

# The impact of carotid stenting on the hemodynamic parameters and cerebrovascular reactivity of the ipsilateral middle cerebral artery

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**Objective:** The study was conducted to determine the effect of carotid angioplasty and stenting (CAS) on the hemodynamic parameters and cerebrovascular reactivity (CVR) of the ipsilateral middle cerebral artery (MCA) and examine the relation between preprocedural exhausted CVR and perioperative neurologic events.

**Methods:** The study included 29 patients with severe extracranial carotid stenosis undergoing CAS. Transcranial Doppler imaging was performed before the procedure, 2 days, and 2 to 4 months postoperatively. Peak systolic velocity, end-diastolic velocity, mean flow velocity, and pulsatility index of the ipsilateral MCA were recorded at rest. CVR was assessed with the breath holding test: the increase of mean flow velocity and the breath holding index were calculated.

**Results:** Peak systolic and mean flow velocities increased significantly in both postoperative studies compared to the preoperative values, end-diastolic velocity was significantly elevated only in the first study, and pulsatility index did not change significantly. When stimulated by breath holding, preoperative mean flow velocity did not increase significantly compared with the resting values; however, it did increase significantly during breath holding in both studies after CAS. The breath holding index improved significantly from  $-0.35$  ( $-0.71$  to  $0.55$ ) to  $0.38$  ( $0.12$  to  $0.61$ ) at 2 days ( $P = .049$ ) and  $0.44$  ( $0.31$  to  $0.92$ ) at 2 to 4 months ( $P = .020$ ). Exhausted CVR of the MCA preoperatively was associated with increased risk of neurologic complications during or after the procedure ( $P = .006$ ).

**Conclusions:** CAS may improve the hemodynamic parameters and the vasomotor reactivity in the ipsilateral MCA. Exhausted CVR is associated with an increased risk of perioperative neurologic complications. (*J Vasc Surg* 2006;44:1016-22.)

Large European and American randomized-controlled trials have demonstrated clearly that carotid endarterectomy is an effective intervention for patients with symptomatic severe carotid stenosis and, to a lesser extent, for patients with asymptomatic stenosis. Carotid angioplasty and stenting (CAS) has also emerged as a potential alternative to endarterectomy over the last decade, and excellent results have been published around the world in terms of stroke and death rate.

The mechanism of stroke caused by severe carotid atherosclerosis is believed to be primarily thromboembolism. In a small group of patients, however, the clinical correlates of cerebral ischemia are attributable to a critical reduction of cerebral perfusion pressure.<sup>1,2</sup> The degree of carotid stenosis does not necessarily correlate with the

cerebral perfusion state because of the functional capacity of the collateral pathways.<sup>3-5</sup>

An indicator used to test the hemodynamic status of the cerebral circulation is the cerebral vasomotor reactivity. Decreased cerebrovascular reactivity (CVR) indicates the presence of pre-existing vasodilatation, which reflects a reduced capacity of cerebral resistance vessels to adapt their caliber in response to changes in cerebral perfusion. Exhausted CVR has been shown to be an important determinant of risk of stroke and transient ischemic attack (TIA) in patients with carotid stenosis and occlusion.<sup>3,5-7</sup>

There are several techniques to assess CVR, including positron emission tomography (PET), single photon emission tomography (SPECT), stable xenon-enhanced computed tomography (Xe-CT), and dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI).<sup>8-11</sup> These methods are expensive, time-consuming, demand specialized equipment, and most involve radiation, so their use in routine clinical practice is limited. Transcranial Doppler with a vasodilatory stimulus is a relatively easy, repeatable, noninvasive, and less expensive method of evaluating CVR.<sup>6,11-18</sup>

As a vasodilatory stimulus, acetazolamide (Diamox, Duramed Pharmaceuticals, Cincinnati, Ohio), carbon dioxide (CO<sub>2</sub>) inhalation, and the breath-holding test have been used, and they have been proven to be equally reliable.<sup>19,20</sup> Breath-holding index (BHI) is a widely used screening method,<sup>21</sup> and the dilatory effect of CO<sub>2</sub> is

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Competition of interest: none.

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mainly restricted to the peripheral arterial bed, particularly the small cortical vessels. With changing CO<sub>2</sub> concentrations, the relationship between flow velocity and volume flow within a large cerebral artery is linear, provided that the CO<sub>2</sub> level does not directly affect the diameter of the large proximal arterial segment.

Velocities measured from the middle cerebral artery (MCA) with changing CO<sub>2</sub> concentrations show a bi-asymptotic, S-shaped curve. The average change in MCA velocity is 87.8% (52.5% hypercapnia and 35.3% hypocapnia, respectively).<sup>14,22</sup> A “preserved” vasomotor reserve implies that a drop in perfusion pressure can be counterbalanced by vasodilatation of cortical arterioles to maintain sufficient cortical blood supply. The vasomotor reserve may become exhausted if the resistance vessels in brain areas with low perfusion pressure are already maximally dilated.

The aim of this study was to determine the effect of CAS on the hemodynamic indicators and the CVR of the ipsilateral MCA. We also examined whether there was any association between an exhausted CVR and the development of neurologic events during or after CAS.

## METHODS

**Patients.** The Ethics Committee of our institution approved this study, and all patients enrolled gave informed consent. The study included 29 patients (22 men and 7 women) with a median age of 68 years (range, 58 to 80 years) undergoing CAS between December 2002 and May 2004. The degree of carotid artery stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria and had to be  $\geq 70\%$  for asymptomatic and  $\geq 50\%$  for symptomatic patients. Thirteen patients were symptomatic, having had ipsilateral stroke (n = 8), TIA (n = 3), amaurosis fugax (n = 1), or amaurosis fugax and TIA (n = 1). Patients’ demographics, cardiovascular risk factors, and status of the contralateral internal carotid artery (ICA) are all presented in Table I.

Preoperatively, all patients underwent full clinical assessment, including a detailed neurologic examination, a digital subtraction angiography of the extracranial carotid arteries, a brain CT scan, and MRI. Any neurologic events during the procedure were recorded.

The patients were examined 8 and 24 hours postoperatively by a neurologist. Brain CT scan was repeated 48 hours postoperatively. All patients were also examined 2 to 4 months after the procedure by the neurologist and a new brain MRI was performed. The brain MRIs were performed  $>2$  months after the operation because a balloon-expandable, stainless steel stent was implanted in most patients and this is the minimum time period required for the endothelialization and stabilization of the stent, as instructed by the manufacturer. An independent radiologist, unaware of the clinical data, evaluated CT and MRI scans.

**Transcranial Doppler imaging.** A transcranial color Doppler examination was performed preoperatively, and twice postoperatively: the first was at 48 hours and the second was at 2 to 4 months. The same operator, who was unaware of the patient’s clinical status, performed all the

**Table I.** Patient details

Details	N = 29 (%)
Male/female	22:07
Median age (years) (range)	68 (58-80)
Symptomatic	13
Asymptomatic	16
Risk factors	
Coronary artery disease	19 (65.5)
Diabetes mellitus	13 (44.8)
Hypertension	23 (79.3)
Hyperlipidemia	28 (96.5)
Smoking (current or ex)	17 (58.6)
Contralateral carotid artery	
Stenosis $<50\%$	18 (62)
Stenosis 50% to 70%	4 (14)
Stenosis 70% to 90%	1 (3)
Occlusion	6 (21)

studies. Doppler examination of the ipsilateral MCA was performed with a 2 MHz phased array imaging transducer using an ATL HDI 3000 Instrument (ATL Philips Medical Systems, Bothell, Wash) with transcranial Doppler imaging. Measurements were recorded on a real-time Doppler imaging. The temporal “window” was used to identify the MCA, which was insonated at a 50 mm depth.

Peak systolic (PSV), end-diastolic (EDV), and mean flow velocities (MFV) of the vessel were recorded, and Gosling’s pulsatility index was calculated as the difference between the PSV and EDV divided by the MFV in the MCA.<sup>23,24</sup> Normal values for PSV are  $78 \pm 15$  cm/s for individuals  $>60$  years<sup>25</sup> and  $82 \pm 10$  cm/s for those aged  $54 \pm 10$  years.<sup>26</sup> For the purpose of this study, and given that the median age of the study group was 68 years (range, 58 to 80 years), we arbitrarily considered a PSV value of  $\leq 60$  cm/s as “low.”

The transcranial Doppler breath-holding test was performed as previously described.<sup>6,16,19</sup> In brief, after normal breathing of room air, patients were instructed to hold their breath for 25 seconds after a normal inspiration. A fixed time period of 25 seconds was chosen for breath-holding because this period of breath-hold has been regarded as enough time to raise CO<sub>2</sub> levels to what is needed to expect an increase of MCA flow rates and velocities.<sup>27</sup> All patients in this study were able to hold their breath for 25 seconds.

During the maneuver, the MFV of the MCA was recorded continuously. The MFV immediately after the end of the breath-holding period was registered as the maximal increase of the MFV. The BHI was calculated as the percent increase in MFV recorded by breath-holding divided by seconds of breath-holding (25 seconds) ( $[V_{bh} - V_r/V_r] \times 100 \times s^{-1}$ ). If mean flow velocity in the MCA was not increased during breath-holding, patients were characterized as having “exhausted” vasomotor reactivity.

**Carotid angioplasty and stenting.** CAS was performed under local anesthesia by a team of vascular surgeons in a dedicated vascular operating room with endovascular facilities. In the first 26 cases, a balloon-expandable stent was used (ACS Multilink Ultra, Guidant, Corpora-

**Table II.** Details of the four patients who experienced transient neurologic events\*

Pt	Age/gender	Pre-op status	Neurologic event	Duration
1	69/M	Asymptomatic L ICA stenosis	Headache, disorientation, confusion and abnormal reflex 7 hours post-procedure	8 hours
2	63/F	Symptomatic R ICA stenosis	Numbness and weakness of the contralateral arm immediately post-procedure	6 hours
3	76/M	Asymptomatic R ICA stenosis	Contralateral hemiparesis, hemisensory loss, and abnormal reflexes immediately post-procedure	12 hours
4	67/F	Asymptomatic L ICA stenosis	Headache, dizziness, vomiting, loss of consciousness, urinary incontinence 8 hours post-procedure	Few min

L, Left; R, right; ICA, internal carotid artery.

\*Only patients 2 and 3 had symptoms consistent with a typical transient ischemic attack of a presumed embolic origin.

tion Inc, Santa Clara, Calif). Later in the study, we changed to self-expandable stents and an Acculink nitinol stent (Guidant; Xact, Abbott, Abbott Park, Ill) was implanted in the remaining three patients. No protection devices were used. All patients received dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) for a week before and for at least a year after the procedure.

**Statistical analysis.** Our data did not fulfil the criteria for parametric tests, and therefore, nonparametric tests were used for statistical analysis. The Wilcoxon signed ranks test was used to compare paired data (PSV, EDV, mean pulsatility index, MFV, and BHI) between the preoperative and the two postoperative transcranial Doppler studies. Categorical data were compared using the  $\chi^2$  test, and the Mann-Whitney *U* test was used to compare two independent samples. All calculations were performed using the SPSS 13.0 statistical software (SPSS, Chicago, Ill). Data are expressed as median and interquartile range (IQR). A *P*  $\leq$  .05 was considered statistically significant.

## RESULTS

No postintervention stent occlusions or residual stenoses were detected on duplex scanning during the study period. No patient died  $\leq$ 30 days.

One patient had a contralateral ischemic stroke. This patient had a pre-existing right ICA occlusion and underwent CAS of a symptomatic left ICA stenosis. Immediately after the procedure, he experienced headache and dizziness. A neurologic evaluation revealed homonymous hemianopia and abnormal reflexes. Urgent brain CT scan demonstrated no hemorrhage or ischemic areas. A second CT scan 48 hours later revealed an ischemic region on the contralateral occipital lobe in a region supplied by the right posterior cerebral artery. A review of the preoperative intracranial magnetic resonance angiography showed that both posterior cerebral arteries seemed to be fed by the vertebrobasilar system. Presumably, the stroke was caused by catheter manipulations in the arch and its major branches.

A further four patients presented transient neurologic symptoms (Table II); in only two of these, the episodes were consistent with a typical TIA, presumably of embolic origin. The symptoms were fully resolved within hours of the procedure and none had abnormal findings on the

**Table III.** Patients with low preoperative peak systolic velocity\* and symptomatic versus asymptomatic status

PSV (cm/s)	Symptomatic	Asymptomatic
<40	1	1
40-50	3	3
50-60	2	5

PSV, Peak systolic velocity.

\*Defined as  $\leq$ 60 cm/s.

postoperative CT or MRI scan performed 48 hours and 2 to 4 months later, respectively. The two patients with atypical neurologic events (patient 1 and 4, Table II) had delayed onset of nonhemispheric neurologic symptoms. No sedatives or narcotics were used in these patients. Additionally, 0.5 mg of atropine was administered in both during the procedure, and there were no changes in heart rate or blood pressure.

The patient with the loss of consciousness had no history of seizures before the procedure and presented no similar episodes during the follow-up. Nevertheless, no other specific investigations for seizure disorder (ie, electroencephalogram) were performed. The symptoms in this patient were likely to be due to hyperperfusion syndrome, as determined by a postoperative SPECT examination that demonstrated massive reperfusion of the frontal, temporal and parietal lobes.

An abnormally low PSV before carotid intervention was found in 15 patients in this series, six of whom were symptomatic (Table III). No cerebrovascular complications developed in these 15 patients. The changes in PSV, EDV, MFV, and pulsatility index after CAS for the entire group, the symptomatic, and the asymptomatic patients, are presented collectively in Table IV. The PSV of the ipsilateral MCA and the MFV significantly increased in both postoperative studies compared with the preoperative values. The EDV significantly increased only in the first postoperative study 48 hours postprocedure, but not 2 to 4 months later.

In contrast, no statistically significant differences were noted in the pulsatility index between preoperative and postoperative levels. We then looked for differences in the hemodynamic parameters in the symptomatic and asymp-

**Table IV.** Hemodynamic indicators of the ipsilateral middle cerebral artery at rest in the whole group, the symptomatic and asymptomatic patients

	<i>Before intervention</i>	<i>After 48 hours</i>	<i>After 2-4 months</i>	<i>P*</i>	<i>P†</i>
PSV (cm/sec)					
Whole group	54.5 (47.2-65.5)	61.8 (52.8-82.1)	65 (52-78.6)	<b>.002</b>	<b>.035</b>
Symptomatic	55.6 (47.4-67.5)	57.6 (46.7-75.1)	61.7 (57-74.9)	NS	NS
Asymptomatic	54.5 (48.8-65)	63.4 (51.5-87)	65.9 (51.5-87)	<b>.012</b>	<b>.034</b>
MFV					
Whole group	32 (29-35)	36.9 (28.8-49.1)	38 (30.1-47.4)	<b>.035</b>	<b>.05</b>
Symptomatic	29.6 (28.6-32.3)	33.9 (26.1-47.6)	34.7 (30.7-42.6)	NS	NS
Asymptomatic	33.5 (31.3-35.1)	38.2 (30.7-49.4)	38.7 (27.3-55.1)	.07	NS
EDV (cm/sec)					
Whole group	23 (19.1-26.5)	27.5 (22.3-36.3)	22.2 (20-32)	<b>.042</b>	NS
Symptomatic	23 (17.6-25.9)	27.7 (22.3-36.3)	21 (20.4-19.4)	NS	NS
Asymptomatic	23.2 (20.1-26.3)	27.5 (23.2-35.9)	23.2 (20-27.4)	NS	NS
PI					
Whole group	1.1 (0.8-1.1)	1.1 (0.9-1.2)	1.1 (0.9-1.2)	NS	NS
Symptomatic	1 (0.9-1.1)	1.1 (0.9-1.2)	1.1 (0.8-1.2)	NS	NS
Asymptomatic	1.1 (0.8-1.2)	1.0 (0.8-1.2)	1.1 (1.0-1.1)	NS	NS

PSV, Peak systolic velocity; MFV, mean flow velocity; EDV, end-diastolic velocity; PI, pulsatility index; NS, not significant. Values are expressed as median (IQR). Statistically significant *P* values appear in bold.

\**P* value when comparing preoperative values with the second study (48 hours later).

†*P* value when comparing preoperative values with the third study (after 2 to 4 months).

**Table V.** Hemodynamic indicators of the ipsilateral middle cerebral artery in the whole group, symptomatic and asymptomatic patients, when the breath-holding test is performed

<i>Examination</i>	<i>Indicator</i>	<i>Whole group</i>	<i>Symptomatic</i>	<i>Asymptomatic</i>
Before intervention (1)	MFV	33.5 (30.4-35.5)	28.4 (25.8-40.6)	34.1 (32.6-35.2)
	MFV BHT	30.5 (23.3-44.6)	15.5 (23-44.2)	30.5 (27-43)
	<i>P</i> (MFV-MFV BHT)	NS	NS	NS
	BHI	-0.35 (-0.71-0.55)	-0.25 (-0.58-0.15)	-0.35 (-0.76-0.76)
After 48 hours (2)	MFV	37.1 (29.1-52.3)	31.6 (25-43)	39.3 (33.6-56.3)
	MFV BHT	41.6 (32.8-60.6)	35.1 (26.6-50)	43.5 (36.1-62.1)
	<i>P</i> (MFV-MFV BHT)	<b>0.010</b>	NS	<b>0.025</b>
	BHI	0.38 (0.12-0.61)	0.61 (0.15-0.66)	0.33 (0.12-0.44)
After 2-4 months (3)	MFV	38 (26.9-48)	34.7 (30.1-39.5)	39.9 (25.4-58.5)
	MFV BHT	44.6 (31.5-57)	44.6 (34.1-49.4)	43.9 (28.3-69)
	<i>P</i> (MFV-MFV BHT)	<b>0.008</b>	0.066	<b>0.037</b>
	BHI	0.44 (0.31-0.92)	0.63 (0.44-1.83)	0.37 (0.23-0.49)
	<i>P</i> BHI (1) vs BHI (2)	<b>0.049</b>	0.075	NS
	<i>P</i> BHI (1) vs BHI (3)	<b>0.020</b>	<b>0.046</b>	NS

MFV, Mean flow velocity at rest; BHT, breath-holding test; MFV BHT, mean flow velocity after 25 seconds of breath-holding; BHI, breath-holding index; NS, not significant.

Values are expressed as median (IQR). *P* value in comparing MFV at rest (MFV) and after the breath holding test (MFV BHT) or the BHI at (1) with (2) or (3). Statistically significant *P* values appear in bold.

tomatic groups separately, symptomatic patients did not demonstrate statistically significant changes in any of the four indicators (PSV, MFV, EDV, and pulsatility index), whereas in the asymptomatic group, only PSV increased significantly postintervention, both at 48 hours and at 2 to 4 months.

When the breath-holding test was performed preoperatively, MFV for the entire group did not increase significantly compared with the resting value (Table V), and the median (IQR) BHI was -0.35 (-0.71 to 0.55). In contrast, during the two postoperative studies, better CVR of the ipsilateral MCA was observed. Both at 48 hours and at 2 to 4 months, the MFV after the breath-holding test

increased significantly compared with the resting value, and the median (IQR) BHI was 0.38 (0.12 to 0.61) and 0.44 (0.31 to 0.92), respectively. Both postoperative BHIs also demonstrated a statistically significant improvement compared with the preoperative examination. This amelioration mainly concerned the symptomatic patients, because the BHI in the asymptomatic group remained unchanged in the two postoperative examinations.

The preoperative BHI did not appear to be influenced by symptomatic or asymptomatic status. The median [IQR] BHI was -0.25 (-0.58 to 0.15) in symptomatic vs -0.35 (-0.76 to 0.76) in asymptomatic patients (*P* = 1.0). However, the preoperative BHI was significantly lower in

men at  $-0.52$  ( $-0.76$  to  $0.24$ ) vs  $1.01$  ( $0.31$  to  $1.72$ ) in women ( $P = .027$ ) and in younger patients ( $<65$  years) at  $-0.68$  ( $-0.76$  to  $-0.59$ ) vs  $0.45$  ( $-0.40$  to  $0.95$ ) in older patients ( $P = .036$ ). In contrast, BHI was not influenced by the presence of coronary artery disease ( $P = .442$ ), diabetes mellitus ( $P = .447$ ), smoking ( $P = .492$ ), hypertension ( $P = .687$ ), contralateral ICA occlusion ( $P = .632$ ), or the degree of carotid stenosis ( $P = .521$ ).

Before carotid stenting, 13 patients, six of whom were symptomatic, presented exhausted CVR of the ipsilateral MCA. The BHI in these patients improved from  $-0.68$  ( $-0.79$  to  $-0.50$ ) preoperatively, to  $0.43$  ( $0.2$  to  $0.60$ ) at 48 hours ( $P = .012$ ) and  $0.43$  ( $0.35$  to  $0.58$ ) ( $P = .018$ ) at 2 to 4 months ( $P = .018$ ) postoperatively. Sixteen patients, 7 of whom were symptomatic, had normal CVR before the intervention. The BHI in this group was not affected significantly by intervention; that is, BHI changed from a median (IQR) of  $0.55$  ( $0.10$  to  $1.01$ ) preoperatively to  $0.37$  ( $0.09$  to  $0.58$ ) at 48 hours ( $P = .48$ ), and  $0.52$  ( $0.31$  to  $1.18$ ) at 2 to 4 months ( $P = .67$ ).

Only two and one patients, respectively, demonstrated exhausted CVR in the second and third postoperative transcranial Doppler studies. No evidence of intracranial disease or dissection was found in any of these patients. One of these patients had an asymptomatic carotid stenosis and exhausted CVR that failed to improve after stenting in either of the two postoperative studies. This patient experienced neurologic symptoms after CAS (patient 1 in Table II). A SPECT scan demonstrated lack of perfusion of the ipsilateral frontal lobe that was not present in the preoperative study, a finding in keeping with a cerebrovascular event. The PSV in this patient initially increased from  $70$  cm/s preoperatively to  $146$  cm/s at 48 hours, but eventually decreased to  $46.1$  cm/s at 2 to 4 months. The second patient had a normal CVR in the preoperative transcranial Doppler study and was found to have exhausted CVR in the second study but normal CVR in the third study. This patient experienced no adverse neurologic events, and no satisfactory anatomic explanation could be found for the failure of the CVR to improve.

Regardless, exhausted CVR of the ipsilateral MCA in the preoperative period was associated with an increased incidence of neurologic complications during, or immediately after the procedure (5 of 13 with exhausted CVR vs 0 of 16 with normal CVR,  $P = .006$ ,  $\chi^2$  test).

## DISCUSSION

This study suggests that patients with severe atherosclerotic disease of the carotid bifurcation may demonstrate diminished blood flow in the ipsilateral MCA that is significantly improved after CAS. In addition, the vasomotor reactivity of the MCA (CVR), as estimated by an increase in flow velocity after breath-holding, may be exhausted before intervention but seems to improve as early as 48 hours after intervention in most cases. This amelioration persists for the following 2 to 4 months. This is in keeping with earlier studies that have demonstrated similar results after treating carotid stenosis with endarterectomy,<sup>1,10</sup> or stenting.<sup>28,29</sup>

CVR also varies with age and gender, and presumably, both of these factors have an impact on elasticity and stiffness of the cerebral arterial tree that results in differences in CVR.

Regional cerebral blood flow (rCBF) is proportional to blood flow velocity in the MCA.<sup>19,30</sup> When blood flow velocity is increased, rCBF is also increased. This is very important in patients with carotid artery disease who usually present with reduced rCBF, because compromised rCBF plays an important role in causing ipsilateral ischemic events.<sup>21,31</sup> By increasing flow velocity, and therefore, rCBF, carotid stenting may additionally prevent ischemic cerebral events, as it does by stabilizing the carotid plaque and avoiding thromboembolism, the main cause of ischemic strokes.

Vasomotor reactivity of the MCA has been suggested as a predictive factor of stroke and TIAs. Exhausted reactivity has been found to be an independent predictor of ipsilateral ischemic events in both symptomatic and asymptomatic patients.<sup>3,18,25,32-35</sup> This characterizes a state of chronic cerebral vasodilatation, caused by reduction in cerebral perfusion pressure. In our study, almost half the patients presented with exhausted reactivity before intervention, a percentage which significantly decreased in the postoperative studies, particularly the one 2 to 4 months after stenting. The presence of an exhausted vasomotor reactivity was also demonstrated by the median preoperative BHI on the whole, and of both the symptomatic and asymptomatic patients, being remarkably low. The index also appears to improve significantly post-stenting in the entire group and in the symptomatic patients.

Hypoperfusion may lead to impaired clearance of emboli and, therefore, an increased risk of embolization resulting in clinical stroke.<sup>31,35</sup> Embolization and reduced ability for vasodilatation are two mechanisms that do not contradict each other. In fact, there is evidence that in areas of the brain where capacity for further capillary vasodilatation is limited, microemboli are more likely to become symptomatic.<sup>11,31,35</sup>

The second and important conclusion of our study, that neurologic complications after stenting were more frequent in patients with exhausted reactivity of the MCA, can perhaps be explained by this mechanism. Microemboli, debris, and thrombus created when carotid plaque is fractured by the stent that cause distal embolization to the cerebral parenchyma appear to be more likely to cause neurologic symptoms in patients with reduced cerebral vascular reactivity. In these patients, the functional capacity of the vascular bed is exhausted and no further vasodilatation can be performed.

If this hypothesis of impaired washout of emboli being a relevant mechanism of brain infarction in patients with cerebral hypoperfusion is valid, one could argue that if emboli occur after stenting, the status of the pretreatment hemodynamics seems less relevant than the circulation at the time the emboli are in the distal vessels. As a result, it would seem more reasonable to consider the post-treatment rather than the pretreatment cerebral hemodynamics. However, only two of our patients demonstrated exhausted CVR in

the immediate poststenting transcranial Doppler examination, and stratification determined by postintervention cerebral hemodynamics would therefore not have been possible in this small study.

The study results must be considered in the context of the specifics of the study and its limitations. Most of the patients in this series received balloon-expandable stents because that was the standard practice of this unit at the time. Later in the study, like most other European and North American centers, we moved away from balloon-expandable stents in favor of self-expandable nitinol ones. Similarly, no protection devices had been used in any of the 29 patients. Again, this was because our unit performed unprotected CAS during the study period. Nowadays, however, we undertake CAS using self-expandable stents and cerebral protection routinely.

It is possible that the use of balloon-expandable stents without cerebral protection has a bearing on the results in this series that may have influenced both the neurologic morbidity and the transcranial Doppler findings. A similar study recruiting patients undergoing CAS under cerebral protection would be extremely interesting to undertake. Nevertheless, prospective comparisons of the hemodynamic parameters between patients undergoing CAS with and without the use of cerebral protection would likely be unethical nowadays.

Finally, standard brain MRI rather than diffusion-weighted imaging was used to assess patients who had neurologic symptoms after CAS. The latter is a more sensitive technique to detect embolic infarcts than the former, and it is therefore possible that small embolic infarcts may have been missed.

## CONCLUSION

Transcranial Doppler and the breath-holding test offers a reliable, relatively inexpensive, noninvasive tool for the assessment of the cerebral vasomotor capacity, and, therefore, potentially recognizing patients at increased risk for ischemic cerebrovascular events. It does not involve radiation and is free from complications resulting from the use of vasodilating agents, such as the acetazolamide and CO<sub>2</sub>. Although the present study suffers from small numbers, it demonstrates clearly that carotid stenting can improve MCA flow velocity and vasomotor reactivity of the ipsilateral MCA, possibly inducing better cerebral irrigation. Carotid stenting also results in better autoregulation of the cerebral perfusion and, possibly, helps to prevent low flow ischemic events. Thus, assessment by transcranial Doppler and the breath-holding test potentially can help identify patients with exhausted reactivity who may be at high risk for neurologic complications during CAS.

## AUTHOR CONTRIBUTIONS

Conception and design: GS, CL, CS, AD, KK, TG  
Analysis and interpretation: GS, CK, CL, CS, AD, KK, TG  
Data collection: GS, CK, CL, AD, KK  
Writing the article: GS, CK, TG

Critical revision of the article: GS, CK, CL, CS, AD, KK, TG

Final approval of the article: GS, CK, CL, CS, AD, KK, TG

Statistical analysis: GS, CK

Obtained funding: CL, AD, KK, TG

Overall responsibility: GS

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## INVITED COMMENTARY

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Therapeutic decisions regarding coronary or peripheral revascularization are often based on the results of provocative stress tests used to assess vascular reserves in those beds. Unfortunately, treatment of carotid artery disease has been focused mostly on the degree of stenosis and symptomatic status without any qualifications related to physiologic parameters. This may relate to the pervasive misconception that "stress tests" do not exist for the evaluation of cerebrovascular occlusive disease and that most, if not all, events are embolic. The investigation of such tests increases our understanding of the hemodynamic correlates of vascular insufficiency of the brain and may refine our selection criteria of patients for revascularization.

As acknowledged by the authors, this study has some shortcomings. The number of patients in the study is quite small, and the techniques of carotid artery stenting (CAS) used are not completely concordant with current practice. In addition, baseline transcranial Doppler measurements without the "challenge test" were of little significance in differentiating patients, and the noted improvement after CAS was expected, as it is after carotid endarterectomy or any other method of revascularization.

The article is most interesting, however, in reminding us that many provocative tests to determine cerebrovascular reserves do exist and can be as simple as a 25-second breath hold while flow is observed in the ipsilateral middle cerebral artery. The normal

response to provocative tests is to have minimal change or an increase in flow, whereas patients who exhibit a significant decrease in velocities have abnormally poor reserves and collateral perfusion. Most patients with decreased reserves responded appropriately to CAS treatment in this series by correcting their abnormality. More notably, this investigation points to cerebrovascular reserves as an important predictor of neurologic complications after CAS, because all five patients with complications had poor collateral perfusion noted on their preoperative breath hold test.

Poor reserves have been associated with a significant increase in stroke risk in natural history studies,<sup>1</sup> and together with plaque characteristics these may one day serve to better select patients for the type of treatment and to predict complications, as noted here. Other tests, such as stable xenon computed tomographic imaging with Diamox challenge, can provide cerebral perfusion maps pinpointing areas at risk. It would be interesting to see, however, if these valuable "cerebral stress tests" will ever become commonplace in our evaluation of patients with carotid disease.

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