Four-Dimensional Ultrasonographic Characterization of Plaque Surface Motion in Patients With Symptomatic and Asymptomatic Carotid Artery Stenosis

Stephen Meairs, MD; Michael Hennerici, MD

Background and Purpose—In vitro studies of atherosclerotic plaque fracture mechanics suggest that analysis of local variations in surface deformability may provide information on relative vulnerability to plaque fissuring or rupture. We investigated plaque surface deformations in patients with symptomatic and asymptomatic carotid artery disease using 4-dimensional ultrasonography and techniques for measuring optical flow.

Methods—Four-dimensional ultrasound examinations of carotid artery plaques were performed in 23 asymptomatic and 22 symptomatic patients with 50% to 90% stenosis of the internal carotid artery. Plaque surface motion during 1 cardiac cycle was computed with a hierarchical model-based motion estimator. Results were compared with plaque echogenicity and surface structure.

Results—Of the 45 patients examined, plaque surface motion estimates were obtained for 18 asymptomatic and 13 symptomatic patients. There were no significant differences in echogenicity or surface structure of asymptomatic and symptomatic plaques (P > 0.05). Results of motion estimation showed that asymptomatic plaques had surface motion vectors of equal orientation and magnitude to those of the internal carotid artery, whereas symptomatic plaques demonstrated evidence of inherent plaque movement. There was no significant difference in maximal plaque velocity between symptomatic and asymptomatic plaques (P < 0.14). Maximal discrepant surface velocity (MDSV) in symptomatic plaques was 3.85 ± 1.26 mm/s (mean ± SD), which was significantly higher (P < 0.001) than MDSV of asymptomatic plaques with 0.58 ± 0.42 mm/s (mean ± SD).

Conclusions—MDSV of carotid artery plaques is significantly different in asymptomatic and symptomatic disease. Further studies are warranted to determine whether plaque surface motion patterns can identify vulnerable plaques in patients with carotid artery stenosis. (Stroke. 1999;30:1807-1813.)

Key Words: carotid embolism ■ carotid stenosis ■ plaque ■ stroke ■ ultrasonography, 4-D

One feature of carotid plaques that has received little attention is plaque motion,1 ie, translational plaque movements coincident with those of arterial walls, plaque rotations, and local, plaque-specific deformations. There is reason to believe that analysis of plaque motion may provide new insights into plaque modeling as well as into mechanisms of plaque rupture with subsequent embolism. This notion is derived from experimental work providing evidence that variable vessel wall distensibilities, geometric asymmetries at branching sites, and blood flow disturbances play key roles as localizing factors for atherosclerosis, presumably reflecting the response of the residential vessel wall to moving blood particles, pulsatile pressure, and tension changes from the adjacent flow field.2,3 This dynamic interaction between plaque geometry and its local hemodynamic environment may be instrumental in plaque modeling and in conditions leading to plaque instability. In particular, heterogeneous plaques would be expected to display different elastic properties that may or may not allow local plaque deformations, depending on the extent and location of calcifications, fibrous matrix, lipid deposits, and intraplaque hemorrhages.

The process of atherosclerotic plaque rupture with superimposed thrombosis is generally considered to play an integral role in acute coronary events and depends more on features of plaque vulnerability than on the degree of stenosis.4 Although the cause of plaque rupture remains unclear, possible mechanisms include tensile stress with stress concentration,5 local hemodynamic turbulence,6,7 and thinning of the plaque cap collagen as a result of enzymatic activity.8 Evidence suggests that plaque rupture may involve features similar to fracture mechanics of simple materials with a mode of failure typical of metals that experience fatigue. Observations on the relative position of fiduciary markers placed along plaque specimens during pressure loading have demonstrated that before plaque fissuring, the markers display...
asymmetrical movement. It is thought that such plaque surface movement may be attributable to deformations resulting from crack propagation of multiple local internal tears in the plaque. Whether such plaque motion phenomena occur in unstable atherosclerotic plaques in vivo is largely unknown. A novel approach to study plaque surface deformations has been recently reported. This technique uses 4-dimensional (4-D) ultrasonography to acquire temporal 3-dimensional (3-D) ultrasound data of carotid artery plaques. The ultrasound data are then analyzed with motion detection algorithms to determine apparent velocity fields, also known as optical flow, of the plaque surface. Initial results with the use of this method have suggested differences in plaque motion patterns between patients with symptomatic and asymptomatic carotid artery disease. The present study implements this approach to systematically investigate the relevance of plaque surface deformations in patients with carotid stenosis. It also attempts to provide new quantitative parameters for assessment of plaque motion.

Subjects and Methods

Patients
Symptomatic internal carotid artery disease was defined by criteria used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Asymptomatic patients were defined with the use of criteria of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and were selected randomly from our cerebrovascular outpatient clinic. All patients gave informed consent for the examination. Patients with cardiac arrhythmia were excluded from the study, and only patients in sinus rhythm as verified by an ECG directly before the examination were included. In symptomatic patients, 4-D ultrasound examinations were performed within 48 hours after onset of symptoms. Asymptomatic patients were followed up 6 months after the 4-D ultrasound study to assess plaque stability and clinical status.

4-D Ultrasonography

4-D ultrasound image acquisition was achieved by attaching a 7.0-MHz linear array transducer (Acuson) to a computerized parallel motor system (Tomtec Imaging Systems), which delivered equidistant, ECG-gated axial B-mode images of the carotid arteries. To ensure exact positional movement of the transducer, the motor system was mounted on a specially designed tripod for multidimensional ultrasound imaging. The image resolution for all examinations was constant. Gain settings and focus were adjusted for each patient to achieve maximal plaque surface definition. A slice thickness of 0.2 mm was chosen to yield near-isovolumetric data sets, each voxel corresponding to 0.18×0.18×0.2 mm. RGB (red-green-blue) video signals were digitized in real time at 25 frames per second, resulting in 16 to 25 frames per cardiac cycle, depending on heart rate. An ECG was performed directly before the investigation. All patients were examined in the supine position by the same investigator. The procedure was repeated 2 times with repositioning of the parallel motor acquisition system.

Stenosis Grading and Plaque Morphology

Grading of carotid stenosis was performed with the use of Doppler sonographic criteria established at an international consensus meeting on grading of carotid stenosis,14 ie, combined use of direct criteria of validated threshold maximum systolic velocities, systolic carotid ratio, area ratio (minimal residual area/total area), and spectral broadening, as well as indirect hemodynamic criteria of asymmetry in pulsatility of the velocity spectra of the common carotid artery, reversed ophthalmic artery flow, and asymmetry in pulsatility of the middle cerebral artery. Assessment of plaque morphology was performed with the use of criteria established at an international consensus meeting on the morphology and risk of carotid plaques. Plaque echogenicity was graded as uniformly anechoic, isoechoic, or hyperechoic; predominantly anechoic, isoechoic, or hyperechoic; or unclassifiable calcific. Plaque surface structure was assessed as smooth, irregular, or ulcerated. Plaque morphology was graded independently by both authors before motion estimation, one of whom was blinded to patient clinical status.

Plaque Surface Segmentation and Motion Estimation

For plaque motion analysis, postprocessing of reconstructed 4-D ultrasonographic data (Figures 1 and 2) involved the use of a semiautomatic, gradient edge detection algorithm to define the plaque surface of the first 3-D volume acquired after the R wave of the ECG cycle. The resulting voxels of the plaque surface were then used as initial 3-D coordinates for motion analysis. To calculate the apparent velocity field, ie, optical flow, of these surface coordinates,
we implemented a nonparametric 3-D extension of a validated hierarchical motion estimation algorithm utilizing a minimization of the sum-of-squared differences of laplacian-filtered pyramid images. This technique computes the best representation of the motion field that aligns a specified 3-D region of interest from one volume frame to the next. Coarse motion vectors were obtained at a low image resolution and then were successively refined down to the original image resolution using Gauss-Newton minimization at each pyramid level. Results of motion estimation between consecutive frames were propagated, ie, vector end points were used as starting coordinates for the next 3-D frame evaluation. The flow estimate at each voxel of interest was obtained by centering a $7 \times 7 \times 7$ cube around this voxel. This empirical value ensures that at least some volume features corresponding to those to be found at the coordinates of the best representation of the motion field will be contained in the cube centered around the initial voxel coordinates in the sequential volume space to be analyzed.

**Statistical Analysis**

Parameters for evaluation of plaque surface motion were maximal surface velocity (MSV) and maximal discrepant surface velocity (MDSV), defined as the maximum of differences between maximal and minimal surface velocities of successive 3-D frame volumes. Statistical analysis of MSV and MDSV was performed with the Student's $t$ test. Measurement reliability was assessed with error SD and coefficient of variation. Plaque classification was assessed with the $\kappa$ coefficient of interobserver agreement. Testing for differences in the mean of distribution of plaque surface structure and plaque echogenicity was performed with the Mann-Whitney $U$ test at the 0.05 significance level.

**Results**

4-D ultrasound examinations were performed on 23 asymptomatic and 22 symptomatic patients with stenosis of the internal carotid artery ranging from 50% to 90%. In 12 of these patients, plaque surface segmentation was inadequate for motion estimation. This was due to extensive plaque calcification in 5 patients (3 symptomatic and 2 asymptomatic), uniformly anechoic plaque echogenicity in 3 patients (2 symptomatic and 1 asymptomatic), and high-grade $\geqslant$90% stenosis in 4 symptomatic patients. High carotid bifurcations could not be adequately imaged in 2 asymptomatic patients. Of the 45 patients examined, plaque surface motion estimates were obtained for 13 symptomatic and 18 asymptomatic patients, the routine follow-up of whom ranged from 11 to 49 months (mean, 23 months) before plaque motion analysis. The mean age of symptomatic patients (8 men and 5 women) was 62.5 years (SD, 8.5 years). Risk factor profiles (hypertension, diabetes, smoking, hyperlipidemia) for both patient groups were similar (Table): no risk factors in 1 symptomatic (7%) and 1 asymptomatic (5%) patient, 1 risk factor in 5 symptomatic (38%) and 8 asymptomatic (44%) patients, 2 risk factors in 5 symptomatic (38%) and 6 asymptomatic (33%) patients, and 3 risk factors in 2 symptomatic (15%) and 2 asymptomatic (11%) patients.

The results for plaque morphology in patients with successful plaque surface motion estimates are presented in the Table. The $\kappa$ coefficients of interobserver agreement on plaque echogenicity and on plaque surface structure were acceptable at 0.78 and 0.83, respectively. Significant differences in these parameters between asymptomatic and symptomatic patients were not observed ($P>0.05$). The number of plaque ulcerations in both groups (asymptomatic, n=3; symptomatic, n=4) were similar.

The error SD for repeated measurements of MDSV (0 to 6.3 mm/s) was $\pm 0.18$ mm/s with a coefficient of variation of 4%, indicating good reproducibility of 4-D ultrasonographic plaque surface motion estimation. Comparison of hierarchical motion estimates of carotid plaques in asymptomatic and symptomatic patients revealed significant differences in plaque motion patterns. Asymptomatic plaques showed a homogeneous orientation and magnitude of computed velocity vectors corresponding to a global pattern of arterial motion without evidence of inherent plaque movement. Symptomatic plaques showed signs of inherent plaque motion, irrespective of arterial wall movements. MDSV ranged from 2.1 to 6.3 mm/s (mean, 3.85 mm/s) in symptomatic plaques. In asymptomatic plaques, MDSV was significantly lower ($P<0.001$) and ranged from 0 to 1.7 mm/s (mean, 0.58 mm/s). Maximal discrepant motion was observed exclusively during cardiac systole. There was no significant difference in MSV between symptomatic and asymptomatic plaques ($P>0.14$). Figures 3 and 4 illustrate differences in plaque motion characteristics between asymptomatic and symptomatic patients.

Clinical follow-up of asymptomatic patients after 6 months revealed no signs or symptoms of carotid artery disease. Plaque progression occurred in only 1 of 18 asymptomatic patients. Eleven of the 13 patients with symptomatic carotid artery disease underwent carotid endarterectomy.

**Discussion**

Of the various pathophysiological etiologies of stroke, embolic cerebral infarction resulting from advanced atherosclerosis in the carotid artery is a common mechanism. Several large multicenter studies have attempted to clarify the question of appropriate medical or surgical treatment in patients with symptomatic and asymptomatic carotid stenosis. While the value of carotid endarterectomy for high-grade stenosis causing transient ischemic strokes, minor ischemic strokes, or amaurosis fugax has been well documented, it remains unclear which individual asymptomatic patients will benefit from prophylactic carotid endarterectomy or experimental approaches such as percutaneous transluminal angioplasty or stent placement. Guidelines and recommendations for selection of asymptomatic patients for surgical therapy are insufficient, and data on the natural history of asymptomatic carotid disease imply that many patients will be treated unnecessarily, thus exposing them to the added risk of stroke during surgery. The uncertainty regarding treatment of asymptomatic carotid stenosis stems directly from the lack of a reliable method for prediction of which individual carotid artery plaques will become symptomatic, ie, cause transient ischemic attacks or strokes through embolization of thrombi forming either on the plaque surface or on the adjacent arterial wall. Previous efforts to identify relevant plaque features with respect to composition or surface structure with the use of clinical imaging techniques such as ultrasound, MRI, and angiography have not been successful in differentiating between symptomatic and asymptomatic carotid artery plaques. This inability to classify plaques on morpholog-
The failure of previous attempts to identify relevant plaque features consistent with plaque instability is strong motivation for investigation of new methods to characterize atherosclerotic plaques. This study evaluated the potential of plaque motion patterns to distinguish between asymptomatic and symptomatic carotid artery plaques. To accomplish this goal, we used 4-D ultrasonography, a new technology capable of providing noninvasive, in vivo information on vessel wall geometry and plaque motion with high spatial and temporal resolution. Since the application of motion detection algorithms for analysis of ultrasound data has found increasing acceptance and validation in recent studies, we chose to analyze 4-D ultrasonographic data with a nonparametric, model-based hierarchical motion estimator to provide a quantitative description of plaque motion.

Our first results with 4-D ultrasonography and optical flow analysis provide evidence that asymptomatic carotid artery plaques may be characterized by homogeneous surface motion vectors reflecting pulsating arterial wall movements undergoing translations and tethering. Absent or minimal

<table>
<thead>
<tr>
<th>Stenosis Grade, %</th>
<th>Sex</th>
<th>Age, y</th>
<th>Risk Factors</th>
<th>MSV, mm/s</th>
<th>MDSV, mm/s</th>
<th>Plaque Surface</th>
<th>Echogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>61</td>
<td>HTN, HL</td>
<td>5.2</td>
<td>3.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>72</td>
<td>HL</td>
<td>5.0</td>
<td>4.3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>80</td>
<td>F</td>
<td>59</td>
<td>DM, SM</td>
<td>3.9</td>
<td>3.1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>49</td>
<td>HTN, SM, HL</td>
<td>9.4</td>
<td>6.3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>67</td>
<td>DM</td>
<td>3.2</td>
<td>2.7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>80</td>
<td>F</td>
<td>62</td>
<td>SM</td>
<td>2.9</td>
<td>2.1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>63</td>
<td>HTN, HL</td>
<td>4.1</td>
<td>3.0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>58</td>
<td>HTN, DM, HL</td>
<td>5.1</td>
<td>3.7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>55</td>
<td></td>
<td>3.6</td>
<td>2.8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>74</td>
<td>SM, HL</td>
<td>4.7</td>
<td>3.6</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>80</td>
<td>M</td>
<td>69</td>
<td>HTN, DM</td>
<td>5.6</td>
<td>4.9</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>61</td>
<td>HL</td>
<td>7.1</td>
<td>6.0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>50</td>
<td>SM</td>
<td>4.7</td>
<td>4.1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>F</td>
<td>72</td>
<td>HTN</td>
<td>2.5</td>
<td>0.7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>58</td>
<td>HTN, DM</td>
<td>1.8</td>
<td>0.3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>47</td>
<td>SM</td>
<td>4.2</td>
<td>1.1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>63</td>
<td>SM, HL</td>
<td>2.7</td>
<td>0.0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>65</td>
<td>HTN, DM, SM</td>
<td>3.4</td>
<td>0.3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; HL, hyperlipidemia; DM, diabetes mellitus; and SM, smoking. Plaque surface and echogenicity scores are according to recommendations of the International Consensus Meeting on the Morphology and Risk of Carotid Plaques. Plaque surface is characterized as follows: 0, smooth; 1, irregular; and 2, ulcerated. Echogenicity scores are as follows: 0, uniformly anechoic; 1, uniformly isoechoic; 2, uniformly hyperechoic; 3, predominantly anechoic; 4, predominantly isoechoic; 5, predominantly hyperechoic; and 6, unclassifiable calcific.
inherent plaque surface motion in asymptomatic plaques was associated with plaque stability at a follow-up of 6 months. In patients with symptomatic carotid artery disease, however, we detected focal movement disparities on the plaque surface. We have characterized such plaque deformations in terms of the MDSV between 2 successive 3-D volume frames in the 4-D ultrasonographic data set.

Data for motion estimation were inadequate in patients with extensive plaque calcification, uniformly anechoic plaque echogenicity, and severe ≥90% carotid stenosis. High carotid bifurcations also presented problems, since the parallel motor system used for guidance of the ultrasound transducer interfered with the examination and prohibited adequate imaging. Emerging developments in ultrasound technology may well improve the success rate for 4-D ultrasonographic image acquisition to assess carotid plaque motion. As frame rates for power Doppler imaging increase, the superiority of this technique for delineation of plaque surfaces may become applicable. Harmonic imaging may be another interesting possibility for improved characterization of plaque morphology. Likewise, new advances in 3-D ultrasound image acquisition techniques may prove useful for motion estimation applications. In particular, those using position and orientation measurement devices capable of tracking scan heads in 6-DOF are of considerable interest, since they may allow registration of irregularly sampled ultrasound images obtained from different perspectives to a regular 3-D volume space, thus potentially maximizing tissue information that is not readily available from 1 imaging plane alone. Several investigations indicate that compounding such data would result in significant improvement in signal-to-noise and speckle contrast. Algorithms for volume reconstruction of irregularly sampled 6-DOF ultrasonographic data are highly complex, however, and will require further refinements before they can be applied to 4-D ultrasonographic motion analysis.

Of considerable interest is the possible complementary role of plaque motion analysis and transcranial Doppler monitoring of high-intensity transient signals (HITS) for identification of vulnerable carotid artery plaques. After the report of HITS during carotid endarterectomy, similar signals occurring spontaneously were recorded in patients with symptomatic carotid artery disease. These signals were presumably microembolic signals, since they were documented to disappear after carotid endarterectomy. Patients with asymptomatic carotid stenoses have also demonstrated HITS, but to a much lesser extent than symptomatic stenosis, with a proportion of approximately 1:5. Few data, however, are available on the predictive value of HITS detection in patients with asymptomatic carotid stenosis. Studies aimed at investigating the complementary role of altered plaque motion and transcranial Doppler monitoring of HITS will demand careful attention to the respective timing of serial examinations, since several recent reports have demonstrated the yield of HITS to increase with early and repeated monitoring in symptomatic patients. Equally important will be adherence to recent guidelines for performing transcranial Doppler HITS monitoring.

The pathophysiological significance of altered plaque surface motion in symptomatic carotid artery plaques remains to be elucidated. We speculate that such motion patterns are related to a dynamic interaction between plaque geometry, plaque composition, and focal hemodynamic alterations. Of particular interest is whether such changes in plaque surface motion may localize vulnerable areas of the plaque. Analogous to experimental studies on plaque rupture in which pressure loading is used to identify asymmetrical plaque movement before fissuring, our identification of similar alterations in vivo suggests that atherosclerotic plaque modeling may involve features similar to fracture mechanics of simple materials with a mode of failure typical of metals that experience fatigue. Further knowledge of the dynamics of

Figure 3. Results of surface motion estimation between 2 digitized frame volumes of an asymptomatic ICA plaque in systole at 80 and 120 ms after the ECG R wave. Color coding of motion vectors on the plaque surface represents the magnitude of computed velocities given in the adjacent color table. The vectors have been magnified (×3) for better visualization. The plaque shows a characteristic motion pattern with a homogeneous velocity distribution of ~2.1 mm/s along the plaque surface (MDSV, 0.7 mm/s).

Figure 4. Motion analysis of a symptomatic ICA plaque that caused stroke through embolism into the ipsilateral middle cerebral artery. The plaque is similar in size and echogenicity to that of the asymptomatic plaque shown in Figure 3. Motion vectors are displayed in the same manner. Note the discrepant motion pattern, with a wide distribution of velocities (MSV, 9.4 mm/s; MDSV, 6.3 mm/s) reflecting plaque deformation.
crack propagation in carotid plaques may be useful for pathophysiological understanding of plaque vulnerability and carotid plaque embolism. In particular, an analysis of local variations in deformability or stiffness coupled with information on local stress distributions may allow an assessment of relative plaque vulnerability. Since few of the symptomatic plaques showing altered motion actually demonstrated ulcerations, the question arises of whether altered plaque motion alone may contribute to thromboembolism.

As in other studies, differentiation between symptomatic and asymptomatic plaques could not be established with the use of morphological criteria such as plaque echogenicity or surface structure. This deficit underscores the importance of plaque motion as a new parameter for evaluation of carotid artery disease. Whether analysis of plaque motion in patients with carotid artery stenosis may allow detection of motion patterns specific to patients with an increased risk for plaque complications must be addressed in new prospective studies.

Acknowledgment

This study was supported by the Forschungsfond Klima 75/95-97 and EU-BAH4-98-3782-UHEI.NK.

References


Four-Dimensional Ultrasonographic Characterization of Plaque Surface Motion in Patients With Symptomatic and Asymptomatic Carotid Artery Stenosis

Stephen Meairs and Michael Hennerici

Stroke. 1999;30:1807-1813
doi: 10.1161/01.STR.30.9.1807

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/30/9/1807

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/