in 2, deterioration developed 3 days later. All died 2 days to 2 weeks later. The single case without atrial fibrillation had a recurrent, contralateral, middle cerebral artery stroke during IV rt-PA infusion and multiple high-signal emboli detected by transcranial Doppler. Early recurrent ischemic stroke accounted for 5 of 12 (42%) cases of early neurologic deterioration in patients with atrial fibrillation.

Conclusion—In this single-center series, the incidence of early recurrent ischemic stroke after IV rt-PA was 2.6% and was associated with previous atrial fibrillation. (Stroke. 2010;41:1990-1995.)

Key Words: acute care ■ atrial fibrillation ■ embolism ■ thrombolysis

Early neurologic deterioration (END) after acute ischemic stroke is common and is associated with a poor outcome.1 Whereas END has no standardized definition, a drop of 4 points or more on the National Institutes of Health Stroke Scale (NIHSS) within the first 48 to 72 hours after acute stroke1,2 has been commonly used. Mechanisms of deterioration include brain swelling after large infarction, and hemorrhagic transformation. Late deterioration has predominantly systemic causes.3 When END occurs after intravenous (IV) thrombolysis with recombinant tissue-type plasminogen activator (rt-PA), this usually raises the possibility of symptomatic intracranial hemorrhage (SICH), the most common safety concern of treatment. Randomized, controlled trials and registries have accordingly concentrated on the risk of SICH but offer only a limited description of alternative mechanisms of END. Arterial reocclusion accounts for some cases of END after thrombolysis, but the clinical scenario is more often deterioration after initial improvement rather than END alone.4,5

Embolic stroke shortly after systemic thrombolysis has been described in acute myocardial ischemia and prosthetic valve thrombosis and more recently in a few cases of acute ischemic stroke. We describe a series of cases wherein early recurrent ischemic stroke (ERIS), confirmed clinically and radiologically, occurred shortly after IV rt-PA, and compare the incidence and clinical associations with other causes of END.

Subjects and Methods
We reviewed the clinical and imaging data of all stroke patients treated with IV rt-PA for 3 years (January 2006 to December 2008) at a single center. All cases were registered with the Safe Implement-
tation of Thrombolysis register. Demographic and clinical data were extracted from the local Safe Implementation of Thrombolysis registry and hospital records.

Patients with ischemic stroke were treated with standard-dose IV alteplase according to the National Institute of Neurological Disorders and Stroke schedule and criteria, with the exception that no age restriction was applied and that treatment was allowed up to 4.5 hours after onset, provided that there were no other contraindications in either situation. Routine pretreatment imaging was performed by noncontrast computed tomography (CT), with follow-up brain imaging ~24 hours after treatment and additional imaging when clinically indicated. Transcranial Doppler ultrasound was used to monitor middle cerebral artery (MCA) flow in some cases during clinically indicated alteplase infusion.

We defined significant END as a drop in NIHSS score of 4 points or more within 72 hours after presenting stroke. SICH was considered to be the cause when a parenchymal hematoma (P1H or P2H) was present on posttreatment CT. ERIS was diagnosed when there was both clinical and imaging evidence of ischemic stroke in an independent arterial territory, so as to exclude deficits explainable by arterial reocclusion, proximal extension, or distal embolism of the original thrombus. Cases of deterioration without either SICH or ERIS were both clinical and imaging evidence of ischemic stroke in an independent arterial territory, so as to exclude deficits explainable by arterial reocclusion, proximal extension, or distal embolism of the original thrombus. Cases of deterioration without either SICH or ERIS was therefore attributed to evolution of their incident stroke.

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### Statistical Analysis

Descriptive statistics present normally distributed variables as mean ± SD and nonnormally distributed variables as median and interquartile range. Proportions are given with 95% CIs. Binary logistic regression was undertaken with the dependent variables of ERIS or SICH and independent variables that included atrial fibrillation (AF), hypertension, age, smoking, NIHSS score, prior anticoagulant/antiplatelet use, diabetes, and previous history of transient ischemic attack or stroke. Variables were entered into a forward stepwise conditional model.

### Results

Data from 228 consecutive patients were reviewed. Clinical characteristics are summarized in Table 1. AF (persistent, paroxysmal, or transient) was documented in nearly one third of all patients (32.4%). Thirty-four patients (15%; 95% CI, 10% to 19.5%) developed neurologic deterioration within 72 hours of treatment, 10 (4.4%) due to SICH, 6 (2.6%) with ERIS, and 18 patients (8%) with neither cause, therefore attributed to evolution of their incident stroke.

Table 2 compares the demographic and premorbid clinical data among the 3 groups of END patients. Premorbid AF was notably common (83.3%) in those with ERIS, and conversely, the incidence of ERIS was significantly higher (Table 1) in those with documented AF (6.8%; 95% CI, 2.6% to 15.2%) compared with those without a history of AF (0.6%; 95% CI, 0% to 3.9%; odds ratio = 11.1; 95% CI, 1.27 to 96.7; P = 0.0146) and also accounted for 5 of 12 cases of END in patients with AF (42%); compared with only 1 of 22 cases of END in those without AF (odds ratio = 15.0; 95% CI, 1.49 to 151.3; P = 0.0136). In logistic regression, only a history of AF was associated with ERIS (odds ratio = 11.1; 95% CI, 1.27 to 96.7; P = 0.029). END due to SICH was associated with prior anticoagulant use and a history of diabetes.
The clinical features of the 6 cases of ERIS are detailed in Table 3. On admission, 5 of 6 had documented AF (4 paroxysmal and 1 permanent). The specific reasons for prior pacemaker use in 2 cases were not documented. There was no evidence of acute or recent myocardial ischemia on the admission ECG. All patients died 2 days to 2 weeks after first stroke (mean, 8 days). In 4 cases, deterioration occurred suddenly during or immediately after IV alteplase infusion, and 2 cases occurred 3 days later. In 5 cases, there was a reduced level of consciousness. Examples of supporting imaging studies are shown in the Figure.

### Discussion

The incidence of END after IV rt-PA treatment in our series (15%) is consistent with that reported by others, but we found a higher incidence of ERIS than has been reported previously. Although the incidence of ERIS was low and certainly should not delay thrombolysis in suitable patients, ERIS accounted for a significant proportion of deterioration and was only slightly less frequent than SICH. A strong association with AF was also noted.

Secondary embolism after systemic thrombolysis, including ischemic stroke, is recognized as an uncommon complication of thrombolysis for acute myocardial ischemia,8–14 prosthetic valvular thrombosis,15–18 or massive pulmonary embolism19 and has been presumed to occur as a consequence of the disintegration of preexisting intracardiac or valvular thrombus. Preexisting left ventricular thrombus has been documented by echocardiography before ischemic stroke complicating thrombolysis for acute myocardial ischemia,10,13 with a disappearance or reduction in thrombus volume after stroke. Possible embolization to other vascular beds has also been reported after IV rt-PA for ischemic stroke, including acute myocardial infarction,20,21 peripheral arterial embolism,22 or embolism to the external carotid artery.23 Embolic sources include intracardiac (intraventricular, intra-atrial, or valvular) or proximal aortic thrombus. In most previously reported cases, the embolic event occurred during or soon after rt-PA infusion, consistent with the majority of our cases.

Although the presence of intracardiac thrombi has been suggested as a relative contraindication for thrombolysis for stroke, secondary embolic stroke after systemic thrombolysis is rare, even in the presence of known intraventricular thrombi24 (no strokes in 37 consecutive patients treated with streptokinase for acute myocardial ischemia24 and 1 late ischemic stroke among 5 consecutive cases after IV rt-PA for acute stroke25).

Applying our definition of ERIS, which attempts to exclude cases of proximal extension, reocclusion, or distal embolization in the same vascular territory, we identified only 5 cases in the literature.26–29 Mechanisms of stroke
recurrence included calcific embolism from an aortic valve. In only 2 cases was AF documented. However, a central embolic source was inferred from multifocal thrombotic vessel occlusions in 2 others. Alternative mechanisms such as proximal arterial thrombi have been present in other cases with a history of paroxysmal AF.

Documented AF was unusually prevalent in our patients and was associated with ERIS. This mechanism accounted for 42% of END cases after thrombolysis in AF patients. Most events caused sudden neurologic deterioration with impaired consciousness and occurred during or shortly after rt-PA infusion. Without echocardiography, the source is specula-

Figure. A, Case 5, presented with symptoms of left MCA territory ischemia and CTP (a, b), confirming increased mean transit time in the left frontal cortex with no other hypoperfusion. C, Noncontrast CT scan 24 hours after deterioration with ischemic changes in both the left MCA and posterior cerebral artery territories. B, CT angiography in case 3 after clinical deterioration shows recanalization of the right MCA (presenting symptomatic vessel) and a proximal left MCA filling defect, consistent with the development of a new contralateral hemiparesis. C, Magnetic resonance imaging of case 6 performed after acute deterioration occurred with generalized seizures 3 days after treatment. T2 fluid-attenuated inversion recovery (a) and diffusion-weighted (b) imaging shows a subacute right MCA infarction (presenting stroke) and an acute left MCA infarct.
tive, and although the time course and clinical associations are consistent with fragmentation of preexisting intra-atrial clot by rt-PA, we cannot exclude the possibility of embolism from other sources known to be common in patients with AF, such as aortic arch atheroma, or intraventricular thrombus secondary to myocardial infarction, although we found no ECG evidence of recent myocardial ischemia in any case.

The single case in our series without documented AF had clinical and radiological evidence of preceding multiple-territory ischemic events, including recent transient ischemic attack, and had multiple, hyperintense, transient signals consistent with emboli during transcranial Doppler monitoring, implicating a central embolic source. In case 5, an irregular, occlusive, calcific thrombus of the vertebral artery was documented before recurrent ipsilateral posterior cerebral artery infarction, so artery-to-artery embolism is a possible alternative mechanism.

Admission ECG did not show AF in all cases in our series, and medical records provided evidence of prior diagnosis. Previous reports of ERIS documented definite AF in only 2 of 5 cases, but this may only reflect limited availability of previous medical history. The low sensitivity of single ECG recordings for paroxysmal AF diagnosis is recognized.15

The uniformly poor outcome of ERIS almost certainly reflects recognition bias in favor of severe events. Because only a small proportion of new ischemic lesions detected on diffusion-weighted magnetic resonance imaging are associated with clinical events,32 the true incidence of new events in other arterial territories can be determined only by imaging studies before and after thrombolysis. AF is recognized as a poor prognostic factor for acute ischemic stroke, in the studies before and after thrombolysis. AF is recognized as a possible alternative mechanism.

The implications for patient management are ambiguous in the light of a poor prognosis. Admission ECG did not show AF in all cases in our series, and medical records provided evidence of prior diagnosis. Previous reports of ERIS documented definite AF in only 2 of 5 cases, but this may only reflect limited availability of previous medical history. The low sensitivity of single ECG recordings for paroxysmal AF diagnosis is recognized.15

The uniformly poor outcome of ERIS almost certainly reflects recognition bias in favor of severe events. Because only a small proportion of new ischemic lesions detected on diffusion-weighted magnetic resonance imaging are associated with clinical events,32 the true incidence of new events in other arterial territories can be determined only by imaging studies before and after thrombolysis. AF is recognized as a poor prognostic factor for acute ischemic stroke, in the severity of presentation and early mortality, either with33,34 or without35–38 thrombolysis. Although other factors such as hemodynamic instability and poorer cerebral perfusion may be contributory,1,9 ERIS might also be a mechanism for this poor prognosis among rt-PA–treated patients.

The implications for patient management are ambiguous in the absence of a clear therapeutic intervention at present for either prevention or rescue therapy. Echocardiographic screening of patients would delay thrombolysis, and it assumes a cardiac source for emboli that is unproven. Transesophageal studies would be required to seek an atrial or atrial appendage clot. The presence of AF on admission ECG alone is insensitive, with low sensitivity and specificity. Both the early timing of deterioration in several of our cases and the increased risk of ICH as part of the natural history of cardioembolic stroke suggest that early introduction of anti-coagulants or antithrombotic therapy after IV rt-PA in patients with AF, even with documented intracardiac thrombus, would unlikely be safe or effective. Awareness of second embolic stroke may allow clinicians to consider intervention treatment approaches in individual cases, which may be justified in the light of a poor prognosis.

Disclosures

None.

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