Altered Hemodynamics and Regional Cerebral Blood Flow in Patients With Hemodynamically Significant Stenoses

Anne C. Roc, MS; Jiongjiong Wang, PhD; Beau M. Ances, MD, PhD; David S. Liebeskind, MD; Scott E. Kasner, MD; John A. Detre, MD

Background and Purpose—Blood oxygen level–dependent (BOLD) contrast largely depends on changes in cerebral blood flow (CBF). Because cerebrovascular disease may result in altered CBF, we assessed the temporal dynamics and magnitude of the BOLD response in patients with major arterial stenoses.

Methods—Seven patients with hemodynamically significant stenoses affecting the anterior circulation (primarily left internal carotid and middle cerebral arteries) were compared with 7 neurologically healthy subjects. Continuous arterial spin-labeled perfusion MRI was used to measure resting CBF globally and within various vascular distributions. The BOLD response was acquired during a visually guided bilateral handball squeeze task while motor performance was recorded by a pressure transducer.

Results—Baseline CBF was reduced in bilateral middle cerebral artery and left anterior cerebral artery territories in patients. A prolonged BOLD hemodynamic response was observed in patients in bilateral primary motor cortices but not visual cortex. Patients also exhibited a larger early negative BOLD response, or “initial dip,” in left primary motor cortex. There were no differences in motor performance between groups, suggesting behavioral differences were not primarily responsible for the characteristics of the BOLD response.

Conclusions—An initial deoxygenation followed by a delayed hyperemic BOLD response was observed in patients, although resting flow values were not within an ischemic range. A simple visuomotor BOLD activation paradigm can reflect alterations in the hemodynamic response in patients with hemodynamically significant stenoses. (Stroke. 2006;37:382-387.)

Key Words: hemodynamics • perfusion • stroke

Blood oxygen level–dependent (BOLD) functional MRI (fMRI) has been used to investigate regional brain activation in healthy subjects and patients in various clinical settings. BOLD contrast is the result of a complex interplay of cerebral blood flow (CBF), cerebral blood volume, and oxygen consumption. During sensorimotor activation, changes in the BOLD signal are largely attributable to overwhelming increases in CBF that exceed increases in oxygen metabolism. Recent evidence from optical imaging studies and BOLD fMRI also suggest a brief early response or “initial dip” occurring immediately after stimulus onset.1 This observation results from an increase in deoxyhemoglobin attributable to a brief uncoupling between blood flow and oxygen utilization.

Because CBF may be altered in patients with major arterial stenosis or occlusion, BOLD fMRI may provide a noninvasive means of determining the hemodynamic status of the cerebral circulation. Recently, the magnitude of the BOLD fMRI signal has been used to probe the hemodynamic response to sensorimotor stimulation in patients with cerebrovascular disease. A muted,2–4 absent,5 or even negative3 BOLD response was observed in vascular territories with impaired vasodilatory reactivity. This may result from increased oxygen consumption in the context of uncoupled or exhausted augmentation of CBF. This was empirically supported by defects in cerebrovascular reserve detected during CO2 challenge using BOLD fMRI.3,6,7 The presence of a pathologically increased initial dip has also been reported in a case study of a 74-year-old male with asymptomatic bilateral carotid stenosis.8 The patient had a pronounced negative dip lasting for minutes, and subsequent BOLD response during CO2 challenge demonstrated a diminished vascular reserve in bilateral middle cerebral artery (MCA) distributions. Temporal alterations in the hemodynamic response have also been reported. A prolonged time-to-peak BOLD response was observed in patients with large vessel steno-occlusion4 and in stroke patients with motor impairment but without carotid occlusion.9 This may reflect dependence on compensatory collateral vessels to provide the alternative sources of blood flow.

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Because BOLD signal is sensitive to changes in neural activity and CBF, possible abnormalities in cerebrovascular patients may reflect impairment in either of these variables. Obtaining baseline perfusion measurements provides additional insight into the influence of CBF on the BOLD signal. Changes in CBF can be quantified using continuous arterial spin-labeled perfusion (CASL) MRI, which uses magnetically labeled arterial blood water as an endogenous tracer. This technique has proven useful in the setting of acute and chronic cerebrovascular disease.10–12

The purpose of this study was to assess the shape of the BOLD hemodynamic response in neurologically stable patients with significant cerebrovascular disease relative to healthy control subjects. We used BOLD fMRI to record the transient hemodynamic response in motor cortex, CASL MRI to measure baseline CBF, and a pressure transducer to measure motor task performance. Baseline perfusion, globally and within vascular territories, was measured to confirm the severity of hemodynamic impairment. Because patients had previous transient neurological deficits, motor task performance was also evaluated to demonstrate that patients had since returned to baseline and was able to perform comparably to healthy controls.

Materials and Methods

Subjects

Seven right-handed patients (5 males and 2 females; 46±13 years of age) with known high-grade arterial stenoses affecting the anterior circulation as diagnosed by magnetic resonance angiography (MRA) or diagnostic cerebral angiography were recruited from the outpatient neurology clinic at the hospital of the University of Pennsylvania. Patients were initially evaluated based on presenting clinical symptoms (Table). At the time of the scan, all patients were stable and had no new neurological symptoms. These patients remained stable on repeat neurological exams (B.A., D.L., S.K., J.D.) at 6 months to 1 year after imaging. Diffusion-weighted MRI performed at the time of the scan revealed no evidence of acute strokes. Axial fluid-attenuated inversion recovery FLAIR images were also acquired to determine the presence of chronic strokes (Table). All patients had significant stenosis within vasculature supplying the left hemisphere, with 4 patients also having cerebrovascular disease in the right hemisphere. Seven neurologically healthy right-handed adults (4 males and 3 females; 28±3 years of age) with no evidence of acute or chronic infarcts served as control subjects. All subjects provided written informed consent before the scan. The study was approved by the institutional review board at the University of Pennsylvania.

Apparatus

MRI data were acquired at 1.5-T clinical MRI system (Signa, GE Medical Systems) using the product head coil and foam cushions to minimize head movement. A standard 3D inversion recovery prepared T1-weighted spoiled gradient echo (GE) sequence (echo time [TE]/repetition time [TR]=8.6/1.6 ms; field of view [FOV] of 24 mm, 1 mm isotropic resolution) was acquired for anatomical localization and a CSF-nulled T2-weighted FLAIR sequence (TE/TR=11 002/145 ms, FOV 24 mm, slice thickness of 5 mm, 256×192 matrix) was acquired to identify regions of prior cerebral infarction. CASL perfusion MRI was acquired as previously described15 using a GE echo-planar imaging (EPI) sequence with TR 4000 ms, TE 17 ms, flip angle 90°, FOV 15×24 cm, 8 slices with a thickness of 8 mm with 2 mm gap, and matrix 40×64. CASL was performed with a 0.225-G/cm gradient and 35-mG radio frequency irradiation applied 8 cm beneath the center of the acquired slices. Tagging duration was 2 s. Control labeling used an amplitude modulated version of the labeling pulse,15 and labeled and control images were interleaved at each TR. A delay of 1.5 s was inserted between the end of the labeling pulse and image acquisition to reduce transit artifact.15 BOLD fMRI used the same GE EPI sequence but with TE=50 msec and 5 mm slices with no gap.

During the BOLD fMRI scan, visual stimuli were back-projected by a liquid crystal display (LCD) projector (Epson Powerlite 5300: Epson America, Inc.) onto a translucent screen placed by the subject’s feet. The screen was viewed via an adjustable mirror attached to the head coil. The LCD projector was connected to an IBM laptop outside the scanner. Behavioral data were collected by a squeeze-ball apparatus that was locally constructed and consisted of 2 rubber balls, 1 for each hand, connected by semirigid plastic tubing to a battery-driven pressure-transducer (Honeywell 185PC15DT). Behavioral data were sampled every 20 ms. Voltages from the pressure transducer were digitized using an A-D card (National Instruments, DAQCard 1200).

Patient Demographics, Clinical Presentation, and Vascular Anatomy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>MM</th>
<th>Initial Presenting Symptoms (1–2 years before study)</th>
<th>Lesions at MRI Scan</th>
<th>Location and Degree of Stenosis/Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>60</td>
<td>Yes</td>
<td>Garbled speech and R arm and leg weakness</td>
<td>L parietal and occipital infarcts in watershed distributions</td>
<td>Occlusion of L M1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>44</td>
<td>Yes</td>
<td>L sided headaches, R arm weakness</td>
<td>None</td>
<td>Severe narrowing at bifurcation of the L ICA, mild narrowing at L A1, and occlusion of L M1</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>28</td>
<td>Yes</td>
<td>Headaches and ataxia</td>
<td>Multiple small (&lt;5 mm) frontal, parietal infarcts</td>
<td>Bilateral ICA occlusions at the level of supra clinoid arteries</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>31</td>
<td>Yes</td>
<td>Migraines and L face, arm and leg numbness</td>
<td>R cerebellar, occipital infarcts</td>
<td>R greater than L ICA stenosis (MRA)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>58</td>
<td>No</td>
<td>L face and arm numbness</td>
<td>R cerebellar infarct</td>
<td>Significant stenosis at the bifurcation of the L ICA (MRA)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>57</td>
<td>No</td>
<td>Transient episodes of R arm and leg weakness</td>
<td>Small (&lt;5 mm) L frontal subcortical white matter lesions</td>
<td>Moderate narrowing at R A1, occlusion at the bifurcation of the L ICA</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>47</td>
<td>No</td>
<td>Migraines and R arm sensory deficits</td>
<td>Small (&lt;5 mm) L internal capsule infarct</td>
<td>Moderate narrowing at L M1</td>
</tr>
</tbody>
</table>

MM indicates Moya-moya disease; M, male; F, female; R, right; L, left; M1, horizontal segment of MCA; A1, segment of the ACA.
CASL MRI Image Analysis
Resting CBF measurements in mL/100 g per minute were obtained using a program written in the Interactive Data Language software (Research Systems Inc). Details on calculating CBF have been described previously. Whole brain CBF was determined by averaging perfusion values across all brain voxels. Perfusion images were further segmented into major vascular territories within each hemisphere, including the MCA, anterior cerebral artery (ACA), and posterior cerebral artery (PCA). Vascular regions were created by a previously described automated program that normalized the images based on the Montreal Neurological Institute template.

BOLD fMRI Activation Paradigm
Before scanning, response pressure was calibrated with respect to a subject’s maximal exertion by having the subject squeeze the ball several times without a concurrent task. Minimum and maximum voltages were recorded from both hands, and the response criterion was set to half the distance from minimum to maximum pressure. After calibration and before scan session, all subjects were trained on the task to reduce practice effects.

The visual stimulus consisted of a black and white checkerboard pattern flashing at a rate of 10 Hz for 200 ms. Subjects were instructed to squeeze both rubber balls, 1 in each hand, as soon as the stimulus turned on. As individual responses were calibrated, all subjects were instructed to make a brief phasic squeeze as quickly, but not necessarily as forcefully, as possible. The stimulus paradigm followed an event-related design with 16 stimulus trials alternating with 20 s of rest. A total of 160 brain volumes were collected in 5 minutes and 2 s.

An additional blocked stimulus paradigm was collected to determine whether a block design is sensitive in detecting changes in the hemodynamic response of patients. Task and image acquisition parameters were similar to the event-related design with the exception of 10 s of task alternating with 30 s of rest. A block consisted of 5 s of rest, followed by 10 1-s trials and concluded with 25 s of rest. Eight blocks were collected totaling 160 brain volumes in 5 minutes and 40 s.

Behavioral Analysis
Two measures of behavioral task performance were obtained: reaction time and mean squeeze pressure. Reaction time was measured as the duration between stimulus onset and subject’s response. Squeeze pressure was calculated as the integrated voltage per trial. This voltage is proportional to the ball pressure (lbs/in²) except for losses attributable to the connective tubing.

BOLD fMRI Image Analysis
Preprocessing and statistical analysis were performed using VoxBo. Preprocessing consisted of the following procedures: conversion of the raw data from k-space to image space (reconstruction) and slice acquisition correction using sinc-interpolation, motion correction, and thresholding (masking). The fMRI data were then analyzed using the modified general linear model.

After individual statistical maps were created, the time course of the event-related BOLD signal was extracted from select regions of interest known to robustly activate during the visuomotor task: primary motor (M1), sensory (S1), and visual (V1) cortices. The MCA territory was of particular interest because this vascular distribution primarily provides the blood supply to M1 and S1, whereas the PCA supplies V1. For each subject, region of interest (ROI) masks were hand-drawn on the anatomical T1-weighted images and coregistered to BOLD fMRI images. Regions were segmented using anatomical landmarks similar to those described previously and guided by MRI atlases.

The time course of the BOLD hemodynamic response was expressed as the percent change from mean baseline value and represented the average signal across all voxels within a particular ROI. Each ROI time course was subsequently averaged across the 16 stimulus trials to represent the mean hemodynamic response during the scan. The mean BOLD response of patients and controls were grouped separately and presented as the mean±SEM (see Figure 2).

As a result of this image processing, the following measurements were acquired: time-to-peak BOLD response (ie, time at maximum excursion from baseline), peak height of the BOLD response (ie, maximum excursion from baseline), time-to-peak initial dip (ie, time at minimum excursion from baseline), and magnitude of the initial negative BOLD response (ie, minimum excursion from baseline). For these measurements, task performance measurements, and global and regional CBF values, an unpaired t test (P<0.05) was performed between patients and controls. In the event that normality and equal variance tests failed when conducting a t test, then a Mann–Whitney rank sum test (P<0.05) was performed.

Results
Baseline CBF
Individual CBF results generally corresponded with clinical findings. As a group, patients’ CBFs were lower than controls both globally and within major vascular distributions (Figure 1). Although global baseline perfusion values for patients were outside of the range of misery perfusion, CBF of patients (42.32±3.77 in mL/100 g per minute) was significantly lower than controls (55.73±5.64 in mL/100 g per minute; unpaired t test; P=0.04). Within vascular regions of interest, a significant difference in resting flow was observed between patients and controls in bilateral MCA distributions (unpaired t test; left MCA P=0.02; right MCA P=0.05; left ACA P=0.02). Baseline CBF in the posterior circulation was not significantly different between these patients and controls.

Behavioral Performance
Patients and controls performed similarly for the task. In the event-related condition, there were no significant performance differences between the 2 groups in the reaction time of both hands (patients 0.52±0.04; controls 0.44±0.03 s; unpaired t test; P=0.1) and mean squeeze pressure of both hands (patients 22.8±3.1; controls 29.9±2.4 lbs/in², unpaired t test; P=0.07). Within the patient group, there were no significant differences observed in handedness in reaction time (left 0.53±0.04 s; right 0.52±0.04 s; paired t test; P=0.4) and mean squeeze pressure (left 22.1±4.8 lbs/in²; right 23.6±4.3 lbs/in²; P=0.2). Similar performance results were observed in the blocked condition in reaction time and mean squeeze pressure between patients and controls (data not shown).

![Figure 1. CBF measurements (mL/100 g per minute) globally and in major vascular territories. Error bars represent SEM. Asterisk signifies CBFs in patients are significantly reduced compared with controls (unpaired t test; P<0.05). L indicates left; R, right.](Image)
**BOLD Hemodynamic Response**

The BOLD hemodynamic response typically consists of a significant increase in signal followed by a poststimulus undershoot. In the event-related condition, within M1, S1, and V1 regions, there were no significant differences between groups in the peak height of the hemodynamic response. However, within M1 the time-to-peak hemodynamic response was prolonged in patients compared with controls (Mann–Whitney rank sum test; left \( P < 0.05 \); right \( P < 0.03 \); Figure 2). A trend toward a delayed time-to-peak BOLD response was also observed in bilateral S1 (unpaired \( t \) test; \( P < 0.06 \)). In addition to a delayed hemodynamic response, patients exhibited a larger early negative BOLD response, or initial dip, in the left M1 (Mann–Whitney rank sum test; \( P = 0.04 \)). The time-to-peak initial dip occurred was delayed by 1 TR epoch in patients compared with controls. In V1 and S1, there were no significant differences between groups in temporal dynamics or initial dip (data not shown).

In the blocked condition, the shape of a patient’s BOLD response generally agreed with the severity of hemodynamic impairment. As a group, the hemodynamic response of patients in left M1 was similar to the response observed in the event-related condition. The time-to-peak BOLD response was significantly longer (unpaired \( t \) test; \( P = 0.03 \); Figure 3A), and the magnitude of the initial dip was larger in patients compared with controls (unpaired \( t \) test; \( P = 0.06 \); Figure 3A).

In one patient with complete left internal carotid artery (ICA) occlusion, a corresponding negative BOLD response was observed in L M1 (patient 6; Figure 3B). There were no significant differences seen in the other regions (data not shown).

**Correlations Between Resting CBF and BOLD Responses**

Because significant differences between patients and controls were present in resting CBF in left MCA distribution and BOLD response in left M1, a nonparametric Spearman rank order correlation \((r < 0.05)\) was performed to determine whether changes in the 2 measures were related. A significant correlation was observed between the time-to-peak initial dip in the event-related condition in the left primary motor cortex and baseline CBF in left MCA (correlation coefficient \(-0.866; P = 0.006\)). There was no significant correlation between the peak height of the BOLD response and CBF (correlation coefficient \(-0.465; P = 0.09\)), which was expected given that responses did not differ between patients and controls. There was also no significant correlation between the time-to-peak positive BOLD response and baseline CBF (correlation coefficient \(-0.2; P = 0.5\)) or between the peak height of the initial negative BOLD response and baseline CBF (correlation coefficient 0.235; \( P = 0.4 \)).

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**Figure 2.** Signal averaged time series of the event-related BOLD fMRI response within primary motor (M1; L indicates left; R, right; top row) and primary somatosensory (S1; bottom row) cortices obtained during bimanual visuomotor task. Error bars represent SEM.

**Figure 3.** A, Signal averaged and block averaged time series for the blocked BOLD fMRI response within the left primary motor cortex. The hemodynamic response is shown for patients and controls. Error bars represent SEM across subjects. B, Block averaged results for patient 6. Error bars represent SEM across trials.
right hemisphere in the event-related condition, and between CBF and BOLD measurements in either hemisphere in the blocked condition were also not significant (data not shown).

Discussion
The goal of the present study was to assess the BOLD hemodynamic response in neurologically stable patients with known high-grade stenosis. This was accomplished by using an empirically derived hemodynamic response function (HRF) to model the BOLD response during a simple event-related visuomotor task. Resting perfusion values and task performance were also measured to determine whether the observed differences in BOLD hemodynamic responses could be explained by these variables.

Overall, the degree of CBF reduction as measured by CASL MRI was mild to moderate. Qualitatively, individual pathologies as seen on MRA or angiography corresponded with reduced resting flow in the individual’s affected vasculature. As a group, patients had reduced baseline CBF in left ACA and left MCA distributions, which is consistent with the distribution of vascular lesions comprising primarily stenosis or occlusion in the left anterior circulation. We also observed reduced flow in the right MCA, which is consistent with the presence of cerebrovascular abnormalities in the right hemisphere of some of the patients.

The magnitude of the BOLD response was not significantly different when patients were grouped together and compared with controls. Our findings of unchanged response magnitudes are similar to findings in a recent fMRI study of patients with unilateral stenosis. However, when patients were evaluated individually, the BOLD response generally corresponded with the degree of hemodynamic impairment. For example, a patient with complete occlusion in left ICA exhibited a protracted negative BOLD response in left M1 during the blocked condition. This agrees with a previous study that reported a negative BOLD response in asymptomatic patients with large vessel stenosis performing a blocked design fist closure task.

Our patients showed significant alterations in the latency of the BOLD response in regions supplied by the anterior circulation. The increase in the delay-to-peak BOLD response observed in our patients may be attributable to collateral sources of blood flow recruited in response to neural activation, resulting in a prolonged delivery or perfusion transit time of increased CBF. A similar effect was observed in a previous animal study showing a delay in the time-to-peak flow response in a rat model with acute carotid occlusion.

In addition to changes in temporal dynamics of the BOLD response, we observed an increase in the magnitude of an early negative response in left primary motor cortex, which is within the vascular region that was consistently impaired in our group of patients. The present results are similar to a case study of an asymptomatic patient with bilateral carotid stenosis except in duration of the initial dip. This specific case reported an initial dip lasting for minutes. However, in our patient sample we observed an initial dip lasting seconds, which reflects a similar duration to that which was reported in healthy subjects. These differences may reflect the degree of collateralization required in patients compared with controls. For example, retrograde collateral perfusion attributable to slow flow and increased oxygen extraction may explain the pronounced initial deoxygenation observed in our patients. Such early uncoupling may therefore reflect the adequacy of the arterial collateral blood supply. Future studies are needed to determine whether an enlarged initial dip is predictive of clinical progression.

Our patients were neurologically asymptomatic at the time of scanning and exhibited preserved task performance because reaction times and squeeze pressures did not differ significantly from controls. However, their BOLD responses clearly demonstrated compromised hemodynamic status as seen by the presence of the initial dip and changes in the temporal dynamics of the response. Resting perfusion and changes in the BOLD hemodynamic response were related as indicated by a significant correlation between decreased resting perfusion in the MCA distribution and prolonged time-to-peak initial dip in M1. These results suggest that the time-to-peak initial dip may be a better indicator of the degree of hypoperfusion compared with the magnitude of the BOLD response. With an already reduced baseline flow in our patients, we speculate that a pronounced initial dip may reflect uncoupling of blood flow and metabolism even during a simple transient visuomotor task. We hypothesize that blood flow responses to meet metabolic demands were compromised in our patients, resulting in initial deoxygenation and a delayed hyperemic response, although resting CBF values were not in an ischemic range. Additional measures of neuronal function, such as somatosensory evoked potential, optical imaging, or fluorodeoxyglucose positron emission tomography (PET), could be performed to further characterize this uncoupling.

There are 3 main limitations to the present study. First, BOLD measurement was only acquired with a temporal resolution of 2 s and was acquired at low field (1.5 T). We are currently attempting to refine these results in a higher field at 3 T with 1 s effective temporal resolution. Second, the mean age of control subjects was 13 years younger than patients. Caution must be provided in the interpretation of results because the influence of age on cerebrovascular status is still poorly understood. However, only 1 patient in the group, at 60 years of age, may be classified as “elderly” at the time of the scan. Moreover, previous studies reported comparable hemodynamic responses between elderly and young controls during visual and motor tasks. Third, although stable and asymptomatic at the time of imaging, some patients in our cohort had chronic strokes within the vascular distributions where BOLD responses were abnormal. Conceivably, some of the changes we observed may reflect mechanisms of recovery.

A consequence of the present study is an increased concern in using an assumed canonical HRF to model the response of patients with cerebrovascular disease. Previous event-related studies have identified significant variability in the shape of the hemodynamic response across healthy young adult and elderly subjects. Less variability has been reported in the time-to-peak BOLD response within healthy individuals. A surprising finding of the present study is that the time-to-peak BOLD response of patients was prolonged in left M1 in
blocked and event-related conditions. Our results indicate that temporal changes in the BOLD response of patients can be observed even with blocked activation paradigms. In patients with significant hemodynamic impairment, using a canonical HRF to model the BOLD response may result in an overestimation of the parameters of the response. Because BOLD effects are sensitive to impaired hemodynamics or compromised neural function, a derived HRF should be considered in BOLD fMRI studies in stroke and stroke recovery.

Finally, because the present study was as a cross-sectional study, future longitudinal studies are needed to assess the predictive value of BOLD fMRI and CASL MRI in the qualitative assessment of autoregulatory capacity or the extent of cerebrovascular reserve. In the past, cerebrovascular reserve has been measured by pharmacological flow augmentation, such as the administration of acetazolamide or CO2, with flow-sensitive methods such as PET or single-photon emission computed tomography. BOLD fMRI and CASL MRI have the advantage of being noninvasive methods and offer the ability to acquire repeated measures. Functional stimulation may be more ecologically valid than acetazolamide or CO2 challenge. Our results suggest that a simple visuomotor activation paradigm is sensitive in detecting alterations in the hemodynamic response. The methods used in this study may have value in identifying patients at risk for subsequent stroke and could contribute to medical decision making for revascularization procedures or other clinical treatments.

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