Deterioration Following Spontaneous Improvement
Sonographic Findings in Patients With Acutely Resolving Symptoms of Cerebral Ischemia

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Background and Purpose—Some stroke patients will deteriorate following improvement (DFI), but the cause of such fluctuation is often unclear. While resolution of neurological deficits is usually related to spontaneous recanalization or restoration of collateral flow, vascular imaging in patients with DFI has not been well characterized.

Methods—We prospectively studied patients who presented with a focal neurological deficit that resolved spontaneously within 6 hours of symptom onset. Patients were evaluated with bedside transcranial Doppler (TCD). Digital subtraction angiography (DSA), computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) were performed when feasible. DFI was defined as subsequent worsening of the neurological deficit by ≥4 National Institutes of Health Stroke Scale points within 24 hours of the initial symptom onset.

Results—We studied 50 consecutive patients presenting at 165±96 minutes from symptom onset. Mean age was 61±14 years; 50% were females. All patients had TCD at the time of presentation, and 68% had subsequent angiographic examinations (DSA 10%, CTA 4%, and MRA 44%). Overall, large-vessel occlusion on TCD was found in 16% of patients (n=8); stenosis was found in 18% (n=9); 54% (n=27) had normal studies; and 6 patients (12%) had no temporal windows. DFI occurred in 16% (n=8) of the 50 patients: in 62% of patients with TCD and angiographic evidence of occlusion, in 22% with stenosis, and in 4% with normal vascular studies (P<0.001, χ²=12.05). DFI occurred in 31% of patients with large-vessel atherosclerosis, 23% with cardioembolism, and 9% with small-vessel disease when stroke mechanisms were determined within 2 to 3 days after admission (P=0.2, NS).

Conclusions—DFI is strongly associated with the presence of large-vessel occlusion or stenosis of either atherosclerotic or embolic origin. Normal vascular studies and lacunar events were associated with stable spontaneous resolution without subsequent fluctuation. Urgent vascular evaluation may help identify patients with resolving deficits and vascular lesions who may be candidates for new therapies to prevent subsequent deterioration. (Stroke. 2000;31:915-919.)

Key Words: angiography ■ cerebral ischemia ■ disease progression ■ ultrasonography

Approximately 15% of consecutive patients may have an unstable course within 24 hours after stroke onset.1 Early resolution of neurological deficits is related to spontaneous recanalization or restoration of collateral flow.2 Early worsening and transient neurological deficits lasting >1 hour are attributable to the presence of large-vessel occlusive disease or embolism rather than small-vessel involvement.3,4

In the current era of urgent stroke therapy, many patients may transiently improve, sometimes after thrombolysis, only to subsequently deteriorate back to their initial deficit. The patterns of such fluctuation are variable, sometimes being continuous deterioration and other times dramatic reversal and recurrence of deficits. Although the mechanisms of such deterioration following improvement (DFI) may include developing brain edema, reperfusion hemorrhage, or other secondary factors such as cardiopulmonary decompensation, most DFIs are due to some as-yet-undefined processes.1 Urgent sonographic evaluation of patients with acutely resolving deficits and DFI has not been well characterized.

The goal of this study was to evaluate the frequency and characteristics of vascular lesions in the setting of acute spontaneously resolving deficits and their potential association with subsequent DFI. We routinely use transcranial Doppler (TCD) in the emergency room to evaluate patients with symptoms of cerebral ischemia and have validated our criteria for diagnosis of large-vessel arterial occlusion and stenoses.5 We sought to establish an association between DFI and findings on urgent TCD and subsequent angiography.
Subjects and Methods

We prospectively studied consecutive patients who presented with a focal neurological deficit attributable to cerebral ischemia and spontaneously resolving to a total NIH Stroke Scale score of \(<4\) within 6 hours of symptom onset. On arrival to the emergency room, patients underwent a standard neurological evaluation and a non-contrast head CT scan. In the emergency room, patients were also evaluated with portable, single-channel 2-MHz TCD equipment (Multigon 500M, Multigon Industries, or MultiDop T, DWL). TCD was performed by experienced sonographers, who used previously published standard insolation protocol.\(^7\) Digital subtraction angiography (DSA), computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) were performed when feasible. Vascular imaging studies were interpreted by a neurologist (TCD) or neuroradiologist (angiography) for the presence of a large-vessel occlusion, stenoses, or patent vessels, following previously published criteria.\(^5\)

To evaluate subsequent fluctuation, the severity of recurrent symptoms was measured by a neurologist not involved in TCD with the National Institutes of Health Stroke Scale (NIHSS). DFI was defined as a worsening of the neurological deficit by \(\geq4\) NIHSS points of variable duration that occurred within 24 hours of the initial symptom onset.

Ethnicity was documented as black, Hispanic, or white. Stroke pathogenic mechanism was determined following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial\(^6\) after the diagnostic work-up was completed, including carotid and cardiac ultrasound, ECG, MRI, and other tests. Briefly, patients were classified as having large-vessel atherosclerotic (LVA) occlusive disease if an angiogram or carotid ultrasound showed a \(>50\%\) stenosis or occlusion of an extracranial or intracranial artery. Patients were presumed to have an embolic stroke if a potential cardiac source of brain embolism was found. Clinical presentation consistent with lacunar symptoms and normal CT or characteristic lesions on CT or MRI was attributed to small-vessel disease. Other causative mechanisms were also documented when applicable (eg, arterial dissection and coagulopathy). If no obvious cause of stroke symptoms was found after standard diagnostic work-up, stroke mechanism remained undetermined.

Statistical analysis included descriptive statistics for patient population and ethnicity. To establish the difference between variables, the data were subjected to testing by the Pearson \(X^2\) test. If \(X^2\) was significant, data analysis was performed with a phi test to establish the relationship between dichotomous predictors and fluctuation. TCD results were grouped as abnormal (occlusion) or normal studies, and 6 patients (12%) had no temporal windows.

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Results

We studied 50 consecutive patients who presented with spontaneously resolving deficits within the first 6 hours after symptom onset. Mean age was 61 ± 14 years, and 50% of patients were women. Mean NIHSS score on admission was 6.4 ± 3.6 (range 2 to 15 points). The NIHSS score at the time of spontaneous symptom resolution was 0.5 ± 0.9 (range 0 to 3). No thrombolytic therapy was given. There were 15 black, 5 Hispanic, and 30 white patients. LVA occlusive disease was diagnosed in 13 patients (26%), cardioembolism (CE) in 13 (26%), lacunar stroke (LAC) in 11 (22%), undetermined etiology in 9 (18%), and other causes (such as dissection or coagulopathy) in 4 (8%); Table 1).

All patients had a clinical examination and TCD in the emergency room at a mean time of 165 ± 96 minutes from symptom onset (range 40 to 360 minutes). Sixty-eight percent of patients had subsequent angiographic examinations (DSA 10%, CTA 4%, MRA 44%). Angiography was performed at mean time of 928 ± 942 minutes (range 90 to 3645 minutes), with 44% of studies performed within the first 6 hours of the initial symptom onset.

TCD examination at the time of presentation in the emergency room was abnormal in 34% of patients with lesion location corresponding to ischemic territory; extracranial or intracranial occlusion was found in 16% of patients (n=8) and stenosis in 18% (n=9). Fifty-four percent of patients (n=27) had normal studies, and 6 patients (12%) had no temporal windows. Arterial lesions were located in the middle cerebral artery (MCA; n=13), internal carotid artery (ICA; n=2), posterior cerebral artery (n=1), basilar artery (n=2), and vertebral artery (n=1) (including 2 patients with tandem lesions in the anterior circulation). Subsequent angiography confirmed the presence of these lesions or showed continuing recanalization in all but 1 patient who had normal MRA with posterior cerebral artery stenosis identified by TCD.

Deterioration within the next 24 hours occurred in 16% (n=8) of all patients. Patients who met TOAST criteria for LVA lesions or CE had a higher incidence of DFI than patients with LAC or stroke of undetermined etiology (LVA 31%, CE 23%, LAC 9%, undetermined 0%; \(\chi^2=5.461, P=0.243\)), however, this difference did not reach statistical significance (Table 1). When TCD identified extracranial or intracranial occlusions of either atherosclerotic or embolic origin, 62% of these patients developed subsequent DFI (Table 2). Twenty-two percent of patients with stenosis and 4% with normal vascular studies developed DFI within the first 24 hours after initial symptom onset (\(\chi^2=12.05, \Phi=0.523, P<0.001\)).

The following example illustrates typical TCD findings in the MCA associated with ICA occlusive disease. MCA flow has delayed systolic acceleration due to its dependence on collateral flow (Figure 1). With elevated head position or elevation of head position, MCA flow velocity decreased by \(>20\) mm Hg, the MCA flow velocity decreased by \(>50\%\) and the clinical

<table>
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<th>TABLE 1. Patient Characteristics</th>
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<td><strong>Ethnicity, %</strong></td>
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<tr>
<td><strong>Stroke Mechanism</strong></td>
</tr>
<tr>
<td>Large-vessel atherosclerosis* (n=13)</td>
</tr>
<tr>
<td>Embolism (n=13)</td>
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<tr>
<td>Small-vessel disease (n=11)</td>
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<tr>
<td>Undetermined (n=9)</td>
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<tr>
<td>Other (eg, dissection) (n=4)</td>
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<td>Total (n=50)</td>
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*Large-vessel atherosclerosis includes intracranial lesions.

<table>
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<th>TABLE 2. Vascular Findings on TCD and Subsequent DFI</th>
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<tr>
<td><strong>Vascular Finding</strong></td>
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<tr>
<td>Occlusion (n=8)</td>
</tr>
<tr>
<td>Stenosis (n=9)</td>
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<td>Normal (n=27)</td>
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deficit worsened. TCD findings indicate significant blood flow reduction, because the angle of insonation was maintained constant. Conversely, flat head position and elevation of blood pressure increased MCA flow velocity and were associated with symptom resolution (Figure 1). Three patients with such TCD findings had subsequent DFI within the first 24 hours after stroke onset (see Case 1).

Case 1
A 54-year-old white male with left-sided hemiplegia (NIHSS score of 9) and a normal CT 2 hours after stroke onset had a right terminal ICA T-type occlusion on TCD (Figure 2). After CT, the patient was briefly reexamined before tissue plasminogen activator (tPA) bolus was given. On command, the patient moved his left arm and leg with no residual weakness. tPA was held, and repeat TCD examination showed persisting ICA and distal MCA occlusions, with recanalization of the terminal ICA/proximal M1 MCA segment and low-resistance flow from the posterior communicating artery to MCA perforators. Urgent DSA confirmed the TCD findings (Figure 2). The patient remained asymptomatic during angiography, and no thrombolysis was given. After DSA, he experienced transient weakness in his arm and leg with elevated head position. He was kept flat, mean blood pressure was maintained at $\geq 100$ mm Hg, and intravenous fluids and heparin

Figure 1. Flow signals in the MCA unilateral to ICA occlusion. Delayed systolic flow acceleration with low mean flow velocity in the MCA was previously described by Giller et al in patients with an ICA occlusion and impending infarction.

Figure 2. Pure motor paresis with the T-type ICA (TICA) occlusion followed by spontaneous TICA recanalization and complete resolution of symptoms despite persisting proximal ICA and distal MCA occlusions. 1 indicates ICA occlusion on the neck; 2, posterior communicating artery; and 3, terminal ICA recanalization (white arrows, low-resistance flow in the TICA and proximal MCA with bruit; black arrows, TICA and MCA perforators).
were given. He spontaneously recanalized the distal MCA 24 hours later while the ICA remained occluded. The patient remained symptom free during the subsequent hospital stay. The next 2 cases illustrate other TCD findings that were helpful to establish arterial lesions and understand the mechanisms responsible for clinical improvement with stable resolution.

Case 2
A 65-year-old black male had resolving left hemiparesis (arm>leg) 40 minutes after symptom onset, with an arrival NIHSS score of 8. TCD detected multiple reverberating flow signals at the proximal right MCA, repeating several times during cardiac cycle and resembling “broken muffler” sounds (Figure 3). A mobile, flow-limiting lesion in the right MCA was suspected. Several minutes later, TCD detected recanalization of the proximal right MCA resulting in a stenotic low-resistance signal. The patient’s symptoms completely resolved at 70 minutes after the onset. One hour later, DSA showed a severe stenosis of the right M1 MCA segment, with good opacification of the distal branches. The patient received heparin and fluids and remained symptom free during hospital stay.

Case 3
A 41-year-old black female had resolving mild left arm paresis and left facial droop (NIHSS score of 3) at 2 hours after the onset. TCD showed a high-grade M1 MCA stenosis. Multiple microembolic signals arrived in large clusters (Figure 4). A continuing MCA clot dissolution was diagnosed by TCD and confirmed by DSA at 235 minutes after symptom onset. No thrombolysis was given, and her symptoms resolved completely within the next 4 hours. The patient received heparin and fluids, follow-up TCD showed no

Figure 3. Mobile flow-limiting lesion in the MCA: “flapping” thrombus attached to a high-grade MCA stenosis followed by spontaneous recanalization.

Figure 4. Continung clot dissolution after spontaneous MCA recanalization with a residual high-grade stenosis. Microembolic signals appear at the bottom of the spectra above as multiple, unidirectional spikes of high intensity (white and green colors). Clusters of microembolic signals distal to MCA stenosis were previously described by Segura et al in a patient with multiple transient ischemic attacks in the MCA distribution. This epiphenomenon may indicate stroke mechanism (artery-to-artery embolism) or continuing clot dissolution with recanalization.
microemboli, and she remained symptom free during the hospital stay.

Discussion

Our study showed that early DFI is strongly associated with TCD findings of an arterial occlusion or stenosis due to either large-vessel atherosclerosis or cardioembolism. Normal vascular studies were associated with stable resolution without subsequent deterioration. Although no significant association was established between stroke subtype and DFI (likely due to the small numbers of patients in subgroups), our findings are consistent with those of previous reports\(^1\)\(^-\)\(^4\) and provide additional information regarding the utility of vascular imaging in this setting.

The yield of urgent TCD or angiography in patients with resolving deficits is high, i.e., 34% of studies showed arterial lesions in patients with resolving deficits. It was previously suggested that diagnostic evaluation of patients with transient ischemic attacks has low yield for etiologies other than atherosclerosis.\(^9\) Our data indicate that if vascular imaging is performed close to symptom onset, patients with embolic arterial lesions can be identified more readily. This information may provide evidence for early recanalization, and if an occlusion or stenosis persist, these patients may be at high risk of subsequent deterioration. Although early resolution of neurological deficits is generally viewed as a favorable sign, this should not preclude these patients from urgent vascular imaging and further diagnostic work-up, because a substantial proportion (8 of 50 [16%] in this study) may worsen.

A 16% rate of early deterioration in our study is consistent with the rate in a previous report\(^1\) but lower than the overall rate of worsening in all patients with ischemic stroke.\(^2\) Yamamoto et al.\(^2\) showed that worsening in the acute phase of stroke occurred in 34% of patients with noncardioembolic infarction and in 15% in patients with cardioembolism. Neurological worsening was less frequent in patients with lacunar stroke than in those with large-vessel atherosclerosis,\(^2\) similar to our results.

Our data suggest that patients with early DFI usually deteriorate due to hemodynamic factors. In 3 of 8 DFI patients, deterioration could be attributed to decreased flow distal to a large-vessel obstruction and could be augmented by increasing perfusion pressure. If TCD shows evidence for large-vessel occlusion or stenosis, measures to prevent further deterioration might include flat head position, volume expansion using intravenous fluids, and maintenance of mean arterial blood pressure at levels $\geq 100$ mm Hg.

Although the hemodynamic mechanism of early DFI may be common, other mechanisms may also play a role, including arterial reocclusion or other as-yet-undetermined mechanisms. Our study was not designed to perform continuous TCD monitoring, but such studies might be useful to document the frequency of reocclusion after early recanalization. A subgroup analysis of the TOAST trial data showed that patients who had an ICA occlusion or high-grade stenosis identified early by duplex imaging may benefit from emergent anticoagulation.\(^10\) This is indirect evidence for the possible occurrence of reocclusion in these patients.

In conclusion, early DFI is strongly associated with TCD findings of large-vessel occlusion or stenosis of either atherosclerotic or embolic origin. These patients often experience early DFI due to hemodynamic factors. Normal vascular studies are associated with stable resolution. Urgent vascular evaluation has a high yield (34% with abnormal studies) in patients who were spontaneously improving within the first hours of cerebral ischemia, and these studies may help guide further management.

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