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# Vasodilatory Response of Border Zones to Acetazolamide Before and After Endarterectomy

## An Echo Planar Imaging–Dynamic Susceptibility Contrast-Enhanced MRI Study in Patients With High-Grade Unilateral Internal Carotid Artery Stenosis

Marlène Wiart, MSc; Yves Berthezène, MD, PhD; Patrice Adeleine, PhD; Patrick Feugier, MD; Paul Trouillas, MD, PhD; Jean-Claude Froment, MD; Norbert Nighoghossian, MD, PhD

**Background and Purpose**—The importance of hemodynamic changes related to a high-grade internal carotid artery (ICA) stenosis remains a matter of controversy. Areas between the vascular territories of major cerebral arteries, namely, the border zones, may be selectively vulnerable to hemodynamic alteration. The aim of this study was to search for any hemodynamic impact of carotid endarterectomy (CEA) on vasodilatory response, in particular, within the border zones, by means of multislice dynamic susceptibility contrast MRI.

**Methods**—Thirteen patients with a high-grade unilateral ICA stenosis (>80%) were examined. Relative regional cerebral blood volume (rCBV) was determined separately for white matter, gray matter, and anterior and posterior border zones by the acetazolamide test. A vasomotor reactivity index was evaluated from the rCBV values. Values from the ipsilateral hemisphere were compared with contralateral ones, before and after CEA.

**Results**—Before CEA, rCBV values in the anterior border zones were significantly ( $P<0.05$ ) higher in the ipsilateral hemisphere than in the contralateral hemisphere. A decrease in vasomotor reactivity indexes was also observed in the lesion side, but the difference from the contralateral side was not statistically significant. In posterior border zones, no differences in rCBV or vasomotor reactivity were found between the ipsilateral and the contralateral hemispheres. After CEA, the rCBV asymmetry in the anterior border zones cleared.

**Conclusions**—High-grade ICA stenosis with efficient primary collateral pathways may have an early limited hemodynamic impact within border-zone areas. The favorable course of these abnormalities after surgery suggests an additional benefit of CEA at this stage. (*Stroke*. 2000;31:1561-1565.)

**Key Words:** acetazolamide ■ border zone ■ carotid endarterectomy ■ carotid stenosis ■ magnetic resonance imaging

Carotid stenosis can produce neurological symptoms by promoting thromboembolic stroke or, less often, by critically lowering the perfusion pressure distal to the lesion. An improvement of hemodynamic parameters after carotid endarterectomy (CEA) could be expected in a small proportion of patients with internal carotid artery (ICA) stenosis who had an impaired cerebrovascular reserve.<sup>1-4</sup> The acetazolamide (ACZ) test is a reliable predictor of critically reduced cerebral perfusion pressure and may unmask perfusion reserve deficits even in patients with normal baseline regional cerebral blood flow.<sup>5,6</sup> Although the importance of hemodynamic factors is a matter of controversy, recent data suggest that impaired cerebral vasomotor reactivity (VMR) may precipitate ischemic stroke in patients with an asymptomatic ICA stenosis.<sup>7-9</sup> A severe unilateral ICA stenosis may also be associated with a border-zone ischemia,

including a low rate of regional blood flow associated with an increased regional cerebral blood volume (rCBV).<sup>10</sup> However, data concerning the hemodynamic benefit of CEA are conflicting in the short-term and long-term periods.<sup>11</sup> These discrepancies can be explained in part by the use of different measurement methods and different timing after CEA.

Dynamic susceptibility contrast-enhanced MRI (DSC-MRI) might be a promising tool to image and assess perfusion.<sup>12-15</sup> The advance of the paramagnetic contrast agent in the capillary bed induces a transient loss of magnetic resonance signal intensity.<sup>16</sup> By use of a fast image sequence, such as echo planar imaging (EPI), it is possible to track the first pass of the bolus through the brain on a dynamic series of images. Baseline hemispheric hemodynamic effects of CEA with EPI-DSC-MRI have been recently investigated,<sup>11</sup> but changes of VMR within

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From CREATIS (M.W., Y.B., J.-C.F., N.N.), CNRS Research Unit (UMR 5515), affiliated with INSERM, Lyon, France; Laboratoire d'Informatique Médicale (P.A.), UFR Laënnec, Lyon, France; the Vascular Surgery Department (P.F.), Hôpital Ed. Herriot, Lyon, France; and the Cerebrovascular Disease and Ataxia Research Center (P.T., N.N.), Department of Neurology, Lyon, France.

Correspondence to Marlène Wiart, MSc, Hôpital Neurologique-Cardiologique, Service de Radiologie, CREATIS UMR-5515, B.P. Lyon Montchat, 69394 Lyon Cedex 03, France. E-mail marlene.wiart@creatis.univ-lyon1.fr

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border-zone areas have not been assessed by this method, to our knowledge, in patients who had a unilateral high-grade ICA stenosis. Accordingly, we have used EPI-DSC-MRI (1) to detect any hemodynamic compromise in patients who had a severe ICA stenosis mainly within vascular areas vulnerable to hypoperfusion and (2) to search for any hemodynamic impact of CEA on vasodilatory response by use of the ACZ test.

## Subjects and Methods

### Patients

Between March 1998 and April 1999, 13 patients (11 men and 2 women, aged 47 to 76 [mean  $64 \pm 10$ ] years) who had only a severe degree of carotid artery stenosis ( $>80\%$  according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria)<sup>17</sup> and 5 control subjects (3 women and 2 men, aged 40 to 68 [mean  $57 \pm 11$ ] years) were prospectively included. Symptomatic carotid artery disease ( $n=8$ ) was diagnosed after transient ischemic attack (TIA) and minor stroke that occurred at least 5 weeks before the study. Asymptomatic ICA stenosis ( $n=5$ ) was detected during routine evaluation in vascular high-risk patients. The quantification of the stenosis was assessed with color-flow Doppler imaging sonography and intra-arterial digital subtraction angiography. The arterial supply to the middle cerebral artery (MCA) territory ipsilateral to the ICA stenosis was determined from the arteriograms and classified as carotid (antegrade via the ipsilateral ICA), Willis (at least via the anterior circle from the opposite carotid circulation), ophthalmic (via the ipsilateral ophthalmic artery from the external carotid artery), or meningeal (via anastomotic channels across the surface of the brain from the anterior cerebral arterial circulation). All patients had a preoperative cranial CT and T2-weighted MRI. Patients who had a significant border-zone or territorial ischemia revealed by T2-weighted MRI were excluded, as were those who had symptoms from the contralateral hemisphere or the brain stem. No patient had conditions that suggested a hemodynamic mechanism, such as hypotension, positional changes, or exertion. Systemic blood pressure was daily recorded in all patients before and after CEA. Routine blood tests, including assessment of hematocrit, were performed before and after CEA in all patients and before MRI studies in control subjects. The EPI-DSC-MRI protocol was realized only in patients who were to undergo CEA, and it was performed without undue delay in the treatment of patients who had a symptomatic ICA lesion. Patients underwent EPI-DSC-MRI before CEA ( $5 \pm 9$  days) and after CEA ( $20 \pm 11$  days). Color-flow Doppler imaging sonography was performed before MRI studies in control subjects and also after CEA in patients. Informed consent was obtained from all subjects before inclusion. The local Human Research Committee approved the study protocols.

### Magnetic Resonance Imaging

MRI and perfusion studies were performed on a 1.5-T Siemens resonance magnetic scanner.

#### IR and T2-Weighted Turbo Spin-Echo MRI Protocols

Inversion recovery (IR) and T2-weighted images were obtained for 10 axial slices. IR imaging parameters were as follows: echo time (TE), repetition time (TR), and inversion time (TI), 60, 7000, and 400 ms, respectively; flip angle,  $30^\circ$ ; slice thickness, 5 mm; field of view,  $240 \times 240$  mm; and matrix,  $256 \times 256$ . T2-weighted turbo spin-echo imaging parameters were as follows: TE and TR, 98 and 3000 ms, respectively; slice thickness, 5 mm; field of view,  $188 \times 250$  mm; and matrix,  $200 \times 512$ .

#### EPI Protocol

A multislice gradient echo sequence with EPI was used to acquire the dynamic series. Identical slice positioning and thickness as for the IR sequence were used. TE and TR were 54 and 800 ms, respectively. Ninety perfusion images were acquired per slice (a total of 900 images for the 10 slices). Time resolution for a given slice was 1 second. Five seconds after the start of acquisition, a bolus of gadopentetate dimeglu-

mine (0.1 mmol/kg) was administered. In patients, after acquisition of a perfusion series at rest, 1 g ACZ was intravenously injected, followed 15 minutes later by the acquisition of another perfusion series.

### Image Analysis

Each image of the series was first smoothed by use of a spatial filter with a  $3 \times 3$  window. Signal intensity changes after contrast injection were converted into transverse relaxation rate changes,  $\Delta R_2(k)$ , by using the following formula:  $\Delta R_2(k) = -(1/TE) \ln[S(k)/S_0]$ , where TE is the time of echo of the sequence,  $S(k)$  is the magnetic resonance signal intensity on the  $k$ th image of the series, and  $S_0$  is the precontrast magnetic resonance signal intensity. The resulting data were then fitted by using a gamma-variate function,  $\Gamma(t)$ , by nonlinear least-squares minimization with the help of the Levenberg-Marquardt algorithm. Relative rCBV (rrCBV) was determined by analytically integrating the fitted curve according to the following:

$$\text{rrCBV} = \int_0^{\infty} \Gamma(t) dt$$

Regions of interest (ROIs) were chosen in ICA territories of both hemispheres for white matter and gray matter, on the relevant slices of the 10 acquired slices. White matter ROIs were chosen within the centrum semiovale. IR images were displayed beside the perfusion images to provide the operator with a reference. Anterior border zones were located in the upper midfrontal region, which anatomically corresponds to the site of anastomotic pial vessels between the anterior internal branches of the anterior cerebral artery and the prefrontal branches of the MCA. Posterior border zones were located between the parieto-occipital and temporo-occipital areas and anatomically correspond to the zone of pial anastomosis between the angular or posterior temporal branches of the MCA and the parieto-occipital branch of the posterior cerebral artery (Figure).<sup>18</sup> An ROI was also drawn for the total cerebellum.

rrCBV was evaluated at rest, rrCBV(rest), and after the ACZ test, rrCBV(ACZ), before and after CEA. For each hemisphere, rrCBV data were averaged over the ROIs separately for white matter, gray matter, anterior border zones, and posterior border zones. Resulting values were divided by the corresponding parameter from the cerebellum to allow intrapatient and interpatient comparison.

Vasodilatory response was calculated by means of a VMR index:

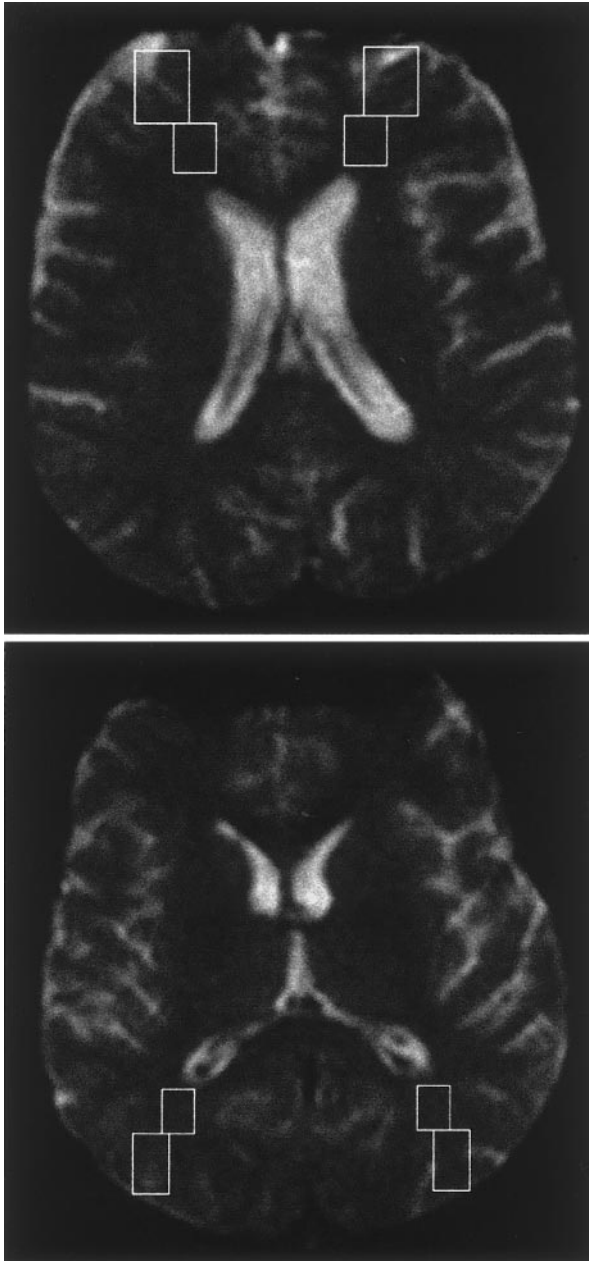
$$\% \text{VMR} = \frac{\text{rrCBV(ACZ)} - \text{rrCBV(rest)}}{\text{rrCBV(rest)}} \times 100$$

### Statistical Analysis

The analysis of data was performed by using paired  $t$  tests. The rrCBV and VMR data from the ipsilateral hemisphere were respectively compared with data from the contralateral hemisphere separately for white matter, gray matter, anterior border zones, and posterior border zones. All results are presented as mean  $\pm$  SD. A value of  $P < 0.05$  was considered statistically significant.

## Results

CEA was successfully carried out in 12 patients in whom color-flow Doppler imaging studies performed after surgery ruled out any residual stenosis or occlusion. One patient experienced a severe hemispheric stroke after CEA related to an early ICA occlusion, whereas 2 patients refused the MRI protocol after CEA; therefore, 10 patients underwent the whole protocol. Four patients had high-grade asymptomatic carotid artery stenosis, and 6 patients had symptomatic ICA stenosis revealed either by TIA ( $n=4$ ) or by minor stroke ( $n=2$ ) with mild ipsilateral ischemic changes within the MCA territory assessed by T2-weighted MRI. A collateral flow of the circle of Willis could be



Anterior border-zone (top) and posterior border-zone (bottom) ROIs, positioned on native perfusion images.

assessed in 10 patients. Of these, 9 had primary collateral flow via the anterior communicating artery. Only 3 patients showed a reverse flow from the ophthalmic artery, whereas 8 patients had collateral pathways through leptomeningeal vessels. Systemic blood pressure as well as hematocrit levels before and after CEA remained unchanged.

### Control Subjects

No difference was found between the left and right hemispheres in control subjects at rest. Therefore, parameters of both hemispheres were pooled (Table).

### Patients

Before CEA, a significant difference ( $P < 0.05$ ) in rCBV was found in the anterior border zones between the ipsilateral and

contralateral sides (Table). Also, VMR indexes were lower in the lesion side than in the contralateral side in the anterior border zones. However, the difference in VMR indexes between the 2 hemispheres was not statistically significant. No other asymmetry in hemodynamic parameters was found before CEA, including VMR indexes, either in posterior border zones or in white or gray matter. After CEA, rCBV asymmetry detected within the anterior border-zone areas cleared. Also, rCBV and VMR were not significantly different in white matter or gray matter or in the posterior border zones from one side to another after CEA.

### Discussion

In patients with carotid stenosis, cerebral ischemia is mainly precipitated by thromboembolic mechanisms. An additional impairment of cerebrovascular reserve may also increase vulnerability to ischemia, especially within border-zone areas. The hemodynamic effect of CEA varies and depends on the preexisting hemodynamic status. CEA may improve cerebral hemodynamics ipsilateral to ICA stenosis only in patients with a significant preoperative side-to-side asymmetry consistent with an inadequate collateralization.<sup>4,19</sup>

Several methods have been used for assessing the hemodynamic impact of CEA,<sup>1-4</sup> but less is known about the ability of EPI-DSC-MRI in this field. The main advantages of this method over existing ones, such as xenon-enhanced CT, single-photo emission CT, or positron emission tomography, are the better spatial resolution, the lower cost, the availability (in case of positron emission tomography), the absence of radiation, and the fact that gadopentetate dimeglumine does not induce any vasomotor changes. Also, because of the multislice acquisition, this technique allows for the investigation of several parts of the brain at once.

Recently, Kluytmans et al<sup>11</sup> used EPI-DSC-MRI to study hemodynamic parameters (rCBV, mean transit time, time of arrival, and time to peak) in white matter and in gray matter, showing that most patients with unilateral carotid artery stenosis did not respond significantly to CEA because they were not hemodynamically impaired before CEA. Our data (rCBV) in white matter and in gray matter confirmed these results. However, border-zone areas may be selectively vulnerable to hemodynamic alteration.<sup>20,21</sup> We found that rCBV was significantly higher in patients on the lesion side within the anterior border-zone areas. No asymmetries were observed in these areas in control subjects. A rise in rCBV is thought to reflect compensatory vasodilatation according to cerebral autoregulation when cerebral perfusion pressure drops.<sup>22</sup>

Conversely, we did not find any differences in rCBV between the 2 sides in posterior border zones. A positron emission tomography study<sup>10</sup> basically devoted to the hemodynamic impact of high-grade ICA stenosis in border zones also indicated hemodynamic alterations only in anterior border zones, whereas posterior border-zone regions showed values in the normal range. Posterior border zones anatomically correspond to the zone of pial anastomosis between the angular or posterior temporal branches of the MCA and the parieto-occipital branch of the PCA.<sup>18</sup> As a result, an efficient collaterality from the vertebrobasilar circulation might explain the



## Normalized rCBV and VMR Index for Control Subjects and Patients

	Control Subjects (n=5)	Patients (n=10)			
		Before CEA		After CEA	
		Side of CEA	Contralateral Side	Side of CEA	Contralateral Side
Anterior border-zone area					
rrCBV	0.84±0.19	1.02±0.24*	0.89±0.21*	1.02±0.28	1.01±0.29
%VMR	...	36.3±39.1	56.5±76.8	25.3±37.3	34.1±39.7
Posterior border-zone area					
rrCBV	0.92±0.14	0.97±0.26	1.00±0.31	1.04±0.30	1.07±0.26
%VMR	...	44.1±46.0	48.2±39.7	34.8±51.5	41.6±53.8
White matter					
rrCBV	0.60±0.14	0.60±0.16	0.61±0.21	0.65±0.33	0.72±0.30
%VMR	...	43.8±41.3	64.3±59.3	67.7±46.5	55.3±88.2
Gray matter					
rrCBV	0.93±0.26	0.91±0.40	0.81±0.19	0.92±0.33	1.12±0.37
%VMR	...	57.4±40.0	65.3±47.5	68.2±64.4	53.1±52.1

Values are mean±SD.

\* $P<0.05$  vs contralateral side.

finding that posterior border-zone hemodynamic parameters are less probably affected by hemodynamic impairment.

The global hemispheric hemodynamic impact of ICA stenosis is modest because an effective collaterality prevents a decrease in cerebral perfusion pressure. Kluytmans et al<sup>23</sup> have described different cerebral hemodynamic impairments in relation to patterns of collateral flow. Collateral flow via the anterior communicating artery is a sign of well-preserved hemodynamic status over the whole hemisphere. One could remark that most of our patients had an efficient collaterality through the anterior communicating artery and that only a few patients had a reverse flow through the ophthalmic artery. Hemodynamic parameters are usually more severely impaired in patients with reverse flow in the ophthalmic artery. The perfusion pressure may be initially lowered in anterior border zones while the cerebral perfusion pressure is roughly maintained in the global hemisphere via an efficient collateral supply.

A single-photon emission CT study<sup>24</sup> showed that VMR is more severely reduced in patients with border-zone infarcts than in patients with territorial infarcts. Therefore, the assessment of a VMR index could be useful for the functional assessment of collateral flow. VMR evaluated by rCBV changes reflects the cerebral vasodilatation response to the ACZ stimulus. The ACZ effect originally involves arterial compliance, and subsequent rCBV variation is then expected.<sup>25</sup> Although statistical significance was not reached, VMR was decreased in the anterior border zones on the lesion side. ACZ activation assessment was based on the laterality of rCBV, ie, asymmetry, because of the rather wide range of ACZ response in normal control subjects.<sup>26</sup> This method assumes a normal ACZ vasoreactivity on the contralateral side. It has been reported that the vasoreactivity might also be decreased on the contralateral hemisphere in some cases.<sup>27</sup> Therefore, an assessment based on asymmetry might provide an underestimation of the effects and thus hamper the detection of significant vasoreactivity impairment.<sup>28</sup> However,

rCBV data in gray matter, white matter, and the posterior border zones support the hypothesis that VMR may not be altered in these regions, inasmuch as no preexistent vasodilatation was observed. A reduced vasodilatory response is usually expected in patients who have limited collateral channels. The efficient collaterality previously described may explain that VMR to ACZ was not compromised in these patients.

The asymmetries within anterior border zones (rCBV and VMR) were substantially attenuated after surgery, thus confirming the potential hemodynamic benefit of CEA when a significant side-to-side asymmetry is present.<sup>4,19</sup> After CEA, compared with control values, rCBV values seem to be over the normal range. This effect may be in relation to the transient effect of hyperperfusion, which may occur shortly after CEA.<sup>11</sup> Later examination, such as 3 months after CEA, would have been suitable.

### Limitations

One limitation of this approach is that only relative hemodynamic parameters are calculated. The method for evaluation of rCBV is based on a tracer kinetic model.<sup>29</sup> In theory, absolute quantification of rCBV could be achieved by deconvolution of the tissue curves with an arterial input function (AIF).<sup>13,14,30</sup> However, in the case of ICA stenosis, estimation of a reliable arterial input is difficult.<sup>31</sup> Schreiber et al<sup>26</sup> have recently established a dynamic MRI method that allows quantification of regional cerebral blood flow, rCBV, and mean transit time by use of pixels in the MCA to assess the AIF. The main drawback of this method, which uses a fast low-angle shot sequence, is that only 1 slice of the brain can be acquired. Furthermore, when the ICA is stenosed, there might be pathways other than the MCA supplying the ipsilateral hemisphere because of collateral recruitment. Multislice capabilities of EPI could permit the determination of an AIF from small vessels instead of a major feeding vessel.

This approach still involves difficulties that are mainly due to partial volume effects, and the reliability of this approach requires further investigation. Although the use of relative values is limited compared with quantitative approaches, relative parameters, such as rCBV, might be useful in helping to detect pathological situations when no information about the AIF is accessible.<sup>15</sup>

The equations used to determine rCBV are derived from the hypothesis of a fast and compact bolus injection of the contrast agent. Another limitation is that, in practice, this requirement is sometimes difficult to obtain. Moreover, inpatient and outpatient variation in parameters may arise as a consequence of manual injection of the contrast agent. In this context, cerebellum values were used for normalization, allowing between-patient comparison. This method assumes a normal cerebellar perfusion. Even though there is no evidence that the posterior circulation remains unaffected in the presence of ICA stenosis, the assumption that possible alterations in cerebellar perfusion are negligible with regard to changes in tissue perfusion seems quite reasonable.<sup>11</sup> Assessment of perfusion reserve was made by use of a vasoreactivity index. This parameter was evaluated by using the relative values and not the normalized values, because the cerebellum also experiences vasoreactivity under ACZ. However, a more reliable evaluation of the vasodilatation capacity would also require the quantification of rCBV.

## Conclusion

Although further studies are warranted, these findings suggest that in patients with high-grade unilateral stenosis, hemodynamic impairment might occur selectively in anterior borderzone areas. These abnormalities were decreased after CEA, also suggesting a hemodynamic impact of CEA in unilateral high-grade ICA stenosis.

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