# **Evaluation of Impaired Cerebral Autoregulation** by the Valsalva Maneuver

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Background and Purpose Transcranial Doppler sonography has recently been used to describe cerebral hemodynamics during the Valsalva maneuver in normal human subjects. Since some changes in flow velocity during the Valsalva maneuver seem to reflect the brain's autoregulatory response to a decrease in cerebral perfusion pressure during the strain, we hypothesized that this method could identify vascular territories with impaired au-

toregulatory capacity.

Methods Eight patients with unilateral (n=7) or bilateral (n=1) severe obstruction of the internal carotid artery and impaired vascular responses to the CO2 reactivity test and to dynamic autoregulation testing were studied. We compared changes in flow velocities and blood pressures during defined phases of the Valsalva maneuver in the patients with the results in a group of 17 normal volunteers. We defined two indices to evaluate autoregulatory capacity based on the response to the Valsalva maneuver.

Results During the Valsalva maneuver, changes in flow velocity in the middle cerebral arteries ipsilateral to the lesions showed characteristic abnormalities compared with the normal pattern. Autoregulatory indices of these vessels as defined by the Valsalva maneuver were significantly different from those with normal vascular reactivity to CO<sub>2</sub> (P<.0001). There were good correlations between an index based on the changes in flow velocity and blood pressure in phase II and the results of the CO2 test (r=.78; P<.0001) or those of dynamic autoregulatory testing (r=.6; P<.0001).

Conclusions Vascular territories with severely impaired vasomotor reactivity due to carotid obstruction can be identified by transcranial Doppler sonography by their pattern of flow velocity changes if their autoregulatory capacity is challenged during the Valsalva maneuver. (Stroke. 1996;27:1177-1182.)

Key Words • autoregulation • blood flow velocity • carbon dioxide reactivity • cerebral blood flow • ultrasonics

erebral autoregulation is the mechanism that maintains constant CBF within a wide range of changing CPP. 1-3 Its clinical importance lies in the protection of the brain from the sequelae of arterial hypotension and hypertension, and information regarding impaired CA may be helpful in the management of patients with cerebrovascular disease. This knowledge could also be valuable for preoperative decision making in carotid obstruction to determine the effects of a given carotid stenosis on the dependent vascular bed.

Routine assessment of CA, however, is not commonly available because of the difficulties involved in the measuring techniques. The classic method of evaluating CA requires repeated measurements of CBF, eg, by the technique of Kety and Schmidt<sup>4</sup> or by the <sup>133</sup>Xe inhalation method,5 and pharmacological manipulations of ABP to decide whether CBF is maintained constant in response to a change in CPP. Aaslid et al6 proposed a less complicated "dynamic" method to evaluate CA using TCD and showed that an autoregulatory response could be analyzed after short-term drops in ABP. This quantitative method, which uses deflation of blood pressure cuffs around the thighs as a stimulus to induce a transient drop in ABP, was later validated by comparison with electromagnetic flowmetry7,8 and by comparison with repeated steady state CBFV measurements before and after pharmacological manipulations of ABP.9 It was furthermore demonstrated that the autoregulatory response, as measured by this cuff method, and the vasomotor reserve, as determined by the CO<sub>2</sub> reactivity test, 10-12 correlate well in normal subjects and patients with obstructive carotid disease. 13

Both the cuff method and the CO2 test, however, are time consuming and require specialized equipment. Thus, a simple and quick test to detect severe impairment of CA is still lacking. A simple bedside test to evaluate CA with the use of TCD measurement of reactive hyperemia after carotid compression has been proposed, 14 but it is obviously not suitable or even dangerous in severe obstructive carotid disease.

We have recently demonstrated in normal adults that simultaneous recordings of CBFV and ABP are able to characterize the interaction of systemic 15,16 and cerebral responses during the VM<sup>17</sup> (Table 1). Typical changes in cerebrovascular resistance occur during the strain. 17,18 These are likely to reflect the brain's autoregulatory response to a decrease in CPP, which is caused by a sustained increase in intracranial pressure and a transient decrease in ABP in the first seconds of the strain.

We therefore hypothesized that recordings of CBFV and ABP during the VM would be able to identify vascular territories with severely impaired vasomotor response as determined by the CO2 test and the cuff method.

# Subjects and Methods

Eight patients with severe internal carotid artery obstruction (occlusion or >70% stenosis by angiography and/or duplex ultrasound) and 17 healthy volunteers without signs of cerebrovascular disease were studied. All patients selected showed impaired

Received January 24, 1996; final revision received March 21, 1996; accepted March 22, 1996.

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#### Selected Abbreviations and Acronyms

ABP = arterial blood pressure

AI-IV = autoregulatory index based on the ratio of phase IV and I of the Valsalva maneuver

ARI = autoregulatory index ASI = autoregulatory slope index

CA = cerebral autoregulation

CBF = cerebral blood flow

CBFV = cerebral blood flow velocity

CPP = cerebral perfusion pressure

MCA = middle cerebral artery

TCD = transcranial Doppler sonography

VM = Valsalva maneuver

vascular responses to the CO2 test as determined by Bishop et al, 11 and 7 of 8 individuals also demonstrated impaired autoregulatory capacity by the cuff method in at least one of the MCA perfusion territories<sup>6</sup> (measurement of CA by the cuff method was impossible in 1 patient due to severe peripheral vascular disease of both legs). The study was approved by the University of Washington Human Subject Review Committee, and written informed consent was obtained from each subject. All the testings were performed weeks to months after the acute phase of the respective vascular event or during routine follow-up examinations. The most prevalent risk factor for cerebrovascular disease was arterial hypertension. The mean baseline ABP in the patients was significantly higher than in our control subjects (who were not matched in terms of age) despite antihypertensive medication (eg, ABP in phase IIb was 117±27 versus 83±10 mm Hg). None of our patients demonstrated significant abnormalities of blood viscosity.

Continuous ABP measurements were started in each individual with the use of a tonometric noninvasive device at the radial artery (N-Cat N-500, Nellcor). The MCAs were identified according to standard criteria. 19 We simultaneously monitored CBFV in both MCAs using a bilateral multichannel TCD recording system with a headband (Multidop X, DWL). Stable baselines were recorded for at least 5 minutes. The VM was then performed for 15 seconds by forceful expiration against a closed valve connected to an aneroid pressure gauge at a pressure of 30 mm Hg. Velocity and pressure calculations were performed off-line, and time-averaged mean velocity and mean ABP values were noted at defined stages of the VM15-17 (Table 1). These stages were phase I, early phase II, and phase IV (Fig 1). In phases I and IV, the respective maximal values of CBFV and ABP were used for calculations, whereas in early phase II, measurements were taken at the time of the minimum CBFV and 3 seconds later.

To quantify the autoregulatory response, we introduced two indices, which require some explanation. According to our hypothesis, the VM is suitable for the analysis of the autoregulatory response because there is a marked decrease in CPP shortly after the onset of the strain. This occurs in early phase II, when ABP is transiently markedly decreased because of impaired atrial filling 15-17 and cerebrospinal fluid pressure and intracranial pressure are thought to be increased because of transmission of the elevated intrathoracic pressure. 17,18,20 Therefore, the expected autoregulatory response to the decrease in CPP should lead to dilatation of the cerebral resistance vessels to maintain normal CBF. This should be reflected in the speed of the restoration of CBFV (ie, its "slope" on the recordings), which should exceed the concomitant restoration of the ABP as a result of sympathetic regulation.

Since the stimulus is strongest before the onset of ABP restoration and because the CBFV slope tapers off after a few seconds, <sup>16,17</sup> the autoregulatory effect should be most purely detectable during the first few seconds of restoration of CBFV. We therefore calculated the difference between the respective slopes of CBFV and ABP at this critical time period by performing two measurements of both CBFV and ABP and calculating the respective percent changes. We chose an interval of 3 seconds between the measurements because it is long enough to provide a reasonable difference between the data points, whereas later the CBFV slope starts to taper off in many subjects (while the ABP slope may still be on its rise). We therefore defined the ASI as follows:

$$ASI = \left(\frac{CBFV_{(t+3s)} - CBFV_{(t)}}{CBFV_{(t)}} - \frac{ABP_{(t+3s)} - ABP_{(t)}}{ABP_{(t)}}\right) \times 100\%$$

where t is time of the beginning of the CBFV slope at phase II and t+3s is 3 seconds later.

Thus, the ASI calculates the difference between the percent change of CBFV and the concomitant percent change in ABP, ie, the angle between the two slopes, corrected to percentage. [For illustration, see Fig 1A, in which  $d_v=CBFV_{(t+3s)}-CBFV_{(t)}$  and  $d_p=ABP_{(t+3s)}-ABP_{(t)}$ ].

Vasodilatation of the resistance vessels should, however, still be detectable in phase IV after the sudden release of the strain (and the presumable normalization and overshoot of CPP), since autoregulation is not instantaneous. <sup>6,18</sup> Therefore, the autoregulatory response should be reflected at this phase as an increase in CBFV relative to ABP.

We define the AI-IV as follows:

AI-IV=
$$\frac{\text{CBFV (phase IV)/CBFV (phase I)}}{\text{ABP (IV)/ABP (I)}} \times 100\%$$

TABLE 1. Phases of the Valsalva Maneuver

\*Autoregulatory action is not immediate.

Phase	Extracranial Effects	Effects on CPP	Autoregulatory Response	Effects on CBF
ı	Intrathoracic pressure+transmission on vascular tree ABP+, venous pressure+	ABP+ ICP+ →CPP (+)	None→CVR 0	CP (+) CVR 0 →CBF (+)
lla	Atrial filling- →cardiac output- ABP-, pulse pressure-	ABP− ICP+ →CPP	Onset*→CVR 0	CPP CVR 0 →CBF
lib	Sympathetic response vascular resistance+ ABP+, heart rate+	ABP-/0 ICP+ →CPP-	Cont→CVR-	CPP CVR CBF (-)/0
III	Intrathoracic pressure →transmission on vascular tree ABP	ABP− ICP 0 →CPP	Cont→CVR-	CPP- CVR CBF 0
īV	Atrial filling+, sympathetic tone 0 ABP+→baroreceptor-response heart rate—	ABP+ ICP 0 →CPP+	End*→CVR-	CPP+ CVR− →CBF++

ICP indicates intracranial pressure; CVR, cerebrovascular resistance; +, elevated; 0, normal: -, reduced: →, leads to; and Cont, continued.

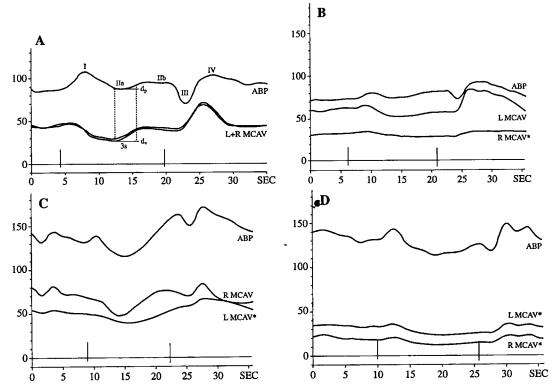


Fig 1. Recordings during the VM in a normal subject (A) and in unilateral (B and C) and bilateral (D) carotid obstructions. On the x axis time is shown in seconds; y axis, CBVF (bottom channels) in centimeters per second and ABP (top channel) in millimeters of mercury; marked interval, duration of strain; I to IV, phases of the VM (phase I, increased intrathoracic and ABP; phase IIa, fall in ABP due to decreased atrial filling; phase IIb, rise in ABP due to increased heart rate; phase III, sudden decrease in ABP due to release of intrathoracic pressure; phase IV, overshoot in ABP with resumed atrial filling and increased sympathetic tone); LMCAV, left middle cerebral artery velocity; and RMCAV, right middle cerebral artery velocity. \*Curve ipsilateral to the lesion. (Recordings are filtered at 9.3 Hz.) Additionally, panel A illustrates the derivation of the ASI: d<sub>v</sub>, difference between minimum velocity and the velocity reading 3 seconds later; d<sub>p</sub>, difference between pressure readings in the same time interval. Note that these differences are to be corrected to percentage values before they can be compared with each other.

We chose the phase I value instead of baseline for normalization because the response in phase I represents and standardizes the magnitude of each individual's response to the strain.

Noninvasive testing of dynamic cerebral autoregulation was accomplished with the use of previously described techniques. 6.8.9 Subjects were tested in the supine position with continuous monitoring of both MCA velocity signals. Continuous monitoring of ABP was also accomplished with the use of the previously described tonometric noninvasive blood pressure monitor. Brief transient blood pressure drops were induced by rapid deflation of large thigh blood pressure cuffs. ARI values were calculated on a scale of 0 to 9 by a previously described computer model for each MCA perfusion territory.

We tested reactivity to CO<sub>2</sub> by initially obtaining baseline bilateral continuous MCA velocity tracings at normocapnia. Endtidal CO<sub>2</sub> was continuously measured with the use of a side point end-tidal CO<sub>2</sub> monitor (Datex Corp). Subjects were instructed to breathe a mixture of 6% CO<sub>2</sub>/40% O<sub>2</sub> with the balance nitrogen that a new stable baseline was reached. Subjects were then placed on room air and instructed to hyperventilate until a new baseline was reached. CO<sub>2</sub> reactivity was calculated as the percent change in MCA velocity per millimeter change in end-tidal CO<sub>2</sub> over the entire range of CO<sub>2</sub> change. <sup>11</sup>

Statistical analysis was performed to compare these indices between the MCA territories ipsilateral to the carotid obstruction with the contralateral side and the values of the normal volunteers. Regression analysis was performed to evaluate the correlation between these indices and the percent change in CBFV per millimeter of mercury change in end-tidal CO<sub>2</sub> during the CO<sub>2</sub> test.

In addition, we wanted to investigate whether CBFV recordings alone could—beyond pattern recognition—reveal vessels

with an impaired autoregulatory response. Therefore, 95% confidence intervals were derived from the CBFV data of presumably normal vessels. We calculated confidence intervals of the slope during the first 3 seconds of the CBFV restoration in phase II and the CBFV ratio between phases I and IV (ie, the two indices introduced above without consideration of the ABP). These values were compared with those of the MCAs on the side of the lesion.

Finally, the side-to-side differences in the velocity slope in normal subjects were compared with those in patients with unilateral carotid obstruction.

Student's t test and simple regression analysis were used for statistical comparisons. All data are shown as mean $\pm$ SD.

#### Results

Characteristics of patients are shown in Table 2. Fig 1 illustrates typical CBFV and ABP recordings in a normal control subject (Fig 1A) and patients with unilateral (Fig 1B and 1C) or bilateral (Fig 1D) obstructive carotid disease. The pattern of CBFV was severely impaired on the side of internal carotid artery obstruction in every patient studied. In contrast to the normal CBFV pattern, each patient with impaired vasomotor response showed one or more of the following three criteria: (1) The appearance of the CBFV recording was "flat" with practically no slope or even a negative slope during phase II. (2) The CBFV peak in phase IV did not exceed the peak in phase I. (3) There was a gross side-to-side difference between the CBFV recordings (ie, CBFV recordings were not parallel).

**TABLE 2. Patient Profiles** 

Pt	Age, y/Sex	Diagnosis	Side	Symptoms	CO₂ Relative, %/mm Hg	ARI (Cuff)	ASI, %	AI-IV, %
1	40/M	e ICA occlusion	Right	TIA	0.05	0	-11	0.91
2	57/F	i ICA stenosis (severe)	Right	TIA	1.07	2	1	1.13
3	59/M	e ICA occlusion	Left	TIA	1.11	0	-18	0.99
4	63/M	e ICA occlusion	Left	Stroke	1.11		-8	0.91
5	52/F	i ICA stenosis (severe)	Left	TIA	1.50	0.5	-2	1.21
6	62/M	I ICA occlusion	Left	Stroke	1.16	0.0	-11	0.74
7	23/F	e ICA ligation	Left	None	0.94	1.0	9	1.02
8a	62/M	e ICA occlusion (bilateral)	Left	Stroke	1.09	2	0	
8b	See above	See above	Right	See above	1.78	0	-11	0.97 1.06

Pt indicates patient; e, extracranial; ICA, internal carotid artery; i, intracranial; TIA, transient ischemic attack; CO<sub>2</sub> Relative, percent change in CBFV per change in end-tidal CO<sub>2</sub> in millimeters of mercury; and ARI (Cuff), autoregulatory index determined by the cuff method.

In combination with ABP recordings, there was one additional distinct criterion: (4) Recordings from normal subjects showed that the onset of CBFV restoration in phase II occurs earlier than the corresponding ABP increase (Fig 1A), whereas CBFV restoration in vessels with impaired vasomotor reactivity started simultaneously or later than the concomitant ABP increase (Fig 1B, 1C, and 1D).

Results from the CO<sub>2</sub> test and autoregulatory tests by the cuff method and by the VM are shown in Table 3 for normal vessels (recordings from volunteers and from the contralateral side in unilateral carotid disease) and vessels ipsilateral to the carotid obstruction.

Both the AŞI (P<.0001) and the AI-IV (P<.0001) were significantly different between yessels on the side of the carotid obstruction and normal vessels. They were also significantly different between both sides in unilateral carotid disease in the same patients (ASI, P<.002; AI-IV, P<.003),

There was a highly significant correlation between the ASI and the  $CO_2$  test (r=.78, P<.0001) (Fig 2) and to a lesser extent also between the AI-IV and the  $CO_2$  test (r=.50, P<.0001). Both the ASI and AI-IV also correlated well with dynamic autoregulatory testing (ASI: r=.6, P<.0001; AI-IV: r=.63, P<.0001) (Fig 3).

Data from the calculations of the velocity measurements alone are given in Table 4. While in individual persons the side-to-side differences of the velocity responses in the volunteers were small (eg, 4.6±3.9% difference in CBFV slope), they were marked in unilateral carotid obstruction (17.1±8% difference in CBFV slope).

### Discussion

Using TCD during the VM, we have demonstrated in patients with obstructive carotid disease that vascular territories with impaired vasomotor reactivity show characteristic anomalies in flow velocity. Continuous recordings of CBFV and ABP are able to quantify the autoregulatory response, which correlates reasonably well with vasomotor reactivity as determined by the  ${\rm CO}_2$  test.

During VM there are complex changes in relevant cardiovascular (ABP, cardiac output, pulse pressure, heart rate, systemic vascular resistance) and cerebrovascular (systemic ABP, venous outflow pressure, intracranial pressure, cerebrovascular resistance) variables within a short time span (Table 1). It is therefore surprising that a quantitative analysis of autoregulation is possible at all. There is, however, a period of relatively stable intracranial pressure during the strain, <sup>18,20,21</sup> which means that CPP is primarily dependent on ABP. Since CPP and cerebrovascular resistance determine CBF, flow velocity (which changes with CBF)<sup>7,8,22</sup> would be expected to passively follow the ABP course, if cerebrovascular resistance was unchanged. Therefore, relative differences of the changes in velocity/ pressure should reflect changes in cerebrovascular resistance and thus, in the absence of major CO<sub>2</sub> changes. 21 the autoregulatory response.

Most of these assumptions apply most purely to the first seconds of the strain, since CPP may be practically restored toward the end of the strain if the ABP markedly exceeds baseline levels (eg, see Fig 1C). Therefore, the difference in slope between ABP and CBFV during the first few seconds of CBFV restorations should reflect the efficiency and the latency of the autoregulatory response best. Thus, it is explicable that our ASI correlates better with the CO<sub>2</sub> test than the AI-IV. The characteristic finding of an earlier onset of CBFV restoration in comparison to ABP in normal subjects is in itself clear evidence of autoregulatory, action and was not present on the side ipsilateral to the carotid lesion in any patient.

Because it provides quantitative data of vasomotor reactivity in somewhat less time, our new method could therefore be used as an alternative if patients do not tolerate the CO<sub>2</sub> test or if the cuff method of autoregulation testing cannot be applied (eg, because of peripheral vascular disease).

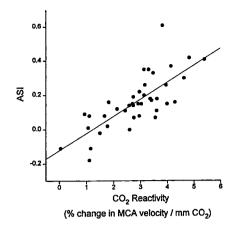
It would, however, be desirable to obtain sufficient information regarding the autoregulatory response without the special equipment needed for the cuff method or the

TABLE 3. CO<sub>2</sub> Reactivity and Autoregulatory Capacity in Normal Vascular Territories and Carotid Obstruction

	CO <sub>2</sub> Total, %	CO <sub>2</sub> Relative, %/mm Hg	ARI (Cuff)	ASI, %	Al-IV, %
Normal vascular territory	86±20	3.3±0.8	5.0±1.1	22±14	133±19
Carotid obstruction	29±13*	1.1±0.5*	0.7±0.9*	-4±8*	99±14*

CO<sub>2</sub> Total indicates percent change in CBFV during the total CO<sub>2</sub> test; CO<sub>2</sub> Relative, percent change in CBFV per change in end-tidal CO<sub>2</sub> in millimeters of mercury; and ARI (Cuff), autoregulatory index determined by the cuff method. Data are mean±SD.

<sup>\*</sup>P<.001 by Student's t test, significant difference between normal and carotid obstruction.



 $_{\rm G}$  2. Correlation between the results of the ASI obtained with he use of the VM and the CO<sub>2</sub> test in each MCA territory. On he x axis is shown percent change in blood flow velocity per fillimeter of mercury change in end-expiratory Pco<sub>2</sub>; y axis, ASI = .78, P< .0001).

O<sub>2</sub> test. Our data show some easily recognizable charcteristics of CBFV recordings, which seem to be highly pecific for an absence of autoregulatory capacity.

First, since the rise in CBFV in phase I of the VM is sually less marked than the corresponding ABP increase because of a concomitant increase in intracranial pressure, which provides a fairly unchanged CPP<sup>17</sup>), the rise in CBFV during phase IV (when ABP regularly exceeds a seline and usually equals the value in phase I<sup>17</sup>) should e normally greater than in phase I. A CBFV ratio of phase V to phase I of less than 1.00 therefore seems incompatble with an autoregulatory response.

Second, if we assume a normal ABP response to VM, aflat CBFV curve in phase II with a continuously negative ar zero slope excludes an autoregulatory response.

Third, in unilateral disease, the side-to-side difference another important criterion. Based on the data from our formal volunteers (mean side-to-side difference in CBFV, 4.6±3.9%), a side-to-side difference of more than 12.4% (mean+2 SD) would only be likely in less than 5% of a normal population. In contrast, the mean side-to-side difference for the slope in the first 3 seconds of CBFV responsion was 18% in our patients with unilateral carotid obstruction.

Thus far, we have not seen one of the above criteria in any vascular territory with normal autoregulatory capacity. Similar (bilateral) CBFV patterns could, however, be expected in patients with a pathological systemic (ABP) response to the VM, as in mitral stenosis, congestive heart failure, or autonomic nervous failure. These diseases can, however, be differentiated by the absence of the typical changes in heart rate due to the sympathetic response. 15,16

On the other hand, a "normal" CBFV pattern with a positive slope in phase II and phase IV clearly exceeding phase I should, in combination with little or no side-to-side difference, exclude severe unilateral impairment of autoregulatory capacity.

All of these characteristics can be easily obtained without simultaneous blood pressure recordings and, since the recordings were usually well reproducible, may be obained by consecutive measurements of each side with the use of handheld probes. This would allow one to obtain

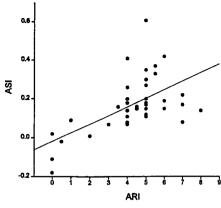


Fig 3. Correlation between the ARI obtained by rapid blood pressure drops and the ASI in each MCA territory obtained by analyzing the VM (r=.6, P<.0001).

additional qualitative information on the vasomotor reserve during routine TCD examination.

There may be, however, one more interesting aspect of measuring autoregulatory capacity as an index of vasomotor reserve. We have used the CO2 test as our gold standard because it is a widely applied noninvasive test to evaluate vascular reactivity, which is well established. 26-28 From a theoretical point of view, however, it may be advantageous to predict vascular reactivity by the use of another challenging stimulus. It is the decrease in CPP (eg, due to periodic hypotension) that constitutes the actual ischemic threat to vascular territories distant to a stenosis, and it is the ability of the resistance vessels to respond to this situation; in other words, it is the autoregulatory capacity that may be essential to prevent ischemia, It is known in several diseases, including stroke, that autoregulation may be already impaired while CO<sub>2</sub> reactivity is still preserved, a state that has been termed dissociated vasoparalysis. 29,30

Interestingly, two of our patients demonstrated partially preserved CO<sub>2</sub> reactivity while they had practically no autoregulatory capacity by both the cuff method and the ASI. One of these patients became clinically symptomatic for the first time after the administration of antihypertensive drugs to control essential arterial hypertension. Only studies in larger patient populations, however, can help to reveal whether the CO<sub>2</sub> test may underestimate the impairment of the vasomotor response to a decrease in CPP in some patients and whether this would be of clinical relevance. Longitudinal data by our method on the spontaneous course of autoregulatory capacity or the effects of the therapeutic intervention (rheological or antihypertensive medication or endarterectomy) would

TABLE 4. Velocity Slope and Side-to-Side Differences in Normal Vascular Territories and in Unilateral Carotid Obstruction

	Velocity Slope, %	Side-to-Side Difference, %
Normal vascular territory	26.5±19.7	4.6±3.9
Carotid obstruction	-2.9±12.5*	17.1±8.2*

Data are mean±SD. Velocity slope indicates percentage increase in CBF velocity in the first 3 seconds after the CBF velocity minimum in phase IIa of the Valsalva maneuver.

\*Significant difference between normal and carotid obstruction (P<.01 by Student's t test).

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Most of these assumptions apply most purely to the first seconds of the strain, since CPP may be practically restored toward the end of the strain if the ABP markedly exceeds baseline levels (eg, see Fig 1C). Therefore, the difference in slope between ABP and CBFV during the first few seconds of CBFV restorations should reflect the efficiency and the latency of the autoregulatory response best. Thus, it is explicable that our ASI correlates better with the CO<sub>2</sub> test than the AI-IV. The characteristic finding of an earlier onset of CBFV restoration in comparison to ABP in normal subjects is in itself clear evidence of autoregulatory action and was not present on the side ipsilateral to the carotid lesion in any patient.

Because it provides quantitative data of vasomotor reactivity in somewhat less time, our new method could therefore be used as an alternative if patients do not tolerate the CO<sub>2</sub> test or if the cuff method of autoregulation testing cannot be applied (eg, because of peripheral vascular disease).

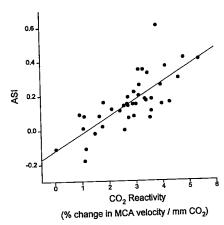
It would, however, be desirable to obtain sufficient information regarding the autoregulatory response without the special equipment needed for the cuff method or the

TABLE 3. CO<sub>2</sub>:Reactivity and Autoregulatory Capacity in Normal Vascular Territories and Carotid Obstruction

,	CO <sub>2</sub> Total, %	CO₂ Relative, %/mm Hg	ARI (Cuff)	ASI, %	Al-IV, %
Normal vascular territory	86±20	3.3±0.8	5.0±1.1	22±14	133±19
Carotid obstruction	, 29±13*	1.1±0.5*	0.7±0.9*	4±8*	99±14*

CO<sub>2</sub> Total indicates percent change in CBFV during the total CO<sub>2</sub> test; CO<sub>2</sub> Relative, percent change in CBFV per change in end-tidal CO<sub>2</sub> in millimeters of mercury; and ARI (Cuff), autoregulatory index determined by the cuff method. Data are mean+SD

<sup>\*</sup>P<.001 by Student's t test, significant difference between normal and carotid obstruction.



is 2. Correlation between the results of the ASI obtained with the use of the VM and the  $CO_2$  test in each MCA territory. On the x axis is shown percent change in blood flow velocity per nillimeter of mercury change in end-expiratory  $PcO_2$ ; y axis, ASI r=.78, P<.0001).

 $CO_2$  test. Our data show some easily recognizable characteristics of CBFV recordings, which seem to be highly specific for an absence of autoregulatory capacity.

First, since the rise in CBFV in phase I of the VM is usually less marked than the corresponding ABP increase (because of a concomitant increase in intracranial pressure, which provides a fairly unchanged CPP<sup>17</sup>), the rise in CBFV during phase IV (when ABP regularly exceeds baseline and usually equals the value in phase I<sup>17</sup>) should be normally greater than in phase I. A CBFV ratio of phase IV to phase I of less than 1.00 therefore seems incompatible with an autoregulatory response.

Second, if we assume a normal ABP response to VM, a flat CBFV curve in phase II with a continuously negative or zero slope excludes an autoregulatory response.

Third, in unilateral disease, the side-to-side difference is another important criterion. Based on the data from our normal volunteers (mean side-to-side difference in CBFV, 4.6±3.9%), a side-to-side difference of more than 12.4% (mean+2 SD) would only be likely in less than 5% of a normal population. In contrast, the mean side-to-side difference for the slope in the first 3 seconds of CBFV restoration was 18% in our patients with unilateral carotid obstruction.

Thus far, we have not seen one of the above criteria in any vascular territory with normal autoregulatory capacity. Similar (bilateral) CBFV patterns could, however, be expected in patients with a pathological systemic (ABP) response to the VM, as in mitral stenosis, congestive heart failure, or autonomic nervous failure. These diseases can, however, be differentiated by the absence of the typical changes in heart rate due to the sympathetic response. 15,16

On the other hand, a "normal" CBFV pattern with a positive slope in phase II and phase IV clearly exceeding phase I should, in combination with little or no side-to-side difference, exclude severe unilateral impairment of autoregulatory capacity.

All of these characteristics can be easily obtained without simultaneous blood pressure recordings and, since the recordings were usually well reproducible, may be obtained by consecutive measurements of each side with the use of handheld probes. This would allow one to obtain

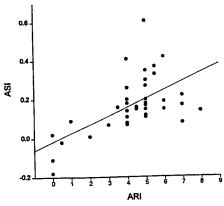


Fig 3. Correlation between the ARI obtained by rapid blood pressure drops and the ASI in each MCA territory obtained by analyzing the VM (r=.6, P<.0001).

additional qualitative information on the vasomotor reserve during routine TCD examination.

There may be, however, one more interesting aspect of measuring autoregulatory capacity as an index of vasomotor reserve. We have used the CO2 test as our gold standard because it is a widely applied noninvasive test to evaluate vascular reactivity, which is well established. 26-28 From a theoretical point of view, however, it may be advantageous to predict vascular reactivity by the use of another challenging stimulus. It is the decrease in CPP (eg, due to periodic hypotension) that constitutes the actual ischemic threat to vascular territories distant to a stenosis, and it is the ability of the resistance vessels to respond to this situation; in other words, it is the autóregulatory capacity that may be essential to prevent ischemia, It is known in several diseases, including stroke, that autoregulation may be already impaired while CO2 reactivity is still preserved, a state that has been termed dissociated vasoparalysis. 29,30

Interestingly, two of our patients demonstrated partially preserved CO<sub>2</sub> reactivity while they had practically no autoregulatory capacity by both the cuff method and the ASI. One of these patients became clinically symptomatic for the first time after the administration of antihypertensive drugs to control essential arterial hypertension. Only studies in larger patient populations, however, can help to reveal whether the CO<sub>2</sub> test may underestimate the impairment of the vasomotor response to a decrease in CPP in some patients and whether this would be of clinical relevance. Longitudinal data by our method on the spontaneous course of autoregulatory capacity or the effects of the therapeutic intervention (rheological or antihypertensive medication or endarterectomy) would

TABLE 4. Velocity Slope and Side-to-Side Differences in Normal Vascular Territories and in Unilateral Carotid Obstruction

	Velocity Slope, %	Side-to-Side Difference, %
Normal vascular territory	26.5±19.7	4.6±3.9
Carotid obstruction	-2.9±12.5*	17.1±8.2*

Data are mean±SD. Velocity slope indicates percentage increase in CBF velocity in the first 3 seconds after the CBF velocity minimum in phase IIa of the Valsalva maneuver.

\*Significant difference between normal and carotid obstruction (P<.01 by Student's t test).

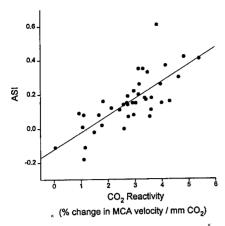


Fig. 2. Correlation between the results of the ASI obtained with the use of the VM and the  $CO_2$  test in each MCA territory. On the x axis is shown percent change in blood flow velocity per millimeter of mercury change in end-expiratory  $PCO_2$ ; y axis, ASI (r=.78, P<.0001).

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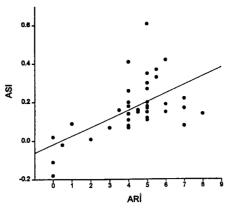


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be very useful for further interpretation but are not yet available.

In conclusion, we present a convenient test to detect severely compromised autoregulatory capacity in patients with unilateral carotid obstruction, which may also prove helpful in the quantitative evaluation of autoregulation in severe central nervous system disease.

## Acknowledgments

This study was supported through clinical investigator development award IK 015969 and National Institutes of Health grant IP 50 NS 30305-01 (Dr Newell) and a grant-of the Freunde und Förderer des Klinikum Großhadern e.V. (Dr Tiecks).

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