

Temporal Profile of Recanalization After Intravenous Tissue Plasminogen Activator

Selecting Patients for Rescue Reperfusion Techniques

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Background and Purpose—Intravenous thrombolysis in stroke achieves arterial recanalization in $\approx 50\%$ of cases. Determining temporal profile of recanalization may address patient selection and potential benefits of further rescue reperfusion techniques.

Methods—We studied 179 consecutive intravenous tissue plasminogen activator (t-PA)-treated patients with intracranial artery occlusion. Continuous transcranial Doppler assessed recanalization (none-partial-complete) at 60 minutes (early), 120 minutes (delayed) after t-PA bolus, and 6 hours (late) from symptom onset. Outcomes were determined: National Institutes of Health Stroke Scale (NIHSS; 48-hour NIHSS) and 3-month modified Rankin Scale (mRS).

Results—On admission, 68% of patients presented proximal middle cerebral artery occlusion, median NIHSS 17. Early recanalization was complete for 30 patients (17%), partial for 50 (28%), and none for 99 (55%). Delayed recanalization was complete for 56 patients (31%), partial for 39 (22%), and none for 84 (47%). Although early flow improvement was observed in up to 45% of patients, only 19% of patients with persistent occlusion (11% of total) presented delayed recanalization (odds ratio [OR] delayed/early recanalization, 0.16; 95% CI, 0.085 to 0.304; $P < 0.001$). Among patients with persistent occlusion at 2 hours, only 13 (7% of total) presented late flow improvement (OR late/early recanalization, 0.09; 95% CI, 0.043 to 0.196; $P < 0.001$). The few patients with late recanalization presented comparable median 48-hour NIHSS to those with early/delayed recanalization (3 versus 4.5; $P = 0.9$) and much lower than those with persistent occlusion after 6 hours (3 versus 15; $P = 0.005$). At 3 months, the rate of mRS ≤ 2 was not statistically different between patients with early/delayed versus late recanalization (55% versus 86%; $P = 0.12$) but was lower if occlusion persisted 6 hours after onset (22%; $P < 0.001$).

Conclusion—The majority of t-PA-induced recanalizations occur during the first hour after treatment. Recanalizations during the following hours are rare but still related to clinical improvement if achieved within 6 hours from onset. Rescue reperfusion techniques should be considered if flow improvement is not observed 60 minutes after t-PA bolus. (*Stroke*. 2006;37:1000-1004.)

Key Words: stroke, acute ■ thrombolysis ■ ultrasonography, Doppler, transcranial

Thrombolytic therapy with intravenous tissue plasminogen activator (t-PA) for acute ischemic stroke has shown to be effective by increasing and anticipating recanalization of the occluded brain vessels.^{1,2} In the last years, different studies using multiple methods to assess cerebral flow described recanalization rates ranging from 30% to 60% in the first 6 to 24 hours after t-PA treatment.²⁻⁶ However, the timing and temporal profile of recanalization in the very first hours after t-PA bolus remain uncertain. Continuous transcranial Doppler (TCD) monitoring at the bedside seems to be the best diagnostic tool to assess real-time recanalization.^{7,8}

The CLOTBUST study recently reported a 38% rate of complete recanalization at 2 hours after t-PA bolus in patients who received continuous ultrasound.³ Nevertheless, detailed description of the temporal profile of partial versus complete recanalization during this time remains unknown. One hour after thrombolytic treatment initiation, information about the likelihood of complete recanalization during the following hours may help physicians identify those patients in whom intravenous t-PA will fail to induce early recanalization, making them eligible for rescue reperfusion therapies. We aim to study the probability and temporal profile of recana-

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lization of cerebral arterial occlusions during the immediate hours after t-PA infusion according to flow improvement in the first hour.

Patients and Methods

From February 2002 to June 2005, all patients with an acute (<6 hours from symptom onset) stroke admitted to the emergency department of a university hospital were prospectively studied. A total of 928 patients were evaluated and underwent urgent extracranial and TCD ultrasound examination. Patients with an inadequate temporal bone window were excluded. A total of 179 patients had a TCD-documented intracranial occlusion and fulfilled established criteria for t-PA treatment (0.9 mg/kg).¹ None of these patients received rescue recanalization therapies.

Clinical Protocol

A detailed history of vascular risk factors was obtained from each patient. To identify potential mechanism of cerebral infarction, a set of diagnostic tests was performed; when indicated, patients also underwent special coagulation tests, transthoracic/transesophageal echocardiography, and Holter monitoring. With this information and the neuroimaging data, previously defined etiologic subgroups were determined.⁹ Short-term clinical outcome was assessed at 48 hours by using the National Institutes of Health Stroke Scale (NIHSS).¹⁰ Long-term functional outcome was assessed with the modified Rankin Scale (mRS) at 3 months;¹¹ we defined functional independence as an mRS score ≤ 2 .

TCD Protocol

A standard TCD examination was performed in the emergency room on admission before t-PA administration using 1-channel 2-MHz equipment (TCD 100M Spencer Technologies; Multidop DWL). A standard set of diagnostic criteria was applied to diagnose arterial occlusions. Proximal middle cerebral artery (MCA) occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA at an insonation depth between 45 and 65 mm, accompanied by flow diversion in the ipsilateral anterior and posterior cerebral arteries, according to the thrombolysis in brain ischemia grading system.¹² Distal MCA occlusion was defined as the presence of an abnormal flow between 30 and 45 mm depth or a diffuse dampening of the mean flow velocity in the affected MCA of $>30\%$ compared with the unaffected MCA with signs of flow diversion.¹³ Occlusions in posterior cerebral and basilar artery were defined according to previously published criteria.^{14,15} To assess recanalization, continuous TCD monitoring was performed during 2 hours after t-PA administration. Recanalization on TCD was diagnosed as partial when blunted or dampened signals appeared in a previously demonstrated absent or minimal flow (ie, when a proximal occlusion becomes a distal occlusion). Complete recanalization on TCD was diagnosed if the end-diastolic flow velocity improved to normal or elevated values (normal or stenotic signals).⁷ No change in the abnormal waveforms indicated that no recanalization had occurred. We scored recanalization as complete, partial, or none at 1 and 2 hours after t-PA bolus administration and 6 hours after symptom onset. Early/delayed flow improvement was defined as any degree of recanalization between 0 and 60 minutes or 60 to 120 minutes after t-PA bolus, respectively. In 134 patients (75%), a follow-up TCD examination was performed 6 hours after symptom onset to assess late flow improvement (Figure 1). In those patients treated between 4 and 6 hours from symptom onset, early and delayed recanalization assessment coincided with 6 hours from symptom onset, and late recanalization was not accounted in these cases.

Statistical Analyses

Descriptive and frequency statistical analysis were obtained and comparisons were made using the SPSS 12.0 statistical package. Odds ratios (ORs) and statistical significance for intergroup differ-

ences for categorical variables were assessed by χ^2 test. For continuous variables, the Mann-Whitney *U* test was used. $P < 0.05$ was considered statistically significant.

Results

We included in the study 179 patients (44% women) with a mean age of 72 ± 11 years (range 26 to 92 years) and an acute intracranial artery occlusion: 174 (97.2%) MCA, 4 (2.2%) basilar arteries, and 1 (0.6%) posterior cerebral artery. On admission, 68% of all patients presented with a proximal MCA occlusion. Median NIHSS score on admission was 17 (range 3 to 28), and mean time to treatment was 171 minutes (range 60 to 360 minutes).¹⁶ According to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, stroke etiologies were: cardioembolic 49%, atherothrombotic 29%, undetermined 18%, and dissection 4%. The outcome measures were: median 48-hour NIHSS, 10 (interquartile range 3 to 17) and at 3 months, 35% of patients achieved functional independence (mRS ≤ 2).

Early Versus Delayed Recanalization

At 1 hour, the recanalization status was: none 99 patients (55%), partial 50 (28%), and complete 30 (17%); at 2 hours, the recanalization status was: none 84 patients (47%), partial 39 (22%), and complete 56 (31%). Although early flow improvement was observed in up to 45% of patients, during the second hour, only 19% of the patients with persistent occlusion presented flow improvement (11% of all patients; Figure 2). The probability of recanalization after the first 60 minutes dropped significantly: OR delayed/early recanalization, 0.16 (95% CI, 0.085 to 0.304; $P < 0.001$). In 3%, the flow worsened during the second hour. Median 48-hour NIHSS was higher in patients with no recanalization at 2 hours compared with early recanalization (15 versus 4; $P = 0.001$); however, the few patients who presented delayed flow improvement achieved similar 48-hour NIHSS to those with early recanalization (5.5 versus 4; $P = 0.92$). Long-term functional outcome was also similar between the latter groups (mRS ≤ 2 : 56% and 50%, respectively; $P = 0.67$; Figure 3).

Late Recanalization

Six hours after symptom onset, the rates of recanalization were: none 55 patients (41%), partial 23 (17%), and complete 56 (42%). Among patients with persistent occlusion at 2 hours, only 13 (7% of all patients) presented a late flow improvement. During this period, the probability of recana-

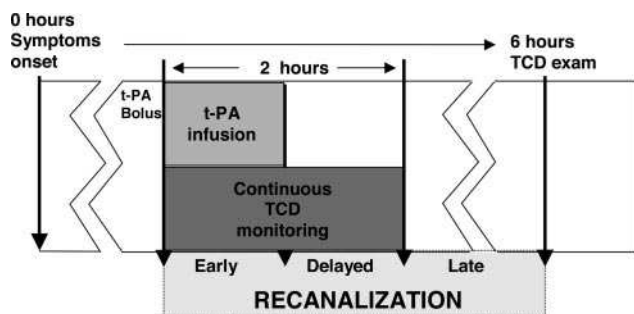


Figure 1. Study design.

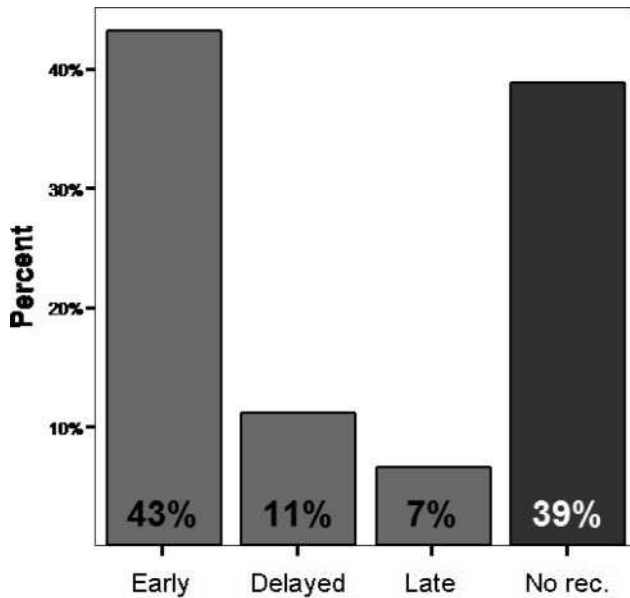


Figure 2. Rates of recanalization at different time points. (no rec indicates no recanalization at 6 hours from symptom onset).

lization continue to drop: OR late/early recanalization, 0.09 (95% CI, 0.043 to 0.196; $P < 0.001$). Four percent of the patients presented a reocclusion during this time. Again, the few patients that recanalized during this period still presented comparable median 48-hour NIHSS to those who recanalized within 2 hours of treatment (3 versus 4.5; $P = 0.9$) and much lower than those in whom arterial occlusion persisted after 6 hours (3 versus 15; $P = 0.005$; Figure 3). At 3 months, the rate of patients that achieved functional independence ($mRS \leq 2$) was not statistically different between patients with early/delayed versus late recanalization (55% versus 86%; $P = 0.12$; median mRS 2 versus 1; $P = 0.37$) but much lower in those who remained occluded 6 hours after onset (22%; $P < 0.001$; Figure 3).

Discussion

In our large group of acute stroke patients treated with intravenous thrombolysis, a high rate of recanalization was observed during the first hour after treatment initiation. Unfortunately, after 60 minutes, once continuous t-PA

infusion ended, the rate of recanalization dropped dramatically. However, reperfusion after 1 hour, even if rather rare, was still associated with good neurological recovery if accomplished within 6 hours from symptom onset.

Two reasons may explain the substantial reduction in recanalization rates after 1 hour. First, clearance of t-PA is very rapid; 15 minutes after infusion, only 1% of the drug remains in the circulation,¹⁷ explaining the fast reduction in the fibrinolytic activity once the total dose is administered. Second, it is possible that because of the different composition or age of the occlusive clots, fibrinolytic therapies may have a ceiling effect in which those clots with low fibrin content will not be satisfactorily lysed.¹⁸ In fact, different series of stroke patients in whom thrombolytic drugs were used either intravenously or intra-arterially (nonmechanical) seem to place this ceiling at an $\approx 60\%$ rate of recanalization.^{3,5,6} The remaining 40% of cases would constitute resistant clots probably only susceptible to mechanical retrieval or disruption.

It is interesting to point the group of patients who presented with an initial proximal MCA occlusion and achieve a partial recanalization after 60 minutes. Unfortunately, up to 73% of them will remain with a persistent distal occlusion (Figure 4), as if only the smooth fibrin-rich external layers of the clot would respond to fibrinolysis while the hard well-organized clot core would remain intact (peach-like clot). Despite the initial encouraging sonographic response, these patients will not experience a favorable clinical outcome (median 48-hour NIHSS 14).

These data encourage the adoption of rescue reperfusion approaches in those cases in which complete recanalization is not observed 1 hour after t-PA bolus. Our data, supporting trials that test recanalization approaches beyond the 3-hour window,¹⁹⁻²¹ showed that reperfusion up to 6 hours after symptom onset may be associated with good neurological recovery. Previous studies already pointed out TCD as an ideal screening tool for combined intravenous/intra-arterial lysis protocols²² because it has the potential to identify and reject those patients who achieved an early recanalization not yet accompanied with neurological recovery or to select patients with persistent occlusion candidates for further interventions. Moreover, TCD monitoring of the affected artery can even be continued in the

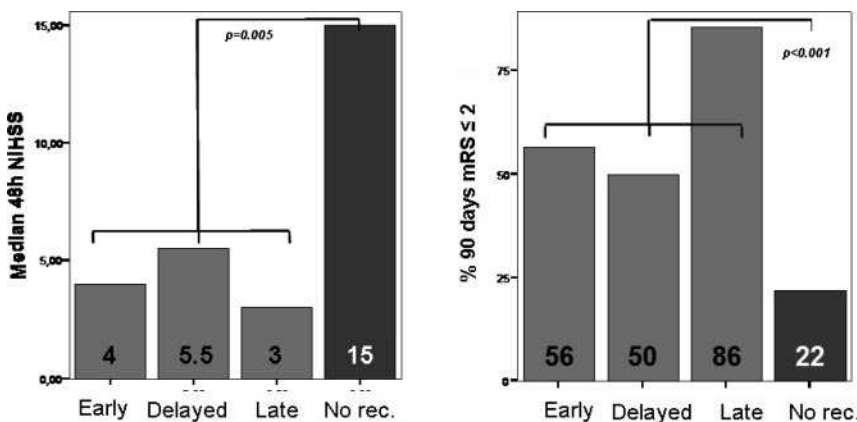


Figure 3. Outcomes at 48 hours and 3 months according to time of recanalization (no rec indicates no recanalization at 6 hours from symptom onset).

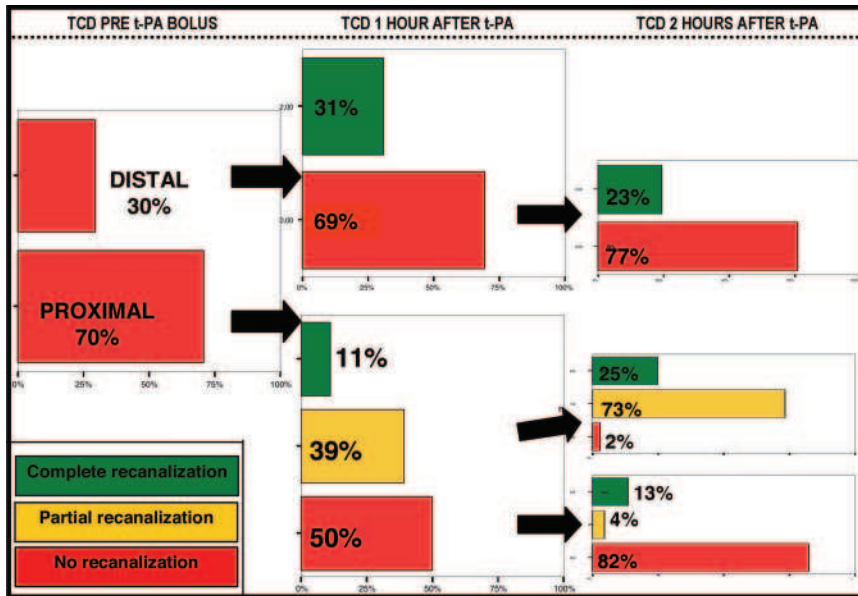


Figure 4. Timing and degree of recanalization in patients with initial MCA occlusion, proximal or distal.

angiography suite, where it offers online continuous information of the flow status as it speeds up thrombolysis. Combining TCD data with information about initial clot location²³ (intracranial carotid T, tandem carotid/MCA occlusions) or presumable etiology¹⁸ (atherothrombotic) would help selecting those patients in whom recanalization is most unlikely.

In this study, all patients were continuously monitored with TCD during the first 2 hours after t-PA bolus. It is likely that in different conditions, without continuous insonation of the offending thrombus, the rates of recanalization may have been lower.³ Unfortunately, our study design did not record recanalization after 6 hours from symptom onset in several patients, avoiding the possibility of evaluating the real potential benefits of very late recanalization.

Conclusions

The majority of t-PA-induced recanalizations occur during the first hour after treatment. Recanalizations during the following hours are rare but still related to clinical improvement if achieved within 6 hours from symptom onset. Rescue reperfusion techniques should be considered if flow improvement is not observed after completion of t-PA infusion.

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References

1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581–1587.
2. Molina CA, Montaner J, Abilleira S, Arenillas JF, Ribo M, Huertas R, Romero F, Alvarez-Sabin J. Time course of tissue plasminogen activator-induced recanalization in acute cardioembolic stroke: a case-control study. *Stroke.* 2001;32:2821–2827.
3. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moya LA, Hill MD, Wojner AW. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med.* 2004;351:2170–2178.
4. Schellinger PD, Chalela JA, Kang DW, Latour LL, Warach S. Diagnostic and prognostic value of early MR imaging vessel signs in hyperacute stroke patients imaged <3 hours and treated with recombinant tissue plasminogen activator. *AJNR Am J Neuroradiol.* 2005; 26:618–624.
5. Neumann-Haefelin T, du Mesnil de Rochemont R, Fiebich JB, Gass A, Nolte C, Kucinski T, Rother J, Siebler M, Singer OC, Szabo K, Villringer A, Schellinger PD. Effect of incomplete (spontaneous and postthrombolytic) recanalization after middle cerebral artery occlusion: a magnetic resonance imaging study. *Stroke.* 2004;35:109–114.
6. Schellinger PD, Fiebich JB, Jansen O, Ringleb PA, Mohr A, Steiner T, Heiland S, Schwab S, Pohlert O, Ryssele H, Orakcioglu B, Sartor K, Hacke W. Stroke magnetic resonance imaging within 6 hours after onset of hyperacute cerebral ischemia. *Ann Neurol.* 2001;49:460–469.
7. Burgin WS, Malkoff M, Felberg RA, Demchuk AM, Christou I, Grotta JC, Alexandrov AV. Transcranial Doppler ultrasound criteria for recanalization after thrombolysis for middle cerebral artery stroke. *Stroke.* 2000;31:1128–1132.
8. Alexandrov AV, Burgin WS, Demchuk AM, El-Mitwalli A, Grotta JC. Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: sonographic classification and short-term improvement. *Circulation.* 2001;103:2897–2902.
9. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* 1993;24:35–41.
10. Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Sheppard GL, Spilker J, Kongable GL, Massey S, Reed R, et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke.* 1992;23:632–640.
11. The Dutch TIA Trial: protective effects of low-dose aspirin and atenolol in patients with transient ischemic attacks or nondisabling stroke. The Dutch TIA Study Group. *Stroke.* 1988;19:512–517.
12. Demchuk AM, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, Alexandrov AV. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke.* 2001;32:89–93.
13. Alexandrov AV, Demchuk AM, Burgin WS. Insonation method and diagnostic flow signatures for transcranial power motion (m-mode) Doppler. *J Neuroimaging.* 2002;12:236–244.
14. Ribo M, Garami Z, Uchino K, Song J, Molina CA, Alexandrov AV. Detection of reversed basilar flow with power-motion Doppler after acute occlusion predicts favorable outcome. *Stroke.* 2004;35:79–82.
15. Demchuk AM, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC, Alexandrov AV. Specific transcranial Doppler flow findings related

- to the presence and site of arterial occlusion. *Stroke*. 2000;31:140–146.
16. Ribo M, Molina CA, Rovira A, Quintana M, Delgado P, Montaner J, Grive E, Arenillas JF, Alvarez-Sabin J. Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial Doppler/MRI selection protocol. *Stroke*. 2005;36:602–606.
 17. Keyt BA, Paoni NF, Refino CJ, Berleau L, Nguyen H, Chow A, Lai J, Pena L, Pater C, Ogez J, et al. A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci U S A*. 1994;91:3670–3674.
 18. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabin J. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke*. 2004;35:486–490.
 19. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The desmoteplase in acute ischemic stroke trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66–73.
 20. Abciximab Emergent Stroke Treatment Trial (AbESTT) Investigators. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of a randomized phase 2 trial. *Stroke*. 2005;36:880–890.
 21. IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the interventional management of stroke study. *Stroke*. 2004;35:904–911.
 22. Saqqur M, Shuaib A, Alexandrov AV, Hill MD, Calleja S, Tomsick T, Broderick J, Demchuk AM. Derivation of transcranial Doppler criteria for rescue intra-arterial thrombolysis: multicenter experience from the interventional management of stroke study. *Stroke*. 2005;36:865–868.
 23. Kim YS, Garami Z, Mikulik R, Molina CA, Alexandrov AV. Early recanalization rates and clinical outcomes in patients with tandem internal carotid artery/middle cerebral artery occlusion and isolated middle cerebral artery occlusion. *Stroke*. 2005;36:869–871.