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Editorial Comment**

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# Early Carotid Endarterectomy for Critical Carotid Artery Stenosis After Thrombolysis Therapy in Acute Ischemic Stroke in the Middle Cerebral Artery

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**Background and Purpose**—Tissue plasminogen activator (tPA) has been shown to be effective for acute ischemic stroke. However, if a high-grade cervical carotid stenosis remains despite tPA therapy, patients are at risk for recurrent stroke. Carotid endarterectomy (CEA) has been shown to be effective in symptomatic patients with high-grade cervical carotid stenosis in reducing the risk of stroke, but it is unknown whether CEA can be performed safely after tPA thrombolysis. We describe our experience with 5 patients who underwent early (<48 hours) CEA for residual high-grade cervical carotid stenosis after thrombolytic therapy for acute ischemic stroke in the middle cerebral artery territory.

**Methods**—All patients had a critical (>99%) carotid artery stenosis on the symptomatic side after tPA therapy. All patients received intravenous tPA; 3 patients also received intra-aortic tPA. Three patients received intravenous heparin infusion immediately after administration of tPA. All patients showed marked improvement in their National Institutes for Health Stroke Scale scores after treatment with tPA. CEA was then performed within 45 hours (6 hours in 1 patient, 23 hours in 2, 26 hours in 1, and 45 hours in 1).

**Results**—All 5 patients underwent successful CEA. There were no complications related to surgery. At discharge, 2 patients had a normal examination, and the remaining patients had mild deficits. In a long-term follow-up of 5 to 22 months, no patient had a recurrent cerebrovascular event.

**Conclusions**—Early CEA can be performed safely and successfully in patients after tPA treatment for acute ischemic stroke in appropriately selected patients. (*Stroke*. 2001;32:2075-2080.)

**Key Words:** carotid artery stenosis ■ carotid endarterectomy ■ stroke  
■ thrombolysis ■ tissue plasminogen activator

Carotid endarterectomy (CEA) has proved to be beneficial in the prevention of stroke in patients with high-grade stenosis (70% to 99%) of the cervical internal carotid artery.<sup>1-4</sup> Despite this, the timing of CEA after a stroke remains controversial. Initial reports of intracerebral hemorrhage and increased mortality after early surgery for patients experiencing a recent acute stroke led many to recommend a 4- to 6-week delay before CEA is performed.<sup>5-7</sup> This practice exposes patients to a 2% to 21% risk of recurrent stroke<sup>8-12</sup> or the possibility of carotid occlusion.<sup>13</sup> Recently, several authors reported good to superior results for early CEA in patients with acute stroke, especially those with a normal CT scan of the brain or minor neurological deficit.<sup>8,9,11,14-18</sup> Patients with significant neurological deficit or a large infarct are at highest risk for hemorrhagic transformation after CEA or for poor outcome from CEA. Patients with a stable acute stroke, a normal CT scan, and a normal level of consciousness or those with a small area of low density on CT without

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significant shift, a minor fixed deficit, and a normal level of consciousness have safely undergone early CEA.<sup>8,9,11,14-18</sup>

Urgent intravenous and intra-arterial thrombolysis with tissue plasminogen activator (tPA) has been shown to be effective in acute stroke, with some patients experiencing dramatic improvement.<sup>19,20</sup> Although good distal flow can be achieved through thrombolysis of distal emboli, patients with a critical stenosis of the cervical carotid artery may have residual stenosis. The patient remains at significant risk for recurrent stroke or carotid occlusion. Given the success of early CEA in patients with minor ischemic symptoms and critical stenoses of the cervical carotid artery, we sought to perform CEA immediately after presentation. We describe here our series of 5 patients in whom early CEA was performed after an acute ischemic stroke in the middle cerebral artery (MCA) territory after being treated with tPA,

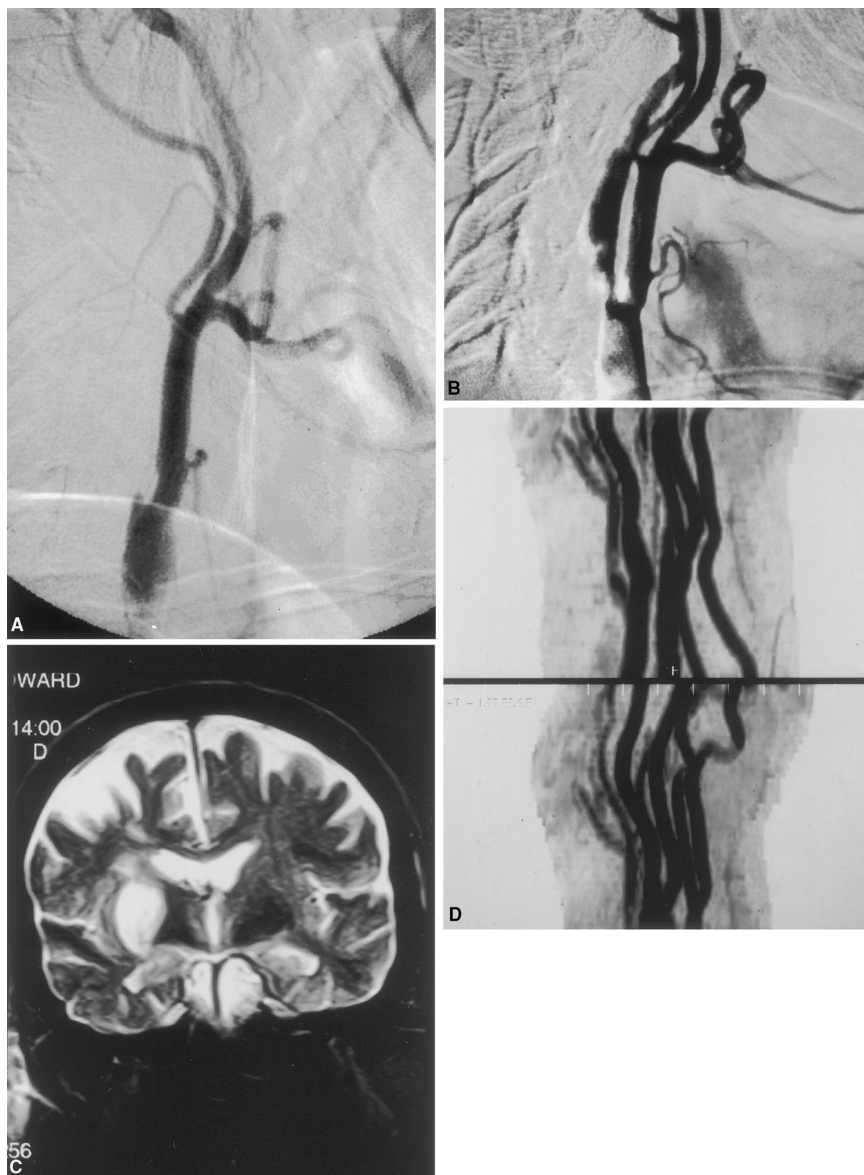
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Radiographic evidence of internal carotid artery stenosis and its resolution by CEA in a 72-year-old white man with acute onset of left-side hemiplegia. A, Right carotid angiogram demonstrating complete occlusion at the bifurcation of the internal carotid artery. B, Right carotid angiogram after administration of intra-arterial tPA that shows residual critical internal carotid artery stenosis. C, Coronal MRI demonstrating increased T2 signal abnormality in the right insular cortex consistent with an area of ischemia; no significant mass effect or midline shift is noted. D, Magnetic resonance angiogram after CEA showing resolution of the right internal carotid artery stenosis.

demonstrating that CEA can be performed safely after an acute ischemic stroke despite the administration of tPA.

### Subjects and Methods

The records of all patients treated with tPA for acute ischemic stroke at the University of Cincinnati Medical Center from January 1, 1997, through September 30, 1999, were reviewed. Five patients received CEA and residual thrombectomy within the first 48 hours of treatment with tPA.

The Greater Cincinnati/Northern Kentucky Stroke Team evaluated all patients with symptoms of acute ischemic stroke and assigned a score on the basis of the National Institutes of Health Stroke Scale (NIHSS). A head CT scan was obtained, and patients who met all inclusion criteria and none of the exclusion criteria for the use of tPA were treated. Selected patients with NIHSS scores >10 underwent a cerebral angiogram after receiving tPA. Treatment with intra-aortic tPA was performed on selected patients with occlusive cerebrovascular disease identified by an angiogram.

In 5 patients, neurosurgical evaluation of residual high-grade carotid artery stenosis on the symptomatic side led to CEA within 48 hours. All procedures were performed in patients under general anesthesia with electroencephalographic monitoring.

### Illustrative Case

An otherwise healthy 72-year-old white man presented with sudden onset of left hemiplegia while working as a volunteer at a homeless shelter. The patient was taken by ambulance to an outside hospital, where he was diagnosed with acute ischemic stroke. His initial NIHSS score was 15. The Greater Cincinnati/Northern Kentucky Stroke Team was then notified. A CT scan of the head showed a hyperdense MCA on the right with no evidence of acute hemorrhage. The patient received a total of 50 mg tPA IV and was transferred to the University of Cincinnati Hospital. A cerebral angiogram showed complete occlusion of the right internal carotid artery at its origin with flow into only 1 right parietal M2 branch and poor distal runoff (the Figure, part A). After injection of 30 mg tPA IA, there was significant improvement in the filling of distal right MCA branches; however, the right cervical internal carotid artery demonstrated minimal recanalization with a residual severe (99%) stenosis (the Figure, part B). The patient experienced significant improvement in his symptoms and was then transferred to the intensive care unit, where he continued to improve to an NIHSS score of 1 (minimal left facial weakness). Because of the patient's residual severe carotid artery stenosis, heparin therapy was initiated and the neurosurgery team was consulted.

**Patients, Presentations, and Timing of Surgery\***

Patient	Age, y	Sex	Initial 24-h NIHSS Score		Angiography Findings				
			Pre-t-PA	Post-t-PA	Initial	After IA t-PA	IV t-PA, mg	IA t-PA, mg	CEA Timing, h
1	45	M	13	0	RICA 100%†	NA	70	0	26
2	72	M	15	1	RICA 100%	RICA 99%	50	30	45
3	49	M	6	2	LICA 100%	LICA 99%	30	23	23
4	64	M	11	0	LICA 99%	NA	44	0	23
5	66	F	24	5	LICA 100%	LICA 99%	36	12.5	6

RICA indicates right internal carotid artery; LICA, left internal carotid artery.

\*No complications related to surgery were experienced by any patient.

†Patient 1 had nearly total occlusion of the RICA with reconstitution of flow beyond the stenotic segment.

An MRI was performed that showed a small area of ischemia in the patient’s right insular cortex (the Figure, part C). Therefore, this patient was believed to be a good candidate for early operative treatment. A right CEA was performed 45 hours after the onset of symptoms. A large plaque was removed from the right internal carotid artery just distal to the bifurcation without complications. Postoperatively, he continued to have mild facial weakness on the left side, which was unchanged. A postoperative MRI showed resolution of his carotid artery stenosis (the Figure, part D). He was discharged home on day 3 after surgery.

In long-term follow-up 22 months after the procedure, the patient had no further cerebrovascular events but continued to experience mild facial weakness.

**Results**

Between January 1, 1997, and September 30, 1999, 5 patients underwent CEA within 48 hours of presentation with acute stroke and treatment with tPA. Four patients were men 45 to 64 years of age at the time of presentation; 1 patient was a 66-year-old woman. All patients presented with neurological deficits referable to a critical carotid artery stenosis with MCA embolus on the side appropriate to their symptoms (the Table). Neurological evaluation and CT scans were obtained in all patients before administration of tPA. All patients had either negative head CT scans or minor findings consistent with hyperacute ischemic changes (dense MCA sign or subtle thalamic hypodensity). One patient had an MRI that showed a small area of increased T2 signal intensity in the right insular cortex. The patients then underwent an angiogram, and 3 patients also received intra-aortic tPA. In the remaining 2 patients, good distal flow had already been achieved by the time of cerebral angiogram and/or the patients had improved clinically. All patients had residual critical stenosis of the internal carotid artery. One patient had nearly total occlusion of the internal carotid artery with reconstitution of flow beyond the stenotic segment.

After the angiogram, 3 patients received maintenance heparin infusions of 600 to 1000 U/h IV (without a bolus dose) because of the residual critical internal carotid artery stenosis. Notably, all patients improved markedly from tPA therapy, with only mild deficits in 3 patients and no deficit by NIHSS score in the remaining 2 patients.

Neurosurgical consultation and evaluation were obtained urgently after therapy in all patients. CEA was performed within 45 hours in 1 patient, 26 hours in 1 patient, 23 hours in 2 patients, and 6 hours in 1 patient. All procedures were performed with patients under general anesthesia with elec-

troencephalographic monitoring. There were no intraoperative or postoperative complications related to surgery in any patient. Patients were then discharged on postoperative day 3 or 4, except 1 patient (patient 5) who had a prolonged stay secondary to myocardial infarction and respiratory failure that occurred before her surgery at the time of her stroke.

In the long-term follow-up of 5 to 22 months, no patient experienced a further ischemic cerebrovascular event. The patient with prolonged stay secondary to medical complications returned to her neurological baseline and had no further ischemic cerebrovascular events.

**Discussion**

The timing of CEA after an acute stroke has long been and remains a controversial issue. Reports of increased morbidity and mortality after early surgery led to a recommendation of a 4- to 6-week waiting period.<sup>5-7</sup> Overall, most studies of early CEA concluded that the highest complication rate was observed when surgery was performed in the first 2 weeks after stroke.<sup>5-7,21</sup> Most patients who experienced poor outcomes with early surgery had either a significant preoperative neurological deficit or an altered level of consciousness and a significant area of cerebral hypoperfusion, indicating impaired cerebral autoregulation. If CEA is performed, subsequent hyperperfusion occurs in the affected area until cerebral autoregulation is re-established.<sup>22</sup> This hyperperfusion can lead to subsequent hemorrhage in the affected area, a well-known but uncommon complication of CEA. The rate of occurrence ranged from 0.3% to 1.2% in several large series.<sup>23-27</sup> Early reports demonstrated increased risk of intracerebral hemorrhage and increased mortality when CEA was performed in the first few weeks after stroke.<sup>5-7</sup> However, these studies were performed before the introduction of CT scans. The use of preoperative CT has helped to eliminate cases in which surgery for cervical carotid stenosis would clearly be contraindicated. In fact, use of CT technology has revealed that up to 15% of all strokes are related to primary intracerebral hemorrhage.<sup>28-30</sup> In addition, preoperative CT has revealed the cases in which large areas of ischemia would represent a substantial risk of postoperative hemorrhage. In 1 study comparing patients with and without CT evidence of infarction, markedly different outcomes were demonstrated after early CEA (within 10 days). Only 1 of 17 patients with a normal CT scan experienced a neurological deficit postop-



eratively. In contrast, 4 of 10 patients with an abnormal preoperative CT scan experienced postoperative deficits, and 1 patient died.<sup>31</sup> Indeed, in patients with abnormal CT scans and large areas of ischemia, immediate surgery can present a substantial risk of postoperative intracerebral hemorrhage.<sup>22,31</sup>

However, there are definite advantages to early CEA after stroke in a patient with high-grade stenosis of the cervical carotid artery. In a large series of 363 strokes, the lowest mortality (1.6%) was in patients who had CEA in the first week and 3.4% mortality for patients undergoing surgery in the second week.<sup>9</sup> Conversely, the highest mortality rate (23.3%) was in patients who underwent CEA in the third week or later. Thus, early surgery for high-grade stenosis not only can reduce the risk of recurrent stroke but also may provide an opportunity for neurological improvement by revascularization of the ischemic penumbra.

It is therefore important to determine which patients are candidates for early CEA after a stroke. The presence of neurological deficit and the infarct size are important determinants of the risk of surgery. Patients with a stable acute stroke and normal CT scan can undergo CEA with no increased risk shortly after diagnosis.<sup>11,14,15,17,22</sup>

Advancements in thrombolytic therapy currently provide patients a significant opportunity for neurological recovery after an acute ischemic event. tPA has been shown to be safe and effective in the treatment of acute stroke when administered within 3 hours.<sup>20</sup> tPA is a recombinant protein expressed by a mammalian cell line into which human complementary DNA sequence has been inserted.<sup>32</sup> It activates plasminogen by proteolysis converting it to plasmin, which is an active protease that lyses a clot by disrupting fibrin linkages. tPA is very short acting, with a serum half-life of only 5 minutes.<sup>33</sup> All 5 patients in this review had nearly complete resolution of symptoms after tPA therapy.

In review of all patients with ischemic stroke treated with tPA by the Greater Cincinnati/Northern Kentucky stroke team, 5 patients were found to have residual stenosis of the cervical carotid artery that could not be treated with current thrombolytic regimens. This residual stenosis places these patients at risk for recurrent stroke that can be up to 21%.<sup>8-12</sup> A patient in this circumstance should be considered for early CEA to prevent the risk of recurrent stroke caused by the high-grade residual stenosis. By judicious patient selection and scrupulous control of postoperative hypertension, the risk for postoperative hemorrhage should be no greater than in patients experiencing transient ischemic attacks. In our series, no patient experienced a hemorrhagic complication after surgery despite the use of heparin in the immediate preoperative period after tPA thrombolysis and despite the fact that all patients had received therapeutic doses of tPA within 48 hours. In addition, no patient had a recurrent stroke in the symptomatic territory after treatment at the most recent follow-up. Therefore, we believe there should be no contraindication to early CEA after the use of tPA, especially in patients with mild stable neurological deficits and/or CT scans with no significant area of ischemia.

Certainly, as tPA becomes more widely used, the scenario of residual carotid stenosis after thrombolysis will become

more common. Although this series is small, it suggests that CEA can be performed safely after thrombolysis. Patient selection is extremely important, and early surgery is appropriate only in patients with mild, stable deficits and a normal CT or a CT without a significant area of ischemia. In these patients, the risk of hyperperfusion to injured brain and resultant hemorrhagic complications is small compared with the overall benefit gained by reducing the risk of recurrent stroke or carotid occlusion.

## Conclusions

In situations in which patients with acute ischemic events have a residual critical carotid artery stenosis despite tPA thrombolysis, we believe it is safe to perform early CEA (<48 hours). Appropriate patients for early CEA are those with mild stable neurological deficits (NIHSS <5) and a CT or an MRI without a significant area of ischemia. The benefit of CEA in reducing the risk of recurrent stroke or carotid occlusion in these patients outweighs the risk of complications from early surgery.

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## Editorial Comment

### Appropriate Timing of Carotid Endarterectomy

The timing of carotid endarterectomy (CE) in a patient with a recent stroke has been an area of longstanding controversy.<sup>1</sup> In the pre-CT era, there were staggeringly high rates of perioperative mortality reported in patients subject to early operation. For example, in the Joint Study of Extracranial Arterial Occlusion,<sup>2</sup> there was a 42% mortality rate after CE in patients with deficits of <2 weeks' duration compared with a 5% mortality rate in patients with neurological deficits lasting >2 weeks.

During the 1980s, there were mixed reports. One study compared 27 patients who had CE within 5 weeks of a stroke and 22 patients with surgery delayed for 5 weeks or longer.<sup>3</sup> The early operation group had a 18.5% incidence of stroke compared with none in the delayed group. In contrast, Whittemore et al<sup>4</sup> reported on 15 patients with "small stable stroke" who underwent surgery within 5 days of symptom onset. None of these patients had worsening of their preoperative neurological status.

In the 1990s, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators reported the results in 42 patients with early CE (within 30 days of stroke) and 58 patients with delayed CE (>30 days after stroke).<sup>5</sup> All patients had severe stenosis, and there was no overall difference in the perioperative stroke rates in the early and delayed groups (4.8% versus 5.2%). These investigators advocated early CE in patients who meet the NASCET criteria of mild, nondisabling stroke.

In this issue of *Stroke*, McPherson et al address a new challenge for the clinician. How early can one safely perform CE in a patient who has recently received thrombolytic treatment for an acute stroke? The authors describe 5 patients who received either intravenous or combination intravenous/intra-arterial thrombolysis. All patients had a severe residual carotid stenosis after thrombolysis. All patients made a good neurological recovery following thrombolysis, with NIH Stroke Scale (NIHSS) scores of 0 to 5 after treatment. Patients were operated on within 45 hours of stroke onset, and none experienced a perioperative stroke.

What should the clinician take away from this interesting but small series? First, it would seem that patients with no neurological deficit or only a mild deficit after thrombolysis administration can be treated in a fashion similar to that used for patients with nondisabling stroke. In patients with NIHSS scores of  $\leq 5$ , there is little reason to delay CE, assuming that all the other necessary elements, such as a stable blood pressure and cardiac and respiratory status, are in place.

Second, postthrombolysis neuroimaging is important. Patients with clinical improvement after thrombolysis and residual carotid stenosis can have a variety of imaging results. There could be a normal CT or MRI, or there could be a small, deep infarction, borderzone infarct, large subcortical infarct, or partial cortical infarct. The authors of this series did not provide postthrombolysis imaging data for all patients, and therefore more data are needed to evaluate the safety of

early CE in the not-uncommon scenario of a patient who has clinical improvement after thrombolysis along with an infarct that shows areas of petechial hemorrhage.

The present study does not address the issue of what to do with patients with moderate or moderate-to-severe deficits. A randomized trial of early versus delayed CE in patients with NIHSS scores of 6 to 15 would be appropriate. One could question the wisdom of performing CE at all in patients with NIHSS scores of >15, since the functional status of these patients is likely to be poor. One would also question the utilization of CE in patients with complete middle cerebral artery territory infarcts.

Finally, although CE was safe in this relatively small series, is early CE always necessary? This may not be the case. The rate of ipsilateral stroke in medically treated patients with severe stenosis is relatively low. At 1 month in the NASCET study, only 3.3% of medically treated patients with 70% to 99% stenosis had an ipsilateral stroke.<sup>6</sup> For patients with near-occlusions, only 1 of 58 patients (1.7%) had a stroke at 1 month with medical management.<sup>7</sup> Thus, although there is no reason to delay the surgery for the conventional 4 to 6 weeks in patients with mild strokes, there also seems to be little reason to plunge ahead as an emergency procedure. The "A team" should be assembled and surgery should proceed once the patient has been medically stabi-

lized. Under these conditions, patients are likely to derive the optimal results from CE.

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