Improvement After Constraint-Induced Movement Therapy Is Independent of Infarct Location in Chronic Stroke Patients

Lynne V. Gauthier, MA; Edward Taub, PhD; Victor W. Mark, MD; Christi Perkins, BS; Gitendra Uswatte, PhD

Background and Purpose—Disruption of the corticospinal tract at various locations in the brain has been shown to predict worse spontaneous motor recovery after stroke. However, the anatomic specificity of previous findings was limited by the categorical classification of infarct locations. Here we used computational methods to more precisely determine the specific anatomic locations associated with impaired motor ability. More important, however, our study also used these techniques to evaluate whether infarct location could influence motor outcomes after Constraint-Induced Movement therapy (CI therapy), a specific and controlled form of physical therapy.

Methods—Quantitative voxel-based analyses were used to determine whether infarct location could predict either initial motor ability or clinical improvement after CI therapy in chronic stroke patients.

Results—Although corona radiata infarcts were associated with worse in-laboratory motor ability at pretreatment, infarct location did not predict improvement in either the laboratory or the life situation after CI therapy.

Conclusions—The extent of improvement from CI therapy does not depend on the location of neurological damage, despite there being a pretreatment relationship between infarct location and in-laboratory motor ability. This dissociation could be explained by brain plasticity induced by CI therapy. (Stroke. 2009;40:00-00.)

Key Words: infarct location ■ CI therapy ■ stroke rehabilitation ■ imaging ■ MRI ■ motor recovery

Several studies have suggested that infarct location influences spontaneous recovery of motor function after stroke.1–5 Subcortical infarcts in the brain stem,2 posterior limb of the internal capsule,1,2 and corona radiata3 have been associated with worse spontaneous motor recovery in both acute4 and chronic1,2,3 stroke. Additionally, prolonged motor disability after stroke was found to be most severe in patients with infarcts involving both the thalamus and posterior limb of the internal capsule.4 Although categorical classification of infarct location limited the anatomic specificity of these studies, a common finding was that damage to the corticospinal tract (CST) appeared to impair spontaneous recovery of motor function after stroke.

Further support for the importance of the CST in motor recovery has been established in studies that used alternate methods of measuring brain structure, excitability, or metabolism. Extensive Wallerian degeneration of the CST after cerebral infarction has been associated with sustained motor disability in stroke patients.6 Transcranial magnetic stimulation (TMS) and magnetoencephalography studies have suggested the importance of CST connectivity for motor recovery after stroke. Patients with worse spontaneous recovery have shown decreased cortical-muscular coherence7 and reduced motor-evoked potentials after TMS of the cortex.2,8 Magnetic resonance spectroscopy has also demonstrated reduced capsular N-acetylaspartate signal (which is presumed to reflect axonal injury) in the posterior limb of the internal capsule that was strongly associated with motor deficit after ischemic stroke.9 Taken together, these studies provide compelling support for the importance of CST integrity in spontaneous recovery of function after stroke.

Despite the abundance of these findings, however, the influence of infarct location on specific motor rehabilitation outcomes remains to be determined. A neurorehabilitation technique termed Constraint-Induced Movement therapy (CI therapy) provides a good vehicle for examining this relationship. In contrast to standard physical therapy, CI therapy is a highly standardized and intensive motor intervention that has been shown to substantially increase the amount of use and motor ability of an affected upper extremity after stroke.10–13 One of the mechanisms associated with improved motor ability through CI therapy is neuroplasticity.14,15 CI therapy has been shown to produce “functional” changes in brain metabolism, blood flow, and electric excitability (summa-
ized in\textsuperscript{15}). More recently, structural remodeling of sensorimotor cortices, more anterior motor areas, and hippocampus has been demonstrated after 2 weeks of CI therapy.\textsuperscript{14} Because these functions or structures can change, whereas the locations of cerebral infarctions cannot, neuroplastic responses to CI therapy have the potential to moderate the limiting effects of infarct location on motor recovery.

We attempted to determine whether infarct location can predict motor improvement in chronic stroke patients given CI therapy. Specifically, we aimed to determine whether CI therapy could override the effects of infarct location, perhaps as a result of neuroplastic changes that CI therapy has been shown to produce.\textsuperscript{14,15}

### Methods

#### Participants

Participants were adults with chronic poststroke upper extremity hemiparesis recruited between 1997 and 2007 for several projects aimed at testing the efficacy of different forms of CI therapy. There were 2 main groups of patients: those who received a full CI therapy protocol (n = 44) and those who were randomly assigned to comparison groups that received attenuated versions of the therapy (see Therapy and Testing).\textsuperscript{11,14,16–18} Those receiving full CI therapy had a mean age of 62.1 ± 12.2 years and median chronicity of 3.0 years; 23 were women, 22 exhibited right hemiparesis, and 41 were right-handed before stroke. The full sample of patients had a mean age of 63.0 ± 12.3 years and median chronicity of 2.3 years; 39 were women, 39 exhibited right hemiparesis, and 71 were right-handed before stroke. A breakdown of participant characteristics is provided in Table 1 (see supplemental materials, available online at http://stroke.ahajournals.org, for a more detailed description). Severity of initial motor impairment was independent of infarct volume, chronicity, age, side of motor deficit, or handedness.\textsuperscript{19} Our institution’s human subjects review board for research approved this study; all patients provided signed informed consent.

#### Procedures

**Therapy and Testing**

Patients received T1-weighted MRI scans within 1 week before receiving therapy. Patients randomized to full CI therapy received all 3 components of the therapy: (1) intensive in-laboratory training of the more impaired arm on functional tasks for 10 consecutive weekdays, (2) restraint of the less-impaired arm for a target 90% of waking hours, and (3) a number of behavioral techniques termed the “transfer package” that lasted an additional 0.5 hours on each treatment day in the laboratory.\textsuperscript{13} The transfer package, designed to facilitate transfer of therapeutic gains in the laboratory to real world activities, included daily monitoring of life situation use of the more affected arm in several ways and problem-solving with a therapist to overcome perceived barriers to using the extremity. Though details of the treatment protocol varied somewhat among different groups of patients receiving full CI therapy\textsuperscript{11,16–18} (eg, some patients received sling restraint of the entire upper extremity rather than the more recently implemented protective mitt\textsuperscript{17}), clinical outcomes were equivalent. Groups of patients receiving the attenuated therapies were denied either in-laboratory motor training or the transfer package and showed significantly decreased improvements in real-world arm use. Therefore, to assess the effect of infarction location on CI therapy outcome, only patients who had received full CI therapy were included in the analysis (n = 44). In contrast, the effect of infarction location on pretreatment motor functions was assessed in the entire patient group (n = 81).

All patients performed the Wolf Motor Function Test (WMFT) and rated the amount and quality of their arm use on the Arm Use scale of the Motor Activity Log (MAL) before and after the therapy course to assess baseline performance and treatment efficacy. The WMFT is a laboratory motor function test that measures performance time as patients perform a series of tasks as rapidly and as well as they can. It is a highly standardized, valid, and reliable objective measure of in-laboratory motor ability.\textsuperscript{20,21} Performance time on the WMFT was recorded as a log\textsuperscript{2} transformation of the mean time in seconds to more accurately portray patient progress.\textsuperscript{19} The MAL is a scripted, structured, therapist-administered interview of how well and how often the patient uses the impaired arm spontaneously in the life situation for 30 frequently performed activities of daily living (eg, brushing teeth, washing hands)\textsuperscript{17}; it is a highly reliable and valid measure of real-world arm use\textsuperscript{22,23} and correlates well with objective measures of arm use in the life situation.\textsuperscript{24} The WMFT and the MAL measure different aspects of motor function and scores on the two tests frequently diverge substantially; therefore, analyses of WMFT and MAL data were performed separately.

#### Infarct Location Analysis

Infarcts were initially identified and manually traced under supervision of a neurologist (V.W.M.). To reduce subjectivity, they were then refined by trained observers using a semiautomated intensity thresholding technique available through MRicro (version 1.4) software. The threshold was selected to approximate the intensity of the cerebrospinal fluid of each image, thus restricting the lesion tracing to regions that were presumed to be necrotic. Images were equated for deficit side by flipping left to right the brains of patients with right arm hemiparesis. Each patient’s T1 scan was normalized to a standard brain template provided by the International Consortium for Brain Mapping (http://www.loni.ucla.edu/ICBM/Downloads/Downloads_ICBMtemplate.shtml) using the Statistical Parametric Mapping toolbox (SPM5, http://www.fil.ion.ucl.ac.uk/spm); infarcts were masked during this process to guard against distortions in the normalization. Deformation parameters from this normalization were applied to each patient’s infarct tracing, resulting in infarcts that were

<table>
<thead>
<tr>
<th>Table 1. Participant Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantity</strong></td>
</tr>
<tr>
<td>All patients (n = 81)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Chronicity</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Right-sided hemiparesis</td>
</tr>
<tr>
<td>Right-handed</td>
</tr>
<tr>
<td>Infarct characteristics</td>
</tr>
<tr>
<td>Volume</td>
</tr>
<tr>
<td>Cortex involved</td>
</tr>
<tr>
<td>Multiple infarcts within single hemisphere</td>
</tr>
<tr>
<td>Bilateral Infarcts</td>
</tr>
<tr>
<td>CI therapy patients (n = 44)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Chronicity</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Right-sided hemiparesis</td>
</tr>
<tr>
<td>Right-handed</td>
</tr>
<tr>
<td>Infarct characteristics</td>
</tr>
<tr>
<td>Volume</td>
</tr>
<tr>
<td>Cortex involved</td>
</tr>
<tr>
<td>Multiple infarcts within single hemisphere</td>
</tr>
<tr>
<td>Bilateral Infarcts</td>
</tr>
</tbody>
</table>

*Mean ± SD; †Median (positively skewed distribution).
mapped to the standard brain template. An infarct overlap map was
generated by overlaying all patients’ infarcts onto the template brain
(supplemental Figure I, available online at http://stroke.ahajournals.org).
To prevent analysis of brain voxels with an insufficient number of
observations from which to draw accurate statistical conclusions, brain
voxels that had an infarct overlap of less than 5 (ie, fewer than 5 patients
had infarcts occupying the particular brain voxel) were excluded from
analysis.

**Determination of Effects of Infarct Location on Motor Scores at Pretreatment**

Two-sample, 2-tailed t tests were performed at each voxel comparing
test scores of patients who had infarcts at that particular voxel location
to those of patients without infarcts at that voxel. The result was a 3D map of t values (and associated probability values) that
encompassed all voxel locations. Given that 14 241 voxels were
tested in the analysis, it was necessary to adjust for family-wise error
(FWE) by using a multiple comparison correction procedure. Infarct
location data are spatially correlated (ie, if a patient’s infarct occupies a particular voxel, it is highly likely that it also occupies
neighboring voxels); therefore, commonly used multiple comparison
procedures (eg, Bonferroni correction) are not appropriate. Permu-
tation analysis is a relatively conservative procedure for multiple
comparison correction of spatially correlated data and has been shown
to be superior to other methods of multiple comparison correction for voxel-based lesion-symptom mapping. The theory
behind permutation analysis is that if the null hypothesis were true
(ie, motor scores at pretreatment are independent of infarct location),
motor scores could be randomly shuffled across patients with no
change in results. Therefore, a null distribution for this data set was
created by performing 5000 shuffles of the data: randomly assigning
motor scores to different patients, and calculating probability values
for each shuffle at each voxel using 2-sample t tests comparing patients
with an infarction at that voxel to those without one. To
correct for multiple comparisons, only the smallest probability value
for each shuffle was stored in the null distribution (ie, of the 14 241
probability values across the brain, only a single probability value—
the smallest of the 14 241 probability values produced in any given
shuffle—was entered into the null distribution). Thus, the null
distribution is a distribution of minimum probability values that
could be anticipated under the null hypothesis, and therefore the
most conservative distribution with respect to rejecting the null.
Voxels from our data set that yielded a probability value within the
smallest 5% of this empirically derived null distribution were deemed
significant. Code specific to this analysis was developed
using Matlab 7.5 software and can be provided on request.

**Determination of Effects of Infarct Location on Motor Outcomes After CI Therapy**

As noted, for the analyses relating treatment change scores on the
WMFT and the MAL to infarct location, only data from patients who
received the full CI therapy intervention were included (n=44). A
separate infarct overlap map was constructed for this subset of
patients, and voxels with an infarct overlap of less than 5 cases were
again excluded from analysis. Two-sample t tests were performed at
each of the remaining voxels (12 079) comparing the WMFT and
MAL, change scores for patients who suffered an infarct at a particular voxel location to those who did not. Permutation analysis
was implemented to correct for FWE.

**Comparison of Findings to Those Obtained Using Older Techniques**

We assessed the validity of our permutation analysis method by
comparing our findings to those obtained using a more common
qualitative infarct overlap analysis technique (eg, Damasio et al). Pretreatment test scores were partitioned into thirds. Separate infarct
overlap images were generated for patients falling within the top
third (n=27) and for those falling within the bottom third (n=27) on
both the WMFT and the MAL. Qualitative differences between
infarct overlap maps for the bottom and top tertiles were then
cross-referenced with our voxel-wise t score maps at pretreatment.

**Results**

**Clinical Outcomes**

Full CI therapy produced significant improvements on the
WMFT (t=4.5, P<0.0001) and the MAL (t=14.6, P<0.0001), indicating that the therapy was effective at
improving both in-laboratory and real-world arm use (Table 2). The magnitude of treatment change is consistent with
studies published previously from this laboratory and reflects a large clinical effect (d=−0.68 & 2.2, respectively, large values according to conventions of the meta-
analysis literature). One study has found that the minimum clinically important difference for the MAL is 1.0
(difference here was 1.7).

**Effects of Infarct Location on Motor Scores at Pretreatment**

Infarction of the centrum semiovale contralateral to the
more-affected arm, specifically the portion of the inferior
corona radiata deep to primary motor cortex that intersects
the crossing fibers of the corpus callosum, was significantly
associated with worse performance on the WMFT at pretreatment
(PFWE=0.004, supplemental Figure Iib). Effect sizes at
each voxel, as calculated using Cohen d (the mean difference
in motor scores between infarcted and noninfarcted subjects
divided by the pooled standard deviation of the motor scores),
exceeded 2.0 (supplemental Figure Iic). No significant
relationship was observed between infarct location and pretreatment
performance on the MAL (PFWE=0.219).

**Effects of Infarct Location on Motor Outcomes After CI Therapy**

Infarct location was not significantly related to CI therapy
treatment outcome as measured by either the WMFT or the
MAL (PFWE=0.741 and PFWE=0.894, respectively).

**Comparison of Findings to Those Obtained Using Older Techniques**

The infarct overlap image for the 27 patients who performed
most poorly on the WMFT was compared to the infarct
overlap image for the 27 patients with the strongest perfor-

---

**Table 2. Motor Scores for the More Impaired Arm Before and After CI Therapy (Mean±SD )**

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Treatment Change</th>
<th>d*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Activity Log Quality of Movement scale (0–5 points)</td>
<td>0.9±0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolf Motor Function Test Log</td>
<td>1.28±1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI therapy patients (n=44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Activity Log Quality of Movement scale (0–5 points)</td>
<td>0.9±0.64</td>
<td>1.7±0.79</td>
<td>2.2</td>
</tr>
<tr>
<td>Wolf Motor Function Test Log</td>
<td>1.35±0.96</td>
<td>−0.28±0.41</td>
<td>−0.68</td>
</tr>
</tbody>
</table>

*Cohen d* is a within subjects measure of effect size; a value of 0.57 is
considered large according to conventions of the meta-analysis literature.

†A log10 transformation was applied to the mean Performance Time scores
to correct for skewness of the distribution of scores. A decrease in performance
time represents an improvement.
manances on the WMFT. Among patients performing the worst on the WMFT, 12 (44%) had infarcts in the centrum semi-ovale. In contrast, infarcts to this region were virtually absent in patients with the strongest performances on the WMFT (supplemental Figure IId). The striking difference between these 2 maps is consistent with quantitative findings that infarcts in the centrum semiovale are associated with poorer pretreatment motor ability. As noted, no relationship was observed between infarct location and pretreatment performance on the MAL using our quantitative measure. Similarly, no qualitative differences were clearly observed between patients scoring in the upper versus lower third on the MAL (supplemental Figure III). Thus, what one observes qualitatively is reflected in our quantitative measures assessing the effects of infarct location on pretreatment motor ability.

Discussion

Infarcts in the inferior corona radiata resulted in poorer in-laboratory motor function in a group of 81 chronic stroke patients with mild to moderate upper extremity hemiparesis. This finding is generally consistent with findings from smaller studies using less sophisticated categorical methods of classifying infarct location:1–4: disruption of the CST is associated with poorer motor ability. Unlike earlier studies, however, we identified only a single specific location within the CST in which the infarction was strongly associated with poorer motor outcomes, whereas infarcts in other regions of the CST, such as the posterior limb of the internal capsule, did not show this relationship. This location was at the intersection of the corona radiata and fibers that traverse the corpus callosum. One might speculate that decreased motor ability after corona radiata infarcts results from the combination of damage to the CST and disrupted interhemispheric communication,30,31 perhaps altering the role of the healthy hemisphere in plastic reorganization of function. Although the role of the undamaged hemisphere in stroke recovery remains unclear, physiological changes have been observed in the undamaged hemisphere after stroke,32–35 and disruption of the intact hemisphere in chronic stroke can exacerbate motor impairment.36,37

Infarcts to inferior portions of the CST (eg, the posterior limb of the internal capsule) were not significantly associated with extent of motor deficit. This discrepancy with other findings1,2 may be explained by methodological differences. The relationship between motor deficit and infarct location in the acute phase of stroke may differ from that seen in chronic stroke because the motor system has more time to reorganize after chronic stroke. In addition, previous studies used different motor measures (with little emphasis on speed), smaller sample sizes, and the use of gross categorical classification of infarct location and motor ability.

It is important to note that although infarct location predicted in-laboratory motor ability (WMFT score), it did not predict the amount and quality of arm use in the life situation (MAL score). This finding demonstrates a dissociation between motor impairment and its associated dysfunction. The former appears to result directly from damage to specific brain tissue, whereas the latter may be modulated by a variety of learning and motivational factors in addition to physical disruption of the motor system.

Although corona radiata infarcts were associated with poorer pretreatment motor ability, infarct location did not predict clinical improvement from CI therapy. Similarly, Dawes and colleagues found that despite a correlation between the extent of infarction to the CST and walking performance, CST involvement did not enhance prediction of outcomes from 4 weeks of treadmill training.5 Perhaps this dissociation between the effect of infarct location on initial motor ability versus treatment outcome can be explained by enhanced brain plasticity promoted by efficacious rehabilitation. CI therapy has been associated with changes in brain structure and function.15 These plastic changes could improve motor function by compensating in part for the damage-induced motor deficit. The lack of relationship between infarct location and CI therapy outcome suggests that CI therapy-induced plasticity may operate effectively irrespective of the pathways in the motor network that are damaged. Moreover, CI therapy has been used to treat the motor deficit associated with a number of different neurological conditions including traumatic brain injury,38 multiple sclerosis,39 cerebral palsy,40 and juvenile hemispherectomy with similar clinical outcomes. Taken together, these findings speak to the robustness of CI therapy for treating motor dysfunction of varying brain pathologies.

Despite the potential contribution of this study to understanding neuroplasticity of the motor system, it should be noted that the results and methods applied here have several limitations. Voxel-based techniques that allow identifying lesion effects on function with greater precision than earlier qualitative techniques require large sample sizes. Because of excluding brain voxels with an infarct overlap of fewer than 5 cases, our analyses were restricted to examining the middle cerebral artery territory (supplemental Figure I) and thus were not able to test the effects of less common infarct locations (eg, cerebellum, brain stem) on motor outcomes attributable to an insufficient number of cases with infarcts in those areas. Voxel-based techniques also do not readily enable examination of infarct effects according to a “functional network” model (eg, perhaps combined damage to different parts of the motor network can yield substantially greater deficits than single infarcts to these areas). This study also recruited patients with mild to moderate upper extremity hemiparesis, all of which had some preserved hand function, perhaps limiting the generalizability of our findings.

Despite these limitations, the results from this study have significant implications. This research has demonstrated that in patients with mild to moderate motor impairment, motor recovery produced by CI therapy is independent of the location of neurological damage, despite a significant relationship between infarct location and one aspect of motor ability at pretreatment. Before treatment, patients with damage to the corona radiata performed worse on a laboratory motor function test, yet these patients benefited as much from CI therapy as those without infarctions in this area. The finding that disparate damage to the central nervous system results in relatively equivalent outcomes provides further evidence for the broad applicability of CI therapy.
Sources of Funding
This work was supported by grant HD34273 from the National Institutes of Health and approved by the University of Alabama at Birmingham Institutional Review Board.

Disclosures
None.

References
17. Gauthier et al CI Therapy Outcome Unrelated to Infarct Location
27. Gauthier et al CI Therapy Outcome Unrelated to Infarct Location
Supplemental Methods

Patients were included in the study if they met the following criteria: poststroke interval >10 months; average item score on the Motor Activity Log (MAL) ≤2.5 (see Therapy and Testing); ability to reliably provide daily MAL scores in the opinion of project therapists; ability to use the more-affected extremity for training under therapist supervision without limitation due to pain, fatigue, severe ataxia, or restricted active range of motion; general medical stability; absence of nonvascular structural brain disorder; and ability to follow directions from project therapists. Patients were enrolled regardless of age, hand preference, laterality of motor deficit, stroke etiology (eg, hemorrhagic vs ischemic), infarction location, or number of strokes and infarctions. Patients were primarily recruited through local hospitals and clinics; however, some were self-referred via internet and resided out-of-state.

Figure I. Infarct overlap map for 81 chronic stroke patients with mild to moderate upper extremity hemiparesis. Brains of patients with right arm hemiparesis were flipped left to right to equate for deficit side. a, Axial cross-section through the basal ganglia. b, Coronal cross-section through the primary motor area. c, Sagittal cross-section through the medial temporal lobe. The color bar indicates the number of patients with infarcts at each voxel. Infarcts were most frequently observed in the posterior limb of the internal capsule contralateral to the side of motor deficit (colored red).
Figure II. Infarct location predicted performance on a laboratory-based measure of pretreatment motor ability. a, Results are displayed in coronal cross-sections through the primary motor area (shown in pink). b, A map of t values from the quantitative voxel-based analysis: red-colored voxels indicate infarct locations that predicted poorer pretreatment performance on the WMFT after correcting for multiple comparisons. c, Map of Cohen d values indicating effect size for the quantitative voxel-based analysis. d, Infarct overlap maps for the third of patients with the strongest performances (left), and weakest performances (right) on the WMFT before treatment.
Figure III. Infarct overlap maps for the patients scoring in the upper third (a) vs lower third (b) on the MAL. In contrast to the pattern for WMFT scores, the location of the infarcts in patients with MAL scores in the upper vs lower thirds are similar. Results are displayed in coronal cross-section through the precentral sulcus.
Improvement After Constraint-Induced Movement Therapy Is Independent of Infarct Location in Chronic Stroke Patients
Lynne V. Gauthier, Edward Taub, Victor W. Mark, Christi Perkins and Gitendra Uswatte

*Stroke.* published online May 21, 2009;
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2009/05/21/STROKEAHA.109.548347.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/