Early Spontaneous Improvement and Deterioration of Ischemic Stroke Patients
A Serial Study With Transcranial Doppler Ultrasonography

D. Toni, MD, PhD; M. Fiorelli, MD, PhD; E.M. Zanette, MD; M.L. Sacchetti, MD; A. Salerno, MD; C. Argentino, MD; M. Solaro, MD; C. Fieschi, MD

Background and Purpose—The purpose of our study was to investigate whether emergency transcranial Doppler (TCD) findings and their modifications over the first 48 hours are related to early neurological changes in acute ischemic stroke patients.

Methods—Ninety-three patients underwent CT scan within 5 hours of a first-ever ischemic hemispheric stroke, and TCD serial examinations at 6, 24, and 48 hours after stroke onset. We classified TCD findings as follows: normal; middle cerebral artery (MCA) asymmetry (asymmetry index between affected and contralateral MCAs below –21%); and MCA no-flow (absence of flow signal from the affected MCA in the presence of ipsilateral anterior and posterior cerebral artery signals through the same acoustic window). We considered early deterioration and early improvement to be a decrease or an increase of 1 or more points, respectively, in the Canadian Neurological Scale score over the same period.

Results—At 6-hour TCD examination, MCA asymmetry and MCA no-flow were present in 6 (22%) and 2 (7%), respectively, of 27 improving patients; in 20 (43%) and 10 (22%) of 46 stable patients, and in 9 (45%) and 8 (40%) of 20 deteriorating patients. TCD findings were normal in the remaining patients (P<0.001). At serial TCD, we detected early (within 24 hours) recanalization (from no-flow to asymmetry or normal and from asymmetry to normal) in 2 (25%) improving patients, in 7 (23%) stable patients, and in 5 (29%) deteriorating patients and late (between 24 and 48 hours) recanalization in 4 (50%) improving patients, in 6 (20%) stable patients, and in none of the deteriorating patients (P=0.03, χ² for trend, improving versus nonimproving irrespective of the timing of recanalization). One deteriorating patient (5%) developed a no-flow from an initial MCA asymmetry. Logistic regression selected normal TCD (odds ratio [OR], 0.17; 95% confidence interval [CI], 0.06 to 0.46) as an independent predictor of early improvement and abnormal TCD (asymmetry plus no-flow) (OR, 5.02; 95% CI, 1.31 to 19.3) as an independent predictor of early deterioration.

Conclusions—TCD examination within 6 hours after stroke can help to predict both early deterioration and early improvement. Serial TCD shows that propagation of arterial occlusion is rarely related to early deterioration, whereas the fact that it can detect early recanalization (within 24 hours) in deteriorating patients and both early and late recanalization (after 24 hours) in improving patients suggests the existence of individual time frames for tissue recovery. (Stroke. 1998;29:1144-1148.)

Key Words: stroke, acute ■ stroke, ischemic ■ ultrasonography, Doppler ■ pathogenesis ■ prognosis

The growing consensus in favor of an emergency hospital referral of ischemic stroke patients has made the study of the clinical course over the first hours of stroke onset of the utmost relevance. We now have the opportunity to witness clinical courses that in the past had already begun or even been completed by the time patients were hospitalized. Hence, it would theoretically be possible to prevent or to counteract a neurological deterioration, or to plan a nonintensive treatment of patients who are likely to improve spontaneously. Understanding the mechanisms underlying these 2 clinical evolutions is obviously the necessary prerequisite to achieve these goals.

In a previous study, three fourths of patients with subsequent progressing course had signs of precocious brain edema, ie, early hypodensity and/or mass effect, at admission CT scan performed within 6 hours of stroke onset. Moreover, in a subgroup of patients submitted to angiography immediately after CT scan, we observed an intra- and/or extracranial arterial occlusion in 91% of deteriorating and in 71% of nondeteriorating patients, with collateral blood supply in one third and in two thirds, respectively, of the cases. Hence, we hypothesized that arterial occlusion with an ineffective collateral blood supply had led to precocious brain edema that was ultimately responsible for early deterioration.
In a subsequent study, we observed an inverse situation in early improving patients. Early CT hypodensity was present in only 29% of patients, and angiography showed an intracranial and/or extracranial arterial occlusion in half of improving patients, with collateral blood supply in 80% and arterial patency (ie, normal angiograms or nonstenosing plaques in the internal carotid artery) in the remaining half of the patients. Since almost all of the latter presented a CT territorial infarct, generally considered to be caused by an embolic arterial occlusion, we presumed that these patients also had had an arterial occlusion, with arterial reopening occurring before angiography. Therefore, the presence of effective collateral blood supply, with preservation of neuronal function, and very early recanalization, with rapid restoration of an adequate perfusion, were the proposed mechanisms underlying early improvement.

However, we were aware that both in deteriorating and in improving patients we had taken a photograph antecedent to any clinical change, not knowing whether any modifications in blood supply that might have been related to the changing clinical picture had subsequently occurred.

In the present study we monitored with TCD the evolution of arterial status of acute ischemic stroke patients, and investigated whether TCD data obtained at hospital admission and their modification within the first 48 hours of stroke onset were related to early neurological deterioration or improvement.

Subjects and Methods
We studied 93 acute ischemic hemispheric stroke patients hospitalized within 5 hours from stroke onset, who underwent TCD examination with a TC 2–64 EME device equipped with a 2-MHz probe. The anterior cerebral artery (ACA), the middle cerebral artery (MCA), and the posterior cerebral artery (PCA) were explored through the temporal window, and the mean flow velocity of each artery was recorded. TCD findings were classified as follows: (1) MCA no-flow, when the flow signal from the symptomatic MCA was absent, while those from the ipsilateral ACA and PCA were detected through the same acoustic window; (2) MCA asymmetry, when the flow velocity in the symptomatic MCA was reduced by 21% or more when compared with the contralateral MCA; and (3) normal MCA, when flow velocities were the same or MCA asymmetry was less than 21%. This 21% threshold value of MCA asymmetry was the upper limit of the confidence intervals (5% of the distribution in the right tail) in a reference sample of normal subjects. TCD was then repeated after 24 and 48 hours, and after comparing these data with those at entry, we considered the modification of TCD findings from no-flow to asymmetry or normal and from asymmetry to normal as arterial recanalization. Reverse changes were considered indexes of propagation of a preexisting arterial occlusion or of a new occlusion.

The routine examination of patients admitted to our Stroke Unit and the classification of early and repeat CT findings are detailed elsewhere. For the purposes of this study, patients underwent the first TCD after the admission CT scan, ie, within 6 hours of stroke onset. Early deterioration and early improvement were defined as a decrease and an increase of 1 or more points, respectively, in the Canadian Neurological Scale (CNS) score from hospital admission to 48 hours after stroke onset; the remaining patients were considered stable. The investigators who determined the CNS score were blind to TCD results.

We followed patients for 30 days, during which we calculated the fatality rate; we then evaluated the residual activities of daily living of survivors, considering a Barthel Index score <60 to be a poor functional outcome.

Statistical Analysis
Univariate tests (χ², t-test, Fisher’s exact test, and ANOVA) were used to analyze the following: clinical characteristics on admission, CT scan and TCD findings, risk factors for stroke in past medical history, and clinical outcome. To look for independent predictors of the improving course (stable or deteriorating=0, improving=1) and deteriorating course (stable or improving=0, deteriorating=1), baseline clinical and CT findings (early hypodensity or mass effect: no=0, yes=1) and 6-hour TCD data (normal=0, abnormal, ie, asymmetry or no-flow, =1), which during the univariate tests were trend related (P≤0.1) to improvement or deterioration, were taken as independent variables in the logistic regression analysis. This model was adjusted according to the therapies administered. A further logistic regression analysis with the same variables was performed only in patients with MCA asymmetry and MCA no-flow at the 6-hour TCD to ascertain whether recanalization at 24 and 48 hours was independently associated with early improvement or deterioration. Finally, we calculated predictive values, sensitivity, specificity, and accuracy of the variables found by logistic regression to be related to the 2 clinical courses.

Results
Of 93 patients studied, 46 (49%) remained stable, 20 (22%) deteriorated, and 27 (29%) improved during the first 48 hours of hospitalization. Of the latter, 25 (92%) started improving, but none of them recovered, within 24 hours.

Table 1 shows the demographic data, baseline clinical characteristics, risk factors for stroke in the medical history, and 30-day clinical outcome of the 3 groups of patients. Deteriorating patients were older and had the highest mean serum glucose levels at entry, whereas improving patients were younger and had the lowest admission serum glucose levels. At the end of follow-up, 6 (22%) improving patients had died or were dependent compared with 26 (56%) stable and 18 (90%) deteriorating patients (P=0.0002).

Findings at baseline and at the time of repeat CT scans (88 patients) or autopsy (5 patients) according to TCD findings at 6 hours and to their modifications at 24 and 48 hours are shown in Table 2. At baseline CT, early hypodensity was found in 8 (30%) improving, 27 (59%) stable, and 16 (80%) deteriorating patients (P=0.04). At repeat CT or autopsy territorial infarcts were detected in 22 (81%) improving, 40 (86%) stable, and 20 (100%) deteriorating patients. The size of the territorial infarcts varied significantly: improving patients had mainly small lesions, while medium- and large-sized infarcts prevailed among stable and deteriorating patients (P=0.01).

At the 6-hour TCD, MCA asymmetry and MCA no-flow were detected in 8 (30%) improving patients, as compared with 30 (65%) stable and 17 (85%) deteriorating patients (P=0.001). Among patients with an abnormal 6-hour TCD, serial TCD showed recanalization within 24 hours in 2 (25%) improving patients, 7 (23%) stable patients, and 5 (29%) deteriorating patients and between 24 and 48 hours in 4 (50%) improving patients, 6 (20%) stable patients, and none of the deteriorating patients (P=0.03 χ² for trend, improving versus nonimproving, irrespective of the timing of recanalization). Finally, the TCD finding of 1 (5%) deteriorating patient changed from asymmetry at 6 hours to no-flow at the 48-hour control.

Among the baseline clinical characteristics, admission CT, and 6-hour TCD findings, logistic regression selected normal
6-hour TCD as a predictor of early improvement (odds ratio [OR], 0.17; 95% confidence interval [CI], 0.06 to 0.46) and abnormal 6-hour TCD as an independent predictor of early deterioration (OR, 5.02; 95% CI, 1.31 to 19.3). No other variable was selected by this analysis, even when repeated to take into account spontaneous recanalization. Predictive values, sensitivity, and specificity of 6-hour TCD findings regarding early improvement and early deterioration are shown in Table 3. The overall accuracy of normal TCD in predicting early improvement was 71% (95% CI, 62 to 80), whereas the accuracy of MCA asymmetry and that of MCA no-flow in predicting early deterioration were 60% (95% CI, 50 to 70) and 74% (95% CI, 65 to 83), respectively.

### Discussion

The frequency of early improvement and deterioration, the baseline clinical and CT characteristics, and the clinical evolution of this series of patients are similar to those reported in previous studies. Approximtely half of all acute ischemic stroke patients either worsen or improve within the first 48 hours of stroke onset, and this early clinical change is predictive of long-term bad and good outcomes, respectively.

Normal 6-hour TCD was the only independent predictor of early improvement, while abnormal TCD was a predictor of early deterioration. The presence or absence of early CT hypodensity, previously identified as predictors of the early clinical course, did not add to the prediction, and the overall accuracy of TCD findings in predicting early clinical course was higher than that of CT findings. Unfortunately, while CT can be performed in all acute patients, TCD cannot, owing to the absence of the acoustic window in a sizable number of cases.

Intracerebral and systemic mechanisms have been proposed by various authors as possibly being responsible for early deterioration. As to intracerebral mechanisms, we investigated whether in addition to brain edema, which we previously had suggested as the main cause of early deterioration, a propagation of arterial occlusion might contribute to this clinical course. In our series, only 1 deteriorating patient showed a TCD change from asymmetry to no-flow between 24 and 48 hours after stroke onset, with early cortical hypodensity at the first CT and a final infarct involving the whole MCA territory. These data indicate an occlusion of the distal portion of the MCA and suggest either a subsequent retrograde propagation of the occlusion to the MCA main stem or, more likely, that a new embolus lodged next to the initial occlusion.

On the other hand, the serial TCD examinations showed a recanalization within 24 hours of stroke onset in 5 deteriorating patients. Because we did not perform TCD examinations at shorter time intervals, we do not know the exact time of recanalization, but we may argue that it was too delayed to save brain tissue. However, for 3 of these patients who had no
or only limited early CT hypodensity and an extended final infarct, we cannot rule out the possibility that a reperfusion injury might have supervened, thus damaging tissue that was still partially viable at hospital entry.

We can presume neither reperfusion injury nor thrombus propagation for the 11 deteriorating patients with asymmetry or no-flow at the 6-hour TCD and no modifications in the subsequent examinations. The remaining 3 deteriorating patients with normal TCD at entry had early hypodensity at the first CT and an extended territorial infarct at the repeat CT. This led us to hypothesize that these patients also had had an arterial occlusion, probably without adequate collateral blood supply, that was no longer present by the time the first TCD was performed.

The questions raised by serial TCD findings on the possible mechanisms underlying early improvement are somewhat more complex. Although in the majority of patients improvement started within 24 hours, none of them had a transient ischemic attack. Seventy percent of improving patients had a normal 6-hour TCD. The fact that lacunar infarcts or permanently normal CT scans were detected in only one fourth of these cases, a frequency similar to that of stable patients, allows us to exclude lacunar stroke as a main cause of early improvement. The other three fourths of patients had a territorial infarct at the repeat CT scan. At least a part of these infarcts can be explained by presuming an occlusion of a few MCA branches, undetected by TCD because it was insufficient to markedly modify the MCA velocity. This was, in fact, what we observed in 38% of normal TCD findings in a previous study in which TCD and digital arterial subtraction angiography were compared.25

There remain, however, half of the improving patients with normal 6-hour TCD and subsequent territorial infarct, for whom very early recanalization before the first TCD can be hypothesized.

### TABLE 2. Baseline and Repeat CT and Autopsy Findings According to TCD Findings at 6 Hours and to Their Changes at 24 and 48 Hours

<table>
<thead>
<tr>
<th>TCD 6 hrs</th>
<th>n</th>
<th>TCD 24–48 h</th>
<th>n</th>
<th>Early Hypodensity</th>
<th>Repeat CT or Autopsy</th>
<th>Size of Infarct</th>
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</thead>
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<tr>
<td>Baseline CT</td>
<td></td>
<td>Repeat CT or Autopsy</td>
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<td></td>
<td></td>
<td></td>
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<td>Medium</td>
<td>Large</td>
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<td>Improving*</td>
<td></td>
<td></td>
<td>No</td>
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<td>Cortex</td>
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<td>Normal</td>
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<td>Recanalization</td>
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<tr>
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<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
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<td>1</td>
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<td>1</td>
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<td>...</td>
<td>...</td>
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<td>Stable</td>
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<tr>
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<td>2</td>
<td>2</td>
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<td>...</td>
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<tr>
<td>Deteriorating</td>
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<tr>
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<td>6</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td>Thrombus propagation</td>
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<td>...</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
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<tr>
<td>No flow</td>
<td>8</td>
<td>Recanalization</td>
<td>3</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>No change</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>...</td>
</tr>
</tbody>
</table>

*Indicates patient groups.
†3 negative CT and 2 lacunes.
‡4 negative CT and 2 lacunes.

### TABLE 3. Predictive Values, Sensitivity, and Specificity of 6-Hour TCD Findings With Respect to Early Clinical Course

<table>
<thead>
<tr>
<th>Types of Early Clinical Course</th>
<th>Improvement</th>
<th>Deterioration</th>
<th>No-Flow</th>
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<tbody>
<tr>
<td>TCD Findings</td>
<td>Normal</td>
<td>Asymmetry</td>
<td>No-Flow</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>50% (19/38)</td>
<td>26% (9/35)</td>
<td>40% (8/20)</td>
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<tr>
<td>Negative predictive value</td>
<td>85% (47/55)</td>
<td>81% (47/58)</td>
<td>84% (61/73)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>70% (19/27)</td>
<td>45% (9/20)</td>
<td>40% (8/20)</td>
</tr>
<tr>
<td>Specificity</td>
<td>71% (47/66)</td>
<td>64% (47/73)</td>
<td>84% (61/73)</td>
</tr>
</tbody>
</table>

Values in brackets below are 95% confidence intervals.
Finally, in half of the improving patients with MCA occlusion at the 6-hour examination, TCD documented recanalization between 24 and 48 hours after stroke onset. This indicates that in a minority of patients delayed recanalization may be related to improvement, suggesting a more prolonged survival of the ischemic penumbra.26

In conclusion, TCD performed a few hours after stroke onset may help to predict the clinical course in the subsequent 48 hours. Serial TCD examinations suggest that early deterioration is rarely, if ever, related to a propagating arterial occlusion. The occurrence of early recanalization (within 24 hours) in patients with a deteriorating course and that of both early and late recanalization (after 24 hours) in patients with an improving deficit confirm that there is not a fixed and universal time frame for tissue recovery but rather an individual therapeutic window.27

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