Reduced Cerebrovascular Reserve at CO_2 BOLD MR Imaging Is Associated with Increased Risk of Periinterventional Ischemic Lesions during Carotid Endarterectomy or Stent Placement: Preliminary Results[1]

Sven Haller, MD, MSc
Leo H. Bonati, MD
Jochen Rick, MSc
Markus Klarhöfer, PhD
Oliver Speck, PhD
Philippe A. Lyrer, MD
Deniz Bilecen, MD, PhD
Stefan T. Engelter, MD
Stephan G. Wetzel, MD

Purpose: To determine whether any initial reductions in cardiovascular reserve (CVR) normalize after carotid revascularization and—because reduced CVR represents a risk factor for ischemic events—whether patients who develop periinterventional infarction have more severely reduced pretreatment CVR than those who do not.

Materials and Methods: Ethics committee approval and informed consent were obtained. Twenty-four consecutive patients with symptomatic high-grade internal carotid artery stenosis (seven women; mean age, 73.1 years ± 9.4 [standard deviation]) were recruited from a prospective, randomized trial that compared carotid artery stent placement with endarterectomy. Magnetic resonance (MR) imaging, including CO_2 blood oxygen level–dependent (BOLD) MR, was performed 1–3 days before, 1–3 days after, and 1 month after carotid revascularization (carotid artery stent placement, $n = 13$; carotid endarterectomy, $n = 11$).

Results: Mean CVR in the ipsilateral middle cerebral artery (MCA) territory was reduced prior to treatment (mean ΔT2* in ipsilateral territory, 1.92% ± 1.18; mean ΔT2* in contralateral territory, 2.28% ± 1.15 [$P < .05$]) and normalized after treatment (mean ΔT2* 1–3 days after treatment in ipsilateral territory, 2.66% ± 1.01; that in contralateral territory, 2.48% ± 1.27 [$P > .05$]; mean ΔT2* 1 month after treatment in ipsilateral territory, 2.27% ± 1.05; that in contralateral territory, 2.14% ± 0.96 [$P > .05$]). Those patients who developed new periinterventional infarcts ($n = 7$ with punctate foci of restricted diffusion) had greater reduction of CVR in the ipsilateral MCA territory prior to treatment (relative reduction, 32.5% ± 46.0; $P < .05$) than those who did not develop infarction ($n = 17$; relative reduction, 9.2% ± 55.9).

Conclusion: CO_2 BOLD MR imaging could be used successfully to monitor the hemodynamic effects of carotid revascularization; initial reductions in CVR normalized after carotid revascularization. Severely reduced pretreatment CVR was associated with increased occurrence of new periinterventional therapy infarction.

[1] From the Department of Diagnostic and Interventional Neuroradiology, Institute of Radiology (S.H., S.G.W.), Department of Diagnostic Radiology, Institute of Radiology (S.H., D.B.), Institute of Neurology (L.H.B., P.A.L., S.T.E.), and Division of Radiological Physics, Institute of Radiology (M.K.), University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland; Department of Diagnostic Radiology, Medical Physics, University Hospital Freiburg, Freiburg, Germany (J.R.); and Department of Biomedical Magnetic Resonance, Institute for Experimental Physics, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany (O.S.). Received September 18, 2007; revision requested January 4, 2008; revision received January 29; accepted April 11; final version accepted April 21. S.T.E., as principal investigator, supported by a grant from the Mach-Gaensslen-[Stiftung]-Foundation, a noncommercial fund. This foundation had no influence on design, analysis, or interpretation of the data. L.H.B. supported in part by a grant from the Swiss National Science Foundation (PBBSB-116873). S.G.W. supported in part by grants from the Swiss National Science Foundation (3200-066634 and 320000-113492). **Address correspondence to** S.H. (e-mail: *shaller@uhbs.ch*).

Severe stenosis of the internal carotid artery (ICA) reduces perfusion pressure in the dependent brain territory when collateral flow is insufficient. Autoregulatory vasodilatation occurs to maintain regional cerebral blood flow within normal limits. As a consequence, cerebrovascular reserve (CVR) may be reduced. CVR is regarded as a potentially important clinical parameter, as it has been shown, for example, that a decrease in CVR is an independent risk factor for ischemic events in patients with carotid stenosis and occlusion (1) and that CVR predicts recurrent stroke in patients awaiting endarterectomy (2).

CVR can be assessed noninvasively and operator independently with magnetic resonance (MR) imaging (3). In principle, the application of a vasoactive agent such as CO_2 (4) or acetazolamide (5) induces a blood oxygen level–dependent (BOLD) response (6) that can be detected on T2*-weighted images in particular. More recently, this CO_2 BOLD technique depicted impaired CVR in patients with severe ICA stenosis and occlusion (7). Note that not all patients with severe ICA stenosis necessarily have reduced CVR, because of possible collateral flow. We consider this an important point of the presented CO_2 BOLD approach because it enables direct assessment of the CVR of the brain tissue. In contrast, the "indirect" assessment of ICA stenosis grade does not take into account collateral flow.

In the present investigation, we evaluated whether this technique of CO_2 BOLD MR imaging enables monitoring of the hemodynamic effect of carotid revascularization. To achieve this end, three serial MR imaging investigations were performed: one before and two after the carotid revascularization procedure.

Our purpose was to determine whether any initial reductions in CVR normalize following carotid revascularization, and—as reduced CVR represents a risk factor for ischemic events—whether patients who develop periinterventional infarction have more severely reduced pretreatment CVRs than those who do not.

We hypothesized that reduced CVR in the territory of the middle cerebral artery (MCA) ipsilateral to the ICA stenosis prior to treatment (7) would normalize after carotid revascularization and that decreased CVR might represent a risk factor for ischemic events in patients with carotid stenosis and occlusion (1,8).

Advances in Knowledge

- It is possible to monitor the hemodynamic effects of carotid revascularization by using CO_2 blood oxygen level–dependent (BOLD) MR imaging.
- Severely reduced cerebrovascular reserve prior to treatment was associated with increased risk of periinterventional infarction during carotid revascularization procedures (stent placement, endarterectomy).

Materials and Methods

Patients

Patients were recruited from an ongoing international prospective randomized trial comparing carotid endarterectomy and carotid artery stent placement (9). The local ethics committee approved this MR imaging substudy, and all patients gave written informed consent prior to inclusion. Twenty-four of 27 consecutive patients from the local study center (University Hospital Basel, Basel, Switzerland) (seven women; mean age, 73.1 years ± 9.4 [standard deviation]) with unilateral or bilateral severe stenosis were included in this study between June 2005 and February 2007. All patients underwent ultrasonography (US) or MR angiography of the carotid arteries as part of their routine clinical care. Severe stenosis was defined as that greater than 70% according to North American Symptomatic Carotid Endarterectomy Trial criteria (10). Because there were no patients with discordant MR angiographic and Doppler US results during routine clinical care, additional digital subtraction angiography was not clinically required. One patient refused the follow-up investigation. Technical problems resulted in acquisition of incomplete data sets in two patients. Thirteen patients underwent carotid artery stent placement, and 11 patients underwent carotid endarterectomy.

Implications for Patient Care

- If the value of CO_2 BOLD MR imaging in predicting periprocedural infarction associated with carotid revascularization therapies could be confirmed in a larger cohort, it may be of value in the routine pretreatment assessment of such patients at risk for stroke.
- CO_2 BOLD MR imaging is safe, fast, and operator independent and could be conveniently added to routine MR imaging protocols for evaluation of patients at risk for stroke.

MR Imaging

MR imaging was performed 1–3 days before (preprocedure), 1–3 days after (postprocedure), and 1 month after (late postprocedure) carotid revascularization. We used a 1.5-T clinical whole-body MR imaging unit (Magnetom Avanto; Siemens, Erlangen, Germany).

Published online
10.1148/radiol.2491071644

Radiology 2008; 249:251–258

Abbreviations:
ACA = anterior cerebral artery
BOLD = blood oxygen level–dependent
CVR = cerebrovascular reserve
ICA = internal carotid artery
MCA = middle cerebral artery
PCA = posterior cerebral artery
VOI = volume of interest

Author contributions:
Guarantor of integrity of entire study, S.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, L.H.B., S.G.W.; clinical studies, S.H., L.H.B., M.K., P.A.L., S.T.E., S.G.W.; statistical analysis, S.H., J.R., M.K., O.S.; and manuscript editing, S.H., L.H.B., J.R., O.S., P.A.L., D.B., S.T.E., S.G.W.

Authors stated no financial relationship to disclose.

In addition to the CO_2 BOLD images, which are described in detail below, the following images were acquired at all time points and in all patients: diffusion-weighted images (single-shot spin-echo echo-planar imaging; b = 0, 500, and 1000 sec/mm^2) to assess apparent diffusion coefficients and acute ischemia (11), T2*-weighted gradient-echo images (flip angle, 20°; repetition time msec/echo time msec, 850/25) to assess intracerebral hemorrhage (12), T2-weighted turbo spin-echo images (4620/98), and fluid-attenuated inversion recovery images (8000/122; inversion time, 2500 msec). None of the patients had a large territorial infarct prior to the revascularization (on T2-weighted images). Twenty-two patients additionally underwent three-dimensional time-of-flight MR angiography of the circle of Willis (resulting voxel size, 0.4 × 0.9 × 1.0 mm^3) and three-dimensional contrast material–enhanced (gadobenate dimeglumine, MultiHance, Bracco) MR angiography of the neck with a neck coil (resulting voxel size, 0.6 × 1.3 × 1.6 mm^3) prior to revascularization.

All patients also underwent duplex US prior to revascularization to determine the degree of the ICA stenosis according to published duplex US velocity criteria (13). The assessment and definition of stenosis were performed in a manner equivalent to that described above. Findings regarding the degree of stenosis from US and MR imaging were averaged to yield the final degree of stenosis (Table).

CO_2 BOLD MR Imaging

CO_2 BOLD MR imaging was performed with the following parameters: single-shot multi–gradient echo echo-planar imaging, an axial orientation, 20 sections, a repetition time of 3000 msec, a flip angle of 90°, a matrix size of 64 × 64, a field of view of 220 × 220 mm, and a section thickness of 5 mm. Four images with effective echo times of 17, 44, 71, and 98 msec were read out after a single excitation for each section of an individual dynamic acquisition. In total, 100 dynamic acquisitions were obtained in 5 minutes. During measurements 21–60—that is, during 2 minutes—synthetic room air enriched with 7% CO_2 was administered through a simple nasal cannula. Compared with the use of tight face masks with bidirectional valves that segregate in- and outflow (7), our approach greatly increased patient comfort. Patients were instructed to breathe only through the nose during the CO_2 BOLD measurement. Patient comfort had a high priority, partly to improve compliance with follow-up examinations. A simple nasal cannula was successfully used in a previous investigation (14). Although we could not measure expiratory CO_2 concentration accurately, our method has been previously validated (7). Moreover, the expected T2* increase following CO_2 application further supported the appropriate application of CO_2.

CO_2 BOLD MR Image Postprocessing

The analysis of the CO_2 BOLD images has been described in detail previously (7). Analysis was performed with software (MATLAB, *www.mathworks.com*; and SPM5, *http://www.fil.ion.ucl.ac.uk/spm*). In essence, a model function based on a compartment model of CO_2 was fitted to the CO_2 BOLD time course to estimate the relative CO_2-induced increase in T2*. Preprocessing of the data included pixelwise T2* estimation by fitting the echo points to an exponential function and motion correction (implemented within the imaging unit reconstruction [15]) and spatial smoothing (Gauss kernel, 12-mm full width at half maximum). Because each patient was examined at three time points, unlike in the previous investigation (7), which used only a single measurement, we additionally normalized all individual brains into standard space (16) in SPM5. This additional normalization is of fundamental importance in comparing corresponding brain areas between time points and subjects and is a standard procedure in functional MR imaging analysis. Brain images of patients with symptomatic ICA stenosis on the right side were flipped. Consequently, the ipsilateral side was always in the "left" hemisphere. Two readers (S.H. and S.G.W.) in consensus defined volumes of interest (VOIs) in the Talairach standard space in the vascular territories of the anterior cerebral artery (ACA), the MCA, and the posterior cerebral artery (PCA) in agreement with a standard vascular territory atlas (17) ipsilateral and contralateral to the symptomatic side (for a total of six VOIs). Owing to the known variability in these vascular territories, we included only the centers of these vascular territories—that is, regions with known variation of vascular supply were excluded (17). Given the larger anatomic territory of the MCA compared with those of the ACA and PCA, the corresponding VOIs also had variable sizes (MCA, 15 876 mm^3; ACA, 4833 mm^3; PCA, 5238 mm^3). Because all individual images were normalized into standard space, the identical VOIs were applied to all patients.

Image Analysis

Stenosis grade was assessed independently by two readers (S.T.E. and S.G.W., who were blinded to patient identity and study group classification) according to the North American Symptomatic Carotid Endarterectomy Trial criteria (10). There was no discrepancy

Summary of Data in 24 Patients

Sex	Age (y)	Consensus Stenosis Grade in Ipsilateral ICA (%)	Consensus Stenosis Grade in Contralateral ICA (%)	No. of Patients with New Periinterventional Lesions at Diffusion-weighted Imaging
Female (n = 7)	73.9 ± 8.6	78.9 ± 10.4	2.6 ± 6.8	2
Male (n = 17)	72.8 ± 10.0	79.8 ± 7.5	17.9 ± 28.7	5

Note.—Data are means ± standard deviations.

in stenosis grade between the two reviewers that exceeded 10%. We report the average consensus stenosis grade of both reviewers. Diffusion-weighted images were assessed independently by two readers (S.H. and L.H.B., who were blinded to patient identity and study group classification). All lesions at diffusion-weighted imaging were obvious, and there was no discrepancy between the readers.

Statistical Analysis

Statistical analysis was performed with software (SAS; *www.sas.com*). The first part of the study (effect of carotid revascularization) was a within-subject repeated measure of the whole group, and we used two-tailed bootstrap *t* tests to make comparisons between corresponding VOIs in the same subject at the same time point—for example, we compared the preprocedure VOI in the ipsilateral MCA with the preprocedure VOI in the contralateral MCA. We did not make comparisons between different time points or between different VOIs. The second part of the study (new ischemic lesions) was a post-hoc subgroup comparison between patients with new periinterventional infarcts and patients without new infarcts. Given the smaller group size of this subgroup analysis, we used a nonparametric two-tailed Mann-Whitney *U* test. Owing to the relative nature of the data, we compared the relative within-subject difference in CVR—defined as (IPSI − CONTRA)/mean (IPSI + CONTRA), where IPSI is the ipsilateral value and CONTRA is the contralateral value—in this between-subjects subgroup analysis. Analogously, we compared the consensus ICA stenosis grade between patients with new periinterventional infarcts and patients without new infarcts by using a nonparametric two-tailed Mann-Whitney *U* test. $P < .05$ was considered to indicate a statistically significant difference.

We did not perform a subgroup analysis comparing carotid artery stent placement with endarterectomy because it was a condition of the randomized trial in which the patients were included that individual patient results should not be published.

Results

Stenosis Grade at Angiography

The mean ipsilateral stenosis grade was 79.5% ± 8.2 (standard deviation). The mean contralateral stenosis grade was 13.4% ± 25.2. Two patients had a fetal configuration of the PCA.

Diffusion-weighted Imaging

Seven patients had new periprocedural lesions at diffusion-weighted imaging (postprocedure vs preprocedure). The majority of these patients (five of seven) had multiple new punctate lesions that were typically located in the border zone areas. All lesions had restricted apparent diffusion coefficients and were demarcated on late postprocedure T2-weighted and fluid-attenuated inversion recovery images. Each patient had at least one such lesion, which we therefore denominated as infarcts. All lesions consisted of punctate foci. No large territorial new infarct was present.

Figure 1

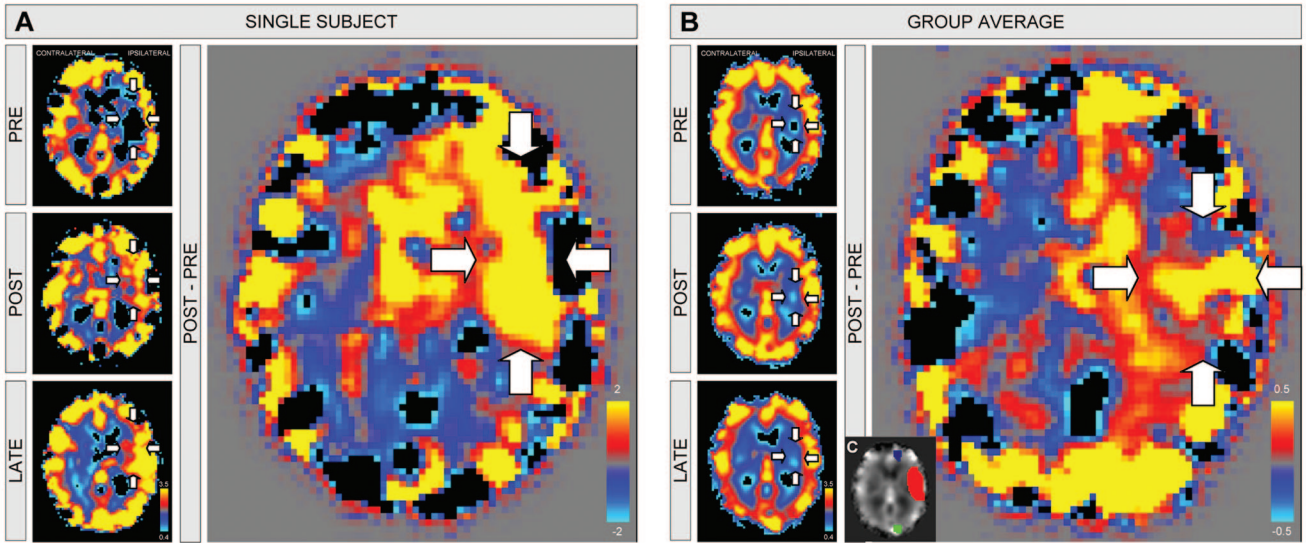

Figure 1: Example of, *A*, individual and, *B*, group average CO_2 BOLD MR imaging CVR maps after normalization into standard space 1–3 days before treatment *(PRE)*, 1–3 days after treatment *(POST)*, and 1 month after treatment *(LATE)*. The ipsilateral side of the ICA stenosis is always flipped to the "left" hemisphere. In the pretreatment images, the CVR is reduced in the MCA territory; this resolves after treatment. Note that the reduction in CVR is less evident in the group average map for two reasons: *(a)* not all patients with high-grade ICA stenosis necessarily have a reduced CVR because of variable collateral flow and *(b)* the exact location of the brain tissue with reduced CVR varies between patients and therefore blurs in the mean image. Arrows = region with increased CVR after treatment. Blue to yellow shades = CO_2-induced relative ΔT2* as a percentage. *C*, Small insert shows VOIs used on the corresponding axial section (blue = ACA VOI, red = MCA VOI, green = PCA VOI).

Figure 2

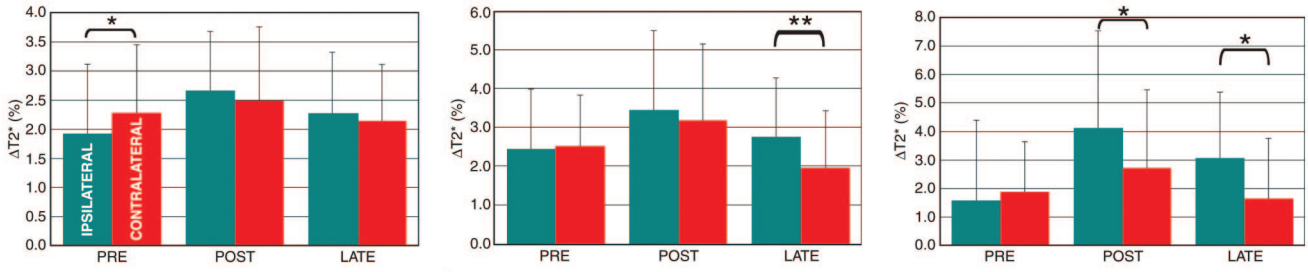

Figure 2: Bar graphs show CVR (ΔT2* at CO_2 BOLD MR imaging) in the territories of the **(a)** MCA, **(b)** ACA, and **(c)** PCA in 24 patients with high-grade stenosis of the ICA at three time points: 1–3 days before treatment *(PRE)*, 1–3 days after treatment *(POST)*, and 1 month after treatment *(LATE)*. Prior to treatment, CVR is reduced in the ipsilateral MCA; this resolves after treatment. CVR is normal prior to treatment in the ACA and PCA. Teal bars = ipsilateral side to high-grade ICA stenosis, red bars = contralateral side. ∗ = $P < .05$, ∗∗ = $P < .01$. Error bars indicate standard deviations.

CO_2 BOLD Perfusion Reserve Map

Examples of an individual CO_2 BOLD perfusion map and the group average CO_2 BOLD perfusion map are given in Figure 1. In correlation with the high-grade ICA stenosis, the mean CO_2 BOLD signal in the ipsilateral MCA territory was reduced preprocedure and normalized at follow-up. Direct comparison of postprocedure versus preprocedure images revealed brain tissue with increased perfusion reserve, predominantly in the MCA territory. Of the 24 patients, nine had no relevant preprocedure reduction in CVR in the ipsilateral MCA territory, defined as relative ipsilateral reduction at CO_2 BOLD of less than 3.0%.

Effect of Carotid Revascularization

Averaged across all patients (Fig 2), ΔT2* in the ipsilateral MCA region was reduced prior to treatment versus that in the contralateral MCA territory (mean ΔT2* in ipsilateral region, 1.92% ± 1.18; mean ΔT2* in contralateral region, 2.28% ± 1.15 [$P < .05$]). After revascularization, there was no significant difference between the hemispheres in the MCA territory (postprocedure ΔT2* in ipsilateral territory, 2.66% ± 1.01; postprocedure ΔT2* in contralateral territory, 2.48% ± 1.27 [$P > .05$] and late postprocedure ΔT2* in ipsilateral territory, 2.27% ± 1.05; late postprocedure ΔT2* in contralateral territory, 2.14% ± 0.96 [$P > .05$]). In the ACA and PCA territories, there was no significant interhemispheric difference prior to treatment, only a nonsignificant trend toward reduced CVR in the ipsilateral ACA (ΔT2* in ipsilateral ACA, 2.42% ± 1.55; ΔT2* in contralateral ACA, 2.50% ± 1.32 [$P > .05$]). After treatment, ipsilateral ΔT2* was increased in the ACA (late postprocedure ΔT2* in ipsilateral ACA, 2.75% ± 1.51; late postprocedure ΔT2* in contralateral ACA, 1.94% ± 1.46 [$P < .01$]) and PCA (postprocedure ΔT2* in ipsilateral PCA, 4.11% ± 3.40; postprocedure ΔT2* in contralateral PCA, 2.70% ± 2.75 [$P < .05$] and late postprocedure ΔT2* in ipsilateral PCA, 3.07% ± 2.30; late postprocedure ΔT2* in contralateral PCA, 1.64% ± 2.10 [$P < .05$]).

New Periprocedural Infarcts

Seven patients had new periinterventional ipsilateral punctate foci at diffusion-weighted imaging (postprocedure vs preprocedure, Table). Post hoc, we compared patients with new periinterventional lesions in the ipsilateral MCA territory at diffusion-weighted imaging ($n = 7$) with the remaining patients without new lesions ($n = 17$, Fig 3). Patients with new infarcts had significantly reduced ($P < .05$) ΔT2* in the ipsilateral MCA territory (preprocedure)—by 32.5% ± 46.0 relative to the contralateral side—compared with patients without new lesions (reduction in ΔT2*, 9.2% ± 55.9). There was no significant difference in the grade of ipsilateral ICA stenosis between patients with and those without new infarcts.

Figure 3

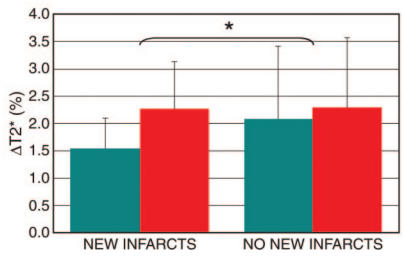

Figure 3: Bar graph shows significantly reduced ipsilateral CVR (ΔT2*) in MCA territory in patients who developed new periinterventional infarcts ($n = 7$) as compared with that in patients without new periinterventional infarcts ($n = 17$). Teal bars = ipsilateral side, red bars = contralateral side. ∗ = $P < .05$. Error bars indicate standard deviations.

Discussion

We assessed CO_2 BOLD MR imaging in the evaluation of changes in CVR before and after carotid revascularization (carotid artery stent placement and endarterectomy) in patients with symptomatic high-grade ICA stenosis. The results of this pilot study demonstrate that the fast, safe, and operator-independent CO_2 BOLD method could be used to successfully monitor the hemodynamic effects of carotid revascularization. Initial reductions in

CVR normalized after carotid revascularization.

Effect of Carotid Revascularization

The mean CVR was reduced in the MCA territory ipsilateral to the side of the high-grade stenosis prior to revascularization, in accordance with the results of a previous investigation (7). As expected, we observed that this reduction in ipsilateral MCA CVR resolved after carotid revascularization. Note that a high-grade stenosis of the ICA does not necessarily imply a reduced CVR, given the potential collateral flow via the circle of Willis (nine of 24 patients in our series). This collateral circuit is variable between subjects. This, we reason, is the particular strength of the CO_2 BOLD technique, which can directly identify the brain tissue with exhausted CVR and, consequently, those patients with insufficient collateral flow. The "indirect" assessment of the ICA stenosis grade, in distinction, does not take into account collateral flow and its potential for augmentation during periods of cerebrovascular stress such as breath holds.

In the majority of previous studies that assessed hemodynamic changes after carotid endarterectomy or carotid artery stent placement with different techniques, at least a trend toward restoration of the CVR was observed. For example, the principle of CO_2-induced vasodilatation for assessment of perfusion reserve has been applied in US for many years (18–22). It is beyond the scope of this article to discuss the (in detail partly inconsistent) findings of these studies. Future studies are needed that directly compare the presented CO_2 BOLD technique with the clinically more established Doppler CO_2 testing (18–21). Moreover, it would be of interest to compare the CO_2 BOLD technique with first-pass gadolinium-enhanced perfusion-weighted MR imaging, which has overall been found to be sensitive in depicting changes after carotid revascularization (23–26). The direct comparison of CO_2 BOLD and perfusion-weighted imaging might be of particular interest because both techniques provide complimentary information. Perfusion-weighted imaging helps estimate cerebral perfusion, while CO_2 BOLD MR imaging helps estimate CVR or cerebral perfusion reserve. Some patients might still have normal perfusion (at perfusion-weighted imaging) yet reduced perfusion reserve (at CO_2 BOLD MR imaging), which may represent a specific preinterventional risk profile.

As additional findings, we observed only a nonsignificant trend toward reduced CVR in the ipsilateral ACA territory at the initial examination, in contrast to the significant reduction of CVR in the ipsilateral MCA territory, although both territories derive blood from the ICA. We assume that this difference can be attributed to the direct anatomic connection between the ACAs of both hemispheres via the anterior communicating artery, as compared with the MCAs. There was no reduction in CVR in the PCA prior to revascularization. After revascularization, CVR in the ipsilateral ACA and, in particular, the PCA was increased. This might be explained by upregulated collateral flow from the ACA and PCA in chronic ICA stenosis via the circle of Willis (27). After revascularization, the collateral flow is no longer required. Consequently, the perfusion reserve is increased in the ipsilateral ACA and PCA.

New Periprocedural Infarcts

Patients with new periinterventional lesions had a significantly reduced CVR in the ipsilateral MCA at the preinterventional examination compared with patients without new lesions. This observation is compatible with the concept that, owing to a variable degree of collateral flow, a high-grade ICA stenosis per se does not necessarily reduce CVR in the ipsilateral MCA. These findings suggest that insufficient collateral flow increases the risk of new periprocedural infarcts.

Note that there was no significant difference in ipsilateral ICA stenosis grade between both patient groups—that is, CO_2 BOLD MR imaging helped discriminate between patients with and those without new periinterventional infarcts, yet the stenosis grade did not. A possible explanation for this apparently high sensitivity of CO_2 BOLD MR imaging is that this method can be used to directly assess the parenchymal CVR, taking into account collateral flow. Assessment of the ICA stenosis grade, in contrast, provides no information with respect to parenchymal perfusion or possible collateral flow.

Most patients with new ischemic lesions after the intervention had multiple microinfarcts, suggestive of an embolic pathogenesis (28). It has been hypothesized that in situations of low brain perfusion, emboli are less likely to be washed out of the vascular bed (29), although this topic is controversial, and the suggested washout hypothesis represents only one possible mechanism for infarction in the setting of reduced CVR.

If our results can be confirmed in a larger study, CO_2 BOLD MR imaging might become important for preinterventional risk assessment. Of course, these results are limited by the small sample size of only 24 patients and require confirmation in a larger study sample. On the other hand, the significant results despite the small sample size imply a high sensitivity of CO_2 BOLD MR imaging, which is a fundamental prerequisite with respect to a potential individual preinterventional risk assessment.

As we present MR imaging substudy data from an ongoing and prospective randomized trial, we cannot at this stage present results of the direct comparison between carotid artery stent placement and endarterectomy or provide details regarding which patients developed new infarcts.

There were limitations to our study. At present, we report only relative CO_2 BOLD CVR. The relationship between CO_2-induced vasodilatation and T2* increase is nonlinear. Consequently, we have only made comparisons between corresponding anatomic regions in the ipsilateral and

contralateral hemispheres within subjects at one time point. We did not make direct comparisons between regions or between time points. This relative nature of the data is the origin of the rather large standard deviations in Figures 2 and 3. The apparent disadvantage of this approach is that if patients have bilaterally yet symmetrically reduced CVR, there is no within-subject interhemispheric difference. However, in principle, it is possible to calculate the absolute CVR with CO_2 BOLD MR imaging. The formal validation of this absolute CVR estimation is not currently available, but should be soon. This will substantially strengthen the CO_2 BOLD MR imaging method, as it will be possible to directly quantify the absolute CVR, which will improve a potential individual preinterventional risk assessment, as well as comparison between subjects and between time points to better monitor the hemodynamic effect of carotid revascularization.

All individual brains were normalized into standard space (16) to align corresponding brain regions. This standard procedure in functional MR imaging (30) is the basis for the group analysis but does not compensate for individual variations in vascular territories (17). We consequently chose VOIs in the center of the well-known vascular territories only—that is, regions with variable vascular supply were excluded. We used the same VOIs for all patients. An alternative approach is to use individual VOIs. We did not use the latter approach because there are no objective criteria for how to define individual VOIs. Furthermore, individual VOIs of different sizes affect the signal-to-noise ratio because of different numbers of voxels within a VOI. Different locations of VOIs are problematic, given the regional difference in the neurovascular coupling (31–33). Owing to these regional differences in the neurovascular coupling (31–33), we compared only corresponding anatomic regions between both hemispheres. Given this putative systematic confound, a direct comparison of different regions (eg, ACA territory vs MCA territory) was not performed. Owing to the small number of patients ($n = 2$) who had a fetal configuration of the ipsilateral PCA (in which the PCA is supplied via the ICA), we did not specifically analyze this subgroup.

Conclusions

Severely reduced CVR prior to treatment was associated with increased risk of periinterventional infarction during carotid revascularization procedures (stent placement, endarterectomy) and might eventually contribute to preinterventional risk assessment.

Acknowledgments: We thank all patients for participation in the study. We thank Tanja Haas-Grabowski for her help regarding data analysis and Christian Schindler, PhD, for his help regarding the statistical analysis.

References

1. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001;124(3):457–467.
2. Blaser T, Hofmann K, Buerger T, Effenberger O, Wallesch CW, Goertler M. Risk of stroke, transient ischemic attack, and vessel occlusion before endarterectomy in patients with symptomatic severe carotid stenosis. Stroke 2002;33(4):1057–1062.
3. Lythgoe DJ, Williams SC, Cullinane M, Markus HS. Mapping of cerebrovascular reactivity using BOLD magnetic resonance imaging. Magn Reson Imaging 1999;17(4):495–502.
4. Rostrup E, Larsson HB, Toft PB, et al. Functional MRI of CO2 induced increase in cerebral perfusion. NMR Biomed 1994;7(1:–2):29–34.
5. Bruhn H, Kleinschmidt A, Boecker H, Merboldt KD, Hanicke W, Frahm J. The effect of acetazolamide on regional cerebral blood oxygenation at rest and under stimulation as assessed by MRI. J Cereb Blood Flow Metab 1994;14(5):742–748.
6. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 1990;87(24):9868–9872.
7. Ziyeh S, Rick J, Reinhard M, Hetzel A, Mader I, Speck O. Blood oxygen level-dependent MRI of cerebral CO2 reactivity in severe carotid stenosis and occlusion. Stroke 2005;36(4):751–756.
8. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000;283(16):2122–2127.
9. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004;18(1):69–74.
10. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325(7):445–453.
11. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. Neurology 1992;42(9):1717–1723.
12. Fiebach JB, Schellinger PD, Gass A, et al. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. Stroke 2004;35(2):502–506.
13. McCabe DJ, Pereira AC, Clifton A, Bland JM, Brown MM. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). Stroke 2005;36(2):281–286.
14. Haller S, Wetzel SG, Radue EW, Bilecen D. Mapping continuous neuronal activation without an ON-OFF paradigm: initial results of BOLD ceiling fMRI. Eur J Neurosci 2006;24(9):2672–2678.
15. Speck O, Hennig J. Motion correction of parametric fMRI data from multi-slice single-shot multi-echo acquisitions. Magn Reson Med 2001;46(5):1023–1027.
16. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York, NY: Thieme, 1988;
17. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of the human brain. Cambridge, England: Cambridge University Press, 2001.
18. Hartl WH, Janssen I, Furst H. Effect of carotid endarterectomy on patterns of cerebrovascular reactivity in patients with unilateral carotid artery stenosis. Stroke 1994;25(10):1952–1957.
19. Visser GH, van Huffelen AC, Wieneke GH, Eikelboom BC. Bilateral increase in CO2 reactivity after unilateral carotid endarterectomy. Stroke 1997;28(5):899–905.
20. D'Angelo V, Catapano G, Bozzini V, et al. Cerebrovascular reactivity before and after

carotid endarterectomy. Surg Neurol 1999; 51(3):321–326.

21. Marshall RS, Rundek T, Sproule DM, Fitzsimmons BF, Schwartz S, Lazar RM. Monitoring of cerebral vasodilatory capacity with transcranial Doppler carbon dioxide inhalation in patients with severe carotid artery disease. Stroke 2003;34(4): 945–949.

22. Reinhard M, Roth M, Muller T, et al. Effect of carotid endarterectomy or stenting on impairment of dynamic cerebral autoregulation. Stroke 2004;35(6):1381–1387.

23. Gillard JH, Hardingham CR, Kirkpatrick PJ, Antoun NM, Freer CE, Griffiths PD. Evaluation of carotid endarterectomy with sequential MR perfusion imaging: a preliminary report. AJNR Am J Neuroradiol 1998;19(9): 1747–1752.

24. Wilkinson ID, Griffiths PD, Hoggard N, et al. Short-term changes in cerebral microhemodynamics after carotid stenting. AJNR Am J Neuroradiol 2003;24(8):1501–1507.

25. Ko NU, Achrol AS, Martin AJ, et al. Magnetic resonance perfusion tracks 133Xe cerebral blood flow changes after carotid stenting. Stroke 2005;36(3):676–678.

26. Fukuda T, Ogasawara K, Kobayashi M, et al. Prediction of cerebral hyperperfusion after carotid endarterectomy using cerebral blood volume measured by perfusion-weighted MR imaging compared with single-photon emission CT. AJNR Am J Neuroradiol 2007;28(4):737–742.

27. van Everdingen KJ, Visser GH, Klijn CJ, Kappelle LJ, van der Grond J. Role of collateral flow on cerebral hemodynamics in patients with unilateral internal carotid artery occlusion. Ann Neurol 1998;44(2):167–176.

28. Baird AE, Lovblad KO, Schlaug G, Edelman RR, Warach S. Multiple acute stroke syndrome: marker of embolic disease? Neurology 2000; 54(3):674–678.

29. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol 1998;55(11):1475–1482.

30. Amaro E Jr, Barker GJ. Study design in fMRI: basic principles. Brain Cogn 2006; 60(3):220–232.

31. Aguirre GK, Zarahn E, D'Esposito M. The variability of human, BOLD hemodynamic responses. Neuroimage 1998;8(4):360–369.

32. Huettel SA, McCarthy G. Regional differences in the refractory period of the hemodynamic response: an event-related fMRI study. Neuroimage 2001;14(5):967–976.

33. Saad ZS, Ropella KM, Cox RW, DeYoe EA. Analysis and use of FMRI response delays. Hum Brain Mapp 2001;13(2):74–93.