Intracranial Hemodynamics Is Altered by Carotid Artery Disease and After Endarterectomy
A Dynamic Magnetic Resonance Angiography Study
Bradley J. MacIntosh, PhD; Ediri Sideso, MBBS, MRCS; Manus J. Donahue, PhD; Michael A. Chappell, DPhil; Matthias Günther, PhD; Ashok Handa, FRCS; James Kennedy, MSc; Peter Jezzard, PhD

Background and Purpose—Carotid endarterectomy (CEA) has become a routine procedure to treat symptomatic carotid artery disease and reduce the risk of recurrent cerebral ischemic events. The purpose of this study was to use an arterial spin labeling dynamic magnetic resonance angiography technique to characterize intracranial hemodynamics before and after CEA.

Methods—Thirty-seven carotid artery disease patients participated in this study, of whom 24 underwent magnetic resonance imaging before and after CEA. Seventeen control subjects spanning 5 decades underwent magnetic resonance imaging to assess age-related changes. Hemodynamic metrics (that is, relative time to peak and amplitude) were calculated with a γ-variate model. Linear regression was used to relate carotid artery disease burden to downstream hemodynamics in the circle of Willis.

Results—Relative time to peak increased with age in controls ($P < 0.020$). For patients, relative time to peak was positively correlated with percent stenosis ($P < 0.050$), independent of age. At 1 day after CEA, the middle cerebral artery ipsilateral to the CEA showed significant dynamic magnetic resonance angiography changes: relative time to peak decreased ($P < 0.017$) and the flow amplitude increased ($P < 0.009$). No pre- versus post-CEA changes were significant in the contralateral middle cerebral artery or posterior segments.

Conclusions—This noninvasive, arterial spin labeling–based method produced time-resolved images that were used to characterize intracranial arterial flow associated with aging, extracranial carotid artery disease, and CEA. Results demonstrate that the technique has the sensitivity to detect hemodynamic changes after CEA. (Stroke. 2011;42:979-984.)

Key Words: endarterectomy ■ carotid stenosis ■ arterial spin labeling ■ angiography ■ dynamic ■ blood flow ■ aging

Atherosclerosis is a major risk factor for ischemic cerebrovascular events. Extracranial steno-occlusive disease influences hemodynamics and physiology in the brain. Therefore, carotid endarterectomy (CEA) is a standard treatment for patients with symptomatic stenosis >70% because surgical therapy is associated with higher event-free survival compared with medical therapy. However, CEA is not without risk; 1 study reported a 4.3% increase in the risk of stroke or death within 30 days of CEA. Other studies report silent infarcts, evident postoperatively on diffusion-weighted images in 17% to 33% of CEA patients. Therefore, there is merit in developing imaging techniques that can be used to assess the downstream impact of extracranial steno-occlusive disease.

Time-of-flight (TOF) magnetic resonance angiography (MRA) measures static arterial anatomy, whereas phase-contrast MRA is capable of quantitative flow information. Using TOF and phase-contrast MRA, others were able to quantify changes in vessel diameter and flow directionality in the circle of Willis after CEA. Time-resolved, contrast-enhanced MRA is well established and provides dynamic MRA information. In the interest of developing noninvasive, dynamic, MRA (DynAngio) techniques, this study introduces a variant on arterial spin labeling (ASL) that allows quantification of magnetically labeled water in arterial blood with good spatial and temporal resolution. Compared with phase-contrast MRA, this method does not involve velocity...
phase encoding, nor does it require that slices be perpendicular to the vessels of interest.

The purpose of this study was to determine whether ASL-based DynAngio could be used to characterize circle of Willis hemodynamics, as it provides the primary means of collateral blood supply in the brain. We collected data from control subjects and patients with carotid artery disease to test the hypotheses that DynAngio hemodynamic measures are capable of showing age and carotid steno-occlusive disease–related influences on intracranial arterial hemodynamics. In patients who underwent CEA, we tested pre- and postsurgery differences.

Methods
This study was conducted with ethics approval from the Oxfordshire Research Ethics Committee.

Carotid Artery Disease Cohort
Thirty-seven patients with confirmed carotid artery disease were recruited to participate in this study. Twenty-four of 37 patients underwent CEA and were recruited to the study consecutively. Magnetic resonance imaging (MRI) data were collected within the 24 hours leading up to CEA and within the 24 hours after CEA. The 24-hour post-CEA MRI corresponds to the time frame in which the hyperperfusion syndrome is likely to occur. The remaining non-CEA carotid artery disease patients were recruited from the vascular surgery laboratory database. Mean patient age was 70 ± 9 years (range, 47 to 85 years; 10 women). Carotid arteries were assessed by Doppler ultrasound and are provided here for demographic information only: 0% to 49% unilateral, 50%, 11; unilateral occlusion and contralateral <50%, 11; 70% to 99% unilateral, and contralateral >50%, 11; unilateral occlusion and contralateral <50%, 2; and unilateral occlusion and contralateral >50%, 4.

Control Cohort
Seventeen participants with no history of symptomatic carotid artery disease were recruited as controls to investigate aging effects as part of other ongoing trials. Mean age was 63 ± 12 years (range, 45 to 87 years; 7 women). Ten of the 17 control participants had a history of transient ischemic attack but no significant carotid or vertebralbasilar artery (VBA) disease.

Magnetic Resonance Imaging
MRI data were collected on a 3-T scanner (TIM Trio; Siemens, Erlangen, Germany) with a 12-channel head receiver coil. DynAngio data were collected at the level of the circle of Willis. Flow-weighted contrast was achieved with a flow-sensitive alternating inversion-recovery pulsed ASL technique. Time-resolved images were obtained by using a low flip-angle look locker spoiled gradient echo readout. Flow information comes from the pulsed ASL difference images by subtracting the tag condition, achieved by a nonselective radiofrequency inversion pulse, from the control condition, in which a slab-selective radiofrequency inversion is used (Figure 1A). Single-slab, 2-dimensional images were acquired with the following parameters: 1×1-mm voxels, 50-mm slab thickness, repetition time/echo time = 1500 ms/3.7 ms/78 ms, 3 segments, flip angle of 10°, 20 inflow phases, and inflow increments of 78 ms. Images were spatially smoothed by using a 1.5-mm, full-width, half-maximum kernel as part of the postprocessing. In the tag images, a nonselective inversion pulse was used. In the control images, a slab-selective inversion thickness of 60 mm was used, compared with the 50-mm imaging slab. Therefore, the inflow blood water signal would come from water spins that are 5 mm above or below the image plane. The scan duration was 2 minutes, 42 seconds (see online-only Figure). Additional MRI consisted of the following: (1) a 3-plane localizer scan; (2) diffusion-weighted imaging (repetition time/echo time = 4436 ms/93 ms, b-values = 0, 1000 s/mm², 27 slices, and voxel dimensions of 1.6×1.6×3.0 mm³); (3) gadolinium contrast-enhanced TOF angiography (field of view = 200 mm, 1.1×0.8×1.0-mm³ voxels, 40 slices per slab, 4 slabs, 6/8th partial Fourier k-space coverage, GRAPPA acceleration factor = 2, repetition time/echo time = 22 ms/4.08 ms, and scan duration = 2:21). Maximum-intensity projection images were reconstructed from the TOF images at equivalent thickness to the DynAngio to facilitate comparison (Figure 1A) with the use of Osirix open-source software. TOF images were used to characterize the anterior and posterior communicating arteries at the circle of Willis.

Dynamic Angiography Analysis
A γ-variate model was used to characterize the DynAngio data in terms of relevant hemodynamic parameters. The model was fit to the
Intracranial Hemodynamics in Endarterectomy

DynAngio time-resolved signal in each voxel, based on the following expression (Figure 1B):\[ S(t) = \frac{A}{r_{TTP}^{sh} \cdot \exp(-sh \cdot (t-t_0-r_{TTP}))} \cdot (t-t_0)^{sh} \cdot r_{TTP} \]

The model parameters to be estimated were bolus arrival time ($t_0$, seconds), relative time to peak ($r_{TTP}$, seconds; Figure 1C), amplitude (Figure 1D), relative amplitude (A, %; Figure 1C), and sharpness (sh, inverse seconds) for $t > t_0$. Initial model estimates (upper and lower bounds) were as follows: $t_0 = 0.1$ (0.28 to 2.26 seconds), $r_{TTP} = 0.7$ seconds (0 to 1.48 seconds), $A = 30\%$ (0% to 400%), and $sh = 3$ seconds$^{-1}$ (0 to 8 seconds$^{-1}$). Amplitude was expressed as a fraction by dividing the peak signal in the sagittal sinus. This step facilitates intrasession and interparticipant comparison. $r_{TTP}$ is the time from $t_0$ to peak flow enhancement and is a measure of the slope from inflowing blood. The $r_{TTP}$ metric is less sensitive to timing delays and/or slice prescription, and matches the $r_{TTP}$ described by Ostergaard for dynamic susceptibility contrast MRI. Model fitting was performed with the use of in-house Matlab code (Mathworks, Natick, MA). The number of estimated voxels was reported by arterial segment, based on the $r_{TTP}$ model-fit parameter. A voxel was significant when the ratio of the $r_{TTP}$ estimate divided by the fit standard deviation was $> 1.96$, so as to approximate a $z$ statistic threshold that would produce a significant fit at $P < 0.05$.

Region-of-interest (ROI) analysis was performed to investigate the $r_{TTP}$ and amplitude hemodynamic metrics. A $5 \times 5$-voxel ROI was placed manually at the inlet arterial segments of the right middle cerebral artery (MCA), left MCA, and VBA for each participant. Correlation and linear regression analysis were performed to determine the effect of age and internal carotid artery (ICA) stenosis on $r_{TTP}$ (SPSS for Macintosh, version 17.0; SPSS, Chicago, IL). Paired 2-tailed $t$ tests were performed to compare pre- and post-CEA data.

**Results**

**DynAngio in the Control Cohort**

Mean $r_{TTP}$ increased significantly with age, when all arterial segments were considered, according the following expression: $r_{TTP} = 0.266 + 0.004 \times$ age, which corresponds to an increase of 40 ms per decade (Figure 2; $P < 0.02$). The number of voxels tended to decrease with age, but this decrease was significant in the VBA segment only ($P < 0.03$).

**Cohort Comparison**

Patients were significantly older than controls, with a mean age of 70±9 years compared with controls who were 63±12 years ($P < 0.03$). Fewer $r_{TTP}$ voxels were found in the right MCA and left MCA segments for patients compared with controls ($P < 0.006$), but no significant difference was found for the VBA segment ($P > 0.93$).

**DynAngio in the Patient Cohort**

Mean $r_{TTP}$ increased significantly with the percent ICA stenosis in a linear-regression model that included age and ICA stenosis as independent variables ($P < 0.05$). For the CEA patients, only pre-CEA data were included. Pre- versus post-CEA differences are shown in the $r_{TTP}$ maps for 2 patients (Figures 3 and 4). Figure 5 shows the ROI analysis for $r_{TTP}$ data before and after CEA. $r_{TTP}$ in the MCA branch ipsilateral to the CEA decreased significantly, from 564±171 ms before CEA to 471±119 ms after CEA (2-tailed paired $t$ test: $t = 2.58$, $df = 21$, $P < 0.017$). $r_{TTP}$ values did not change significantly in the contralateral MCA or VBA ROIs ($P > 0.49$).

Ipsilateral MCA amplitude increased significantly, from 41±25.7% before CEA to 55±24.1% after CEA (Figure 6; 2-tailed paired $t$ test: $t = 2.87$, $df = 22$, $P < 0.009$). Patients with an intact circle of Willis (13 patients) showed larger increases in amplitude before versus after CEA compared with patients with at least 1 communicating artery missing (9 patients; ANOVA $F = 4.5$, $P = 0.045$). Contralateral MCA and VBA ROIs showed no significant amplitude change.
Discussion

This study demonstrates the utility of ASL-based, time-resolved angiography for the characterization of intracranial hemodynamics. There are 3 novel findings: (1) rTTP increased with age among controls, (2) rTTP increased with the degree of extracranial ICA stenosis, and (3) rTTP decreased and amplitude increased in the MCA segment ipsilateral to the surgery at 1 day after CEA compared with before CEA. Results from the patients with carotid artery disease illustrate the clinical potential of this DynAngio technique and extend the work by others.9,10

Among controls, rTTP in the MCA increased with age. The rTTP metric is related to the slope of the bolus inflow and is likely influenced by flow velocity, vessel diameter, and tortuosity, which is related to pathologic aging processes.16 Characterization of aging effects in controls has not previously been reported with this ASL-based technique. Others have used alternative modalities to show that vascular compliance decreases and that common carotid artery stiffness increases with age.17,18 Cardiac gating was not performed in this study, so our hemodynamic metrics were averaged over the cardiac cycle. Future work could address cardiac effects on this DynAngio because this is an area in the literature that is developing.19,20 We found significant differences between patients and controls, such as the number of detected voxels in the right and left MCAs. Differences in vascular anatomy and the fact that the cohorts were not equally matched for age and sex may have influenced the results.

Figure 4. Maximum-intensity projection TOF (A and D) and DynAngio rTTP (B and C) for patient 2 with a right ICA stenosis of 100% and a left ICA stenosis of 65% who underwent left CEA. Arrows indicate the left carotid siphon where rTTP was reduced after CEA.

Figure 5. DynAngio rTTP for patients who underwent CEA. A 2-tailed paired t test showed that post-CEA rTTP was significantly reduced compared with pre-CEA rTTP in the MCA ipsilateral to the CEA \( (P<0.017) \) but not for the contralateral MCA or VBA. Each line represents data from 1 patient (left = before CEA, right = after CEA).

Figure 6. DynAngio amplitude increased significantly after CEA in the ipsilateral MCA compared with before CEA \( (P<0.009) \) but not for the contralateral MCA or VBA ROIs. Each line represents data from 1 patient (left = before CEA, right = after CEA).
Our second finding was that rTTP values increased significantly with ICA stenosis, which illustrates that it is possible to quantify the effect of extracranial stenosis on distal intracranial arteries. Fifteen of a possible 74 MCA ROIs were not included, however, for 1 of the following reasons: (1) the MCA segment showed an insufficient number of voxels to place an ROI, (2) image quality was poor owing to head motion, or (3) a significant bolus delay affected the estimates, such as $t_0$ or rTTP. With respect to the latter, further work is required to determine how best to schedule the inflow measurements. This might be accomplished by preceding the DynAngio sequence with a phase-contrast MRA, for example, to calculate velocity profiles.

The final results pertain to the significant CEA-related changes that were observed. rTTP decreased significantly after CEA, which could argue for an improved flow profile downstream. Amplitude increased significantly after CEA, which is consistent with previous ICA flow changes. Post-CEA data were obtained 24 hours after surgery, before the patients being discharged, which is not a steady-state period but is important in terms of the hyperperfusion syndrome. The DynAngio scan duration was short and does not require injected contrast material; therefore, it would lend itself well to longitudinal monitoring.

Hemodynamic modeling used 20 inflow time points to extract the metrics, producing a temporal precision that was greater than the 78-ms sampling interval. The pulsed ASL technique was not spatially selective for a particular arterial supply and has the advantage of labeling a large volume of arterial blood water. However, there are 2 limitations of the current method. First, the single imaging slab has limited brain coverage, although 3-dimensional dynamic MRA sequences are being developed. Second, the nonselective labeling included venous blood water. The venous ASL signal was principally from the sagittal sinus and was used to normalize arterial amplitude values.

Chronic hyperperfusion and hemodynamic impairment are important factors in cerebrovascular diseases such as stroke and transient ischemic attack. The current study demonstrates that it is possible to characterize intracranial arterial hemodynamics along the length of an arterial segment in a time-efficient manner. Others have shown that significant hemodynamic effects exist in patients with carotid occlusive disease in their ipsilateral cerebral hemisphere.

We have recently reported hemispheric asymmetry in the arterial cerebral blood volume of patients with severe stenoses in their ipsilateral cerebral hemisphere. We acknowledge the Heart and Stroke Foundation of Canada (B.J.M.), the Medical Research Council (P.J.), the Dunhill Medical Trust (P.J., M.J.D.), and the German Ministry of Education and Research (M.G.).

Acknowledgments

We acknowledge the Heart and Stroke Foundation of Canada (B.J.M.), the Medical Research Council (P.J.), the Dunhill Medical Trust (P.J., M.J.D.), and the German Ministry of Education and Research (M.G.).

Source of Funding

This study was supported by the NIHR Oxford Biomedical Research Centre.

Disclosures

None.

References


Intracranial Hemodynamics Is Altered by Carotid Artery Disease and After Endarterectomy: A Dynamic Magnetic Resonance Angiography Study
Bradley J. MacIntosh, Ediri Sideso, Manus J. Donahue, Michael A. Chappell, Matthias Günther, Ashok Handa, James Kennedy and Peter Jezzard

_Science_ 2011;42:979-984; originally published online February 24, 2011;
doi: 10.1161/STROKEAHA.110.590786

_Stroke_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 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/42/4/979

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/02/28/STROKEAHA.110.590786.DC1
http://stroke.ahajournals.org/content/suppl/2012/02/28/STROKEAHA.110.590786.DC2

**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/
Abstract

颈内动脉疾病和内膜剥脱术后颅内血流动力学的改变
一项基于动态磁共振血管造影的研究

Intracranial Hemodynamics Is Altered by Carotid Artery Disease and After Endarterectomy
A Dynamic Magnetic Resonance Angiography Study

Bradley J. MacIntosh, PhD; Ediri Sideso, MBBS, MRCS; Manus J. Donahue, PhD; Michael A. Chappell, DPhil; Matthias Günther, PhD; Ashok Handa, FRCS; James Kennedy, MSc; Peter Jezzard, PhD

背景和目的：颈动脉内膜剥脱术 (Carotid endarterectomy，CEA) 已经成为治疗症状性颈内动脉疾病和减少脑部缺血性事件再复发风险的常规治疗方法。该研究的目的就是采用动态动脉自旋标记磁共振成像技术来描绘 CEA 前后颅内血流动力学特点。

方法：37 位颈内动脉疾病的患者参加了该研究，其中 24 位患者在 CEA 前后进行了核磁共振成像检查。17 名年龄跨度达到 50 岁的受试者作为对照组接受核磁共振成像检查，以评估与年龄相关的变化。血流动力学的测量（也就是相对达峰时间和振幅）由γ变量模型来计算。颈内动脉疾病引起的 Willis 环血流动力学变化应用线性回归分析。

结果：对照组相对达峰时间随年龄而增加 (P<0.020)。在校正年龄影响后，患者的相对达峰时间与血管狭窄程度的百分比阳性相关 (P<0.050)。CEA 术后第一天，CEA 同侧的大脑中动脉出现明显的动态磁共振血流成像变化：相对达峰时间减少 (P<0.017) 和血流振幅增加 (P<0.009)。对侧大脑中动脉或后循环血管在行 CEA 前后血流动力学无明显变化。

结论：这种无创的、基于动脉自旋标记方法而产生的时间分辨影像特征性的描绘了与年龄、颅外颈动脉疾病和 CEA 相关的颅内动脉血流特点。结果显示这种技术可以敏感的检测 CEA 前后血流动力学变化。

关键词：颈动脉内膜剥脱术，颈动脉狭窄，动脉自旋标记，血管造影术，动态，血流，老化

(Stroke. 2011;42:979-984. 傅松生 辛秀峰 译 徐安定 校)