Cerebrovascular Carbon Dioxide Reactivity in Carotid Artery Disease

Relation to Intraoperative Cerebral Monitoring Results in 100 Carotid Endarterectomies

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Background: In patients with carotid artery disease, poor intracerebral collateralization is reflected by impaired cerebrovascular reactivity to carbon dioxide inhalation, which will improve after endarterectomy. The relationship between preoperative reactivity to carbon dioxide using transcranial Doppler sonography (TCD) and intraoperative changes of somatosensory evoked potentials (SEP) and TCD parameters were investigated.

Methods: In 94 patients, preoperative carbon dioxide reactivity was examined and defined impaired if mean blood flow velocity in the middle cerebral artery (Vm-MCA) increased less than 1.5%/mmHg during carbon dioxide challenge. Patients then underwent 100 carotid operations under general anesthesia with both SEP and TCD monitoring. Shunts were placed if SEP amplitude decreased to less than 50% of control or central conduction time increased by 20% after clamping (critical SEP changes). TCD changes were defined as critical in case of a postclamping/preclamping Vm-MCA ratio ≤ 0.4. The incidence of critical SEP and TCD changes was compared to preoperative carbon dioxide testing using Fisher's exact test with \( P < 0.05 \) considered significant. Postoperatively, neurologic state and carbon dioxide responsiveness were reexamined.

Results: Twelve patients showed impaired preoperative carbon dioxide reactivity on the side of operation, which improved markedly after surgery. The incidence of critical SEP changes in these cases (8.3%) was not significantly different from that in the remaining patients (14.8%). Critical SEP changes were significantly correlated with critical TCD changes (\( P < 0.0001 \)).

Conclusions: Patients with poor carbon dioxide reactivity (preoperative TCD testing) did not have an increased risk of cerebral ischemia during carotid surgery, as assessed by intraoperative SEP recording. (Key words: Monitoring; somatosensory evoked potentials; transcranial Doppler sonography. Surgery, vascular: carotid endarterectomy.)

CAROTID endarterectomy is an effective surgical approach to reduce the incidence of ipsilateral strokes in patients with symptomatic carotid stenoses > 70%. Although embolic events predominate in the pathogenesis of transient ischemic attacks (TIA) and minor or major strokes, in a subgroup of patients, hemodynamic factors (poststenotic perfusion pressure decrease, insufficient collateral flow) are, at least partially, responsible for the development of clinical symptoms due to carotid artery disease.

In patients with internal carotid artery stenoses or occlusions, cerebral perfusion changes after carbon dioxide or acetazolamide (Diamox) challenge have been studied extensively using different techniques. Results from these investigations suggest that patients with diminished cerebrovascular reactivity to carbon dioxide or acetazolamide have an increased risk of experiencing clinical symptoms. However, intraoperative data establishing a relationship between cerebrovascular carbon dioxide reactivity and the incidence of postclamping cerebral ischemia are lacking.

Accordingly, it was the aim of the current study to investigate, in patients scheduled for carotid surgery, the relation between preoperative carbon dioxide reactivity and the results of intraoperative cerebral monitoring using transcranial Doppler sonography (TCD) and median nerve somatosensory evoked potentials (SEP).

Methods and Materials

With approval of the local Ethics Committee and after obtaining written informed consent, 94 patients (age 63 ± 7 yr, mean ± SD) scheduled for a total of 100...
carotid operations underwent pre-, intra-, and post-operative investigations. The majority of patients had a history of transient ischemic attacks (TIA, n = 36), completed stroke (n = 32), or prolonged reversible neurologic deficit (PRIND, n = 9). Seven patients were asymptomatic, and 10 subjects had suffered from neurologic symptoms (e.g., vertigo), which could not definitively be related to diminished internal carotid artery (ICA) blood flow. Based on the results of preoperative angiography, high-grade ipsilateral ICA stenosis (70–99%) was found predominately (86% of patients) with contralateral high-grade ICA stenosis in 15 patients, and contralateral ICA occlusion in another 10 cases. When admitted to carotid surgery, all patients were stable regarding neurologic state.

**Preoperative Measurements**

The day before surgery, all patients were tested for cerebrovascular carbon dioxide reactivity using transcranial Doppler sonography (TCD) with a flat fixable ultrasound probe (TC2-64B, EME, Überlingen, Germany). Systolic, diastolic, and mean blood flow velocity of the middle cerebral artery (Vs-MCA, Vd-MCA, Vm-MCA) were recorded, and a pulsatility index (PI) of (Vs-MCA-Vd-MCA)/Vm-MCA was derived with patients spontaneously breathing an oxygen/air mixture (FiO2 = 0.4) via a mouthpiece attached to an infrared carbon dioxide analyzer (Capnograph, Dräger, Lübeck, Germany) under normocapnic, hypocapnic, and hypercapnic conditions. Hypercapnia was achieved by adding 5% CO2 to the oxygen/air mixture, and patients were asked to hyperventilate to produce hypocapnia. Each period lasted for at least 3 min to allow TCD parameters to stabilize. The carbon dioxide response was assessed for the left MCA first and the right MCA subsequently. Heart rate, noninvasive arterial blood pressure, and end-tidal carbon dioxide partial pressure (pCO2,et) were recorded, simultaneously, at the end of each period.

Cerebrovascular carbon dioxide reactivity (%Δ Vm-MCA/mmHg) was assessed separately for each side (left/right) in the individual patient using linear regression analyses (Vm-MCA vs. pCO2,et). Carbon dioxide reactivity was regarded impaired if Vm-MCA changed less than 1.5%/mmHg.

**Intraoperative Data**

Carotid surgery was performed predominantly under general anesthesia with halothane (n = 79) and 50–66% N2O in oxygen. In 21 cases, isoflurane or fentanyl/midazolam was administered. Moderate hyperventilation (mean paco2 = 35 mmHg) was controlled by continuous pCO2,et monitoring and intermittent arterial blood gas analyses.

Blood flow velocities of the MCA ipsilateral to the side of operation and somatosensory evoked potentials after contralateral median nerve stimulation (SEP) were recorded before and after carotid clamping, at short intervals during clamping, and after declamping. Post-clamping TCD results were defined critical if the ratio Vm-MCA within 1 min after clamping/Vm-MCA immediately before clamping was equal to or less than 0.4. Based on our previous investigations, cerebral ischemia was diagnosed by SEP criteria (N20P25 amplitude < 50% and/or central conduction time > 20% compared to the data obtained immediately before carotid clamping). In case of such SEP deteriorations after clamping, the surgeon was asked to insert a temporary intraluminal shunt.

**Postoperative Measurements**

All patients had a brief neurologic examination immediately after recovery from anesthesia. Cerebrovascular carbon dioxide reactivity was reassessed on the fourth postoperative day (mean, range 3–9), whenever possible. Patients with new postoperative neurologic abnormalities underwent a more detailed neurological examination and further diagnostic procedures (e.g., cranial computed tomography).

**Statistical Analysis**

Cerebrovascular carbon dioxide reactivity was assessed in each patient and for each side (left/right) separately, using four-data-point linear regression analyses. If probability analysis of any regression failed to show a linear relation (P > 0.30), these data were removed from further statistical analysis. Pre- and postoperative TCD data were compared by Student's t test. The relationships between preoperative carbon dioxide reactivity and intraoperative TCD and SEP results were investigated by Fisher's exact test. A P < 0.05 was considered significant.

**Results**

Before carotid surgery, an impaired carbon dioxide reactivity (Vm-MCA change < 1.5%/mmHg) was found ipsilateral to the side of operation in 12 patients. Analysis of four-data-point regression lines in these patients showed no relationship between pCO2,et and Vm-MCA.
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Fig. 1. Carbon dioxide reactivity as assessed by TCD (%Δ Vm-MCA/mmHg) in 93 cases before carotid surgery compared to an age-matched group of 19 people without stenoses of the brain-supplying arteries. Seven patients (n = 3 with unilateral ICA stenosis, n = 2 with bilateral ICA stenoses, n = 2 with contralateral ICA occlusion) were excluded (probability of regression line analysis P > 0.30). Carbon dioxide reactivity was regarded impaired if Vm-MCA changes less than 1.5%/mmHg during carbon dioxide testing (broken line). Note that carbon dioxide reactivity varies considerably even in subjects without carotid disease, and two carotid patients showed paradox carbon dioxide reactivity.

Except for one patient, all had ICA stenoses > 80% and/or contralateral occlusions. We were unable to detect any obvious relationship between patients' neurologic history (asymptomatic, TIA, PRIND, completed strokes, others) and altered carbon dioxide reactivity. The relationship of our carbon dioxide reactivity findings to carotid anatomy (without stenosis, ipsilateral ICA stenosis, bilateral stenoses, contralateral occlusion) is given in figure 1.

Intraoperatively, 14 cases presented critical SEP changes indicating cerebral ischemia. These changes were predominately noted within a few minutes after carotid clamping (n = 13), whereas in one patient, critical SEP changes occurred during common carotid artery preparation but before clamping. Except for two cases (SEP changes before clamping, impossibility of shunt placement), these patients received an intraluminal shunt immediately. Another patient in whom a shunt was inserted was excluded from analysis because of a technical defect of the SEP machine. The remaining 85 cases without SEP changes were treated without temporary shunting. Figure 2 gives a scattergram of preoperative carbon dioxide reactivity versus post-preclamping Vm-MCA ratio and intraoperative SEP findings.

Fig. 2. Preoperative carbon dioxide reactivity compared to intraoperative TCD results with cases presenting critical SEP changes marked (X). TCD changes were defined critical in case of post/preclamping Vm-MCA ratio ≤ 0.4 (broken vertical line). Carbon dioxide reactivity cut-off point (1.5%/mmHg) is indicated by the horizontal broken line. Eleven patients were excluded because of preoperative carbon dioxide testing results (n = 7), missing TCD data postclamping (n = 2), technical defect of the SEP machine (n = 1), and critical SEP changes before ICA clamping (n = 1).

Using Fisher's exact test, intraoperative TCD data showed a strong relationship to SEP findings (P < 0.0001, table 1). However, there were discrepancies between SEP and TCD results in a considerable number of cases. Referred to critical SEP deteriorations, TCD presented 3 false-negative and 10 false-positive critical changes. Blood flow in the MCA abruptly stopped (Vm-MCA = 0 cm/s) after carotid clamping in seven cases. Of these, five had critical SEP deteriorations, which thereafter resolved after temporary shunting, whereas two patients showed unaltered SEP (no

Table 1. Critical SEP Changes (N20P25 Amplitude Reduction >50% and/or Central Conduction Time Prolongation >20%) Versus Critical TCD Findings (Post/Preclamping Vm/MCA Ratio ≤0.4) in 97 Cases

<table>
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<th>Critical SEP</th>
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<tr>
<td>Total</td>
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<td>14</td>
<td>83</td>
<td>97</td>
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Three patients were excluded because of missing TCD data (n = 2) or technical defect of the SEP machine (n = 1). Statistical analysis reveals a significant relation between SEP and TCD changes (χ²-square = 31.3; Fisher's exact test, P < 0.0001).
shunt). Related to the incidence of critical SEP findings, sensitivity of TCD was 78.6% and specificity 88.0%.

New postoperative neurologic deficits (n = 4) were all preceded by intraoperative critical SEP and/or TCD findings, but none of these patients had an impaired carbon dioxide reactivity preoperatively. Deficits were due to MCA territory infarctions confirmed by computed tomography in two patients, one of whom died. In both patients, TCD revealed high-intensity signals compatible with massive embolization of atheromatous particles (before ICA clamping n = 1, immediately after declamping n = 1). Transitory deficits in one patient resolved within 3 h. In another case, new postoperative deficits lasted for 6 days, but computed tomography did not show any stroke. Another patient with preexisting deficits and preoperative carbon dioxide reactivity < 1.5%/mmHg had noncritical intraoperative SEP/TCD changes but suffered from residual symptoms deteriorations, which completely resolved within 3 days.

Preoperative cerebrovascular carbon dioxide reactivity did not show any correlation to critical intraoperative SEP or TCD changes (tables 2 and 3). The incidence of critical SEP changes registered in 1 of 12 patients (8.3%) with impaired carbon dioxide reactivity was not significantly different from patients with sufficient carbon dioxide reactivity (12/81; 14.8%). Twenty-one cases had critical TCD changes intraoperatively, out of which only four were suspected to have impaired carbon dioxide reactivity previously. Postoperatively, carbon dioxide reactivity increased significantly (t test, P < 0.05) in all 12 patients showing preoperative impairment and presented little changes in the remaining cases.

Table 2. Critical SEP Changes (N20P25 Amplitude Reduction >50% and/or Central Conduction Time Prolongation >20%) Could Not Be Related to Preoperative CO₂ Reactivity (n = 93; Fisher’s Exact Test, P > 0.05)

<table>
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<th>Critical SEP</th>
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<th>Total</th>
</tr>
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<tbody>
<tr>
<td>CO₂ activity</td>
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<td>11</td>
</tr>
<tr>
<td></td>
<td>&gt;1.5%/mmHg</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>80</td>
<td>93</td>
</tr>
</tbody>
</table>

Seven cases were excluded because of missing CO₂ reactivity data (regression line probability analysis, P > 0.30).

Discussion

Cerebrovascular carbon dioxide reactivity is part of a complex system to control cerebral perfusion. Within the range of physiologic paco₂ alterations (35–45 mmHg), cerebral blood flow (CBF) will normally change approximately 3–4%/mmHg. Mechanism and pattern of cerebrovascular carbon dioxide reactivity have been studied decades ago. In recent years, scientific interest focussed on this topic again, with special regard to anesthetic induced changes and to its clinical application in severe head trauma, subarachnoid hemorrhage, and cerebrovascular disease. In contrast to the “gold standard” of measuring CBF by analyzing the washout of inert or radioactive tracers, transcranial Doppler sonography (TCD) is increasingly used for clinical monitoring purposes as this method is noninvasive and presents on-line data. Moreover, its rapid responsiveness to changes in cerebral blood flow is a substantial advantage.

The current understanding of carbon dioxide reactivity changes in carotid artery disease suggests that high-grade stenoses or occlusions of the brain-supplying arteries will decrease CBF unless blood supply is maintained by an intact circle of Willis and/or extra-intracranial collaterals. In case of poor collateralization, dilatation of cerebral arterioles in the ICA territory in response to post-stenotic perfusion pressure drop may provide adequate regional CBF in the resting state, but the CBF response to stimuli such as carbon dioxide inhalation or the injection of acetazolamide may be diminished, absent, or even paradox (CBF increase with decreasing pCO₂). With cerebral resistance vessels already dilated, the autoregulatory response of these patients may be severely impaired. To compensate for an insufficient response, cerebral oxygen extraction fraction (OEF) may be increased as has been shown in positron emission tomography (PET) studies.

Table 3. Critical TCD Changes (Post/Preclamping Vm/MCA ratio <0.4) Were Not Related to Preoperative CO₂ Reactivity (n = 91; Fisher’s Exact Test, P > 0.05)

<table>
<thead>
<tr>
<th>Critical TCD</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ activity</td>
<td>≤1.5%/mmHg</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>&gt;1.5%/mmHg</td>
<td>17</td>
<td>62</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>70</td>
<td>91</td>
</tr>
</tbody>
</table>

Nine patients were excluded because of missing TCD (n = 2) or bad CO₂ reactivity data (n = 7).
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showing a paradox cerebral blood flow reactivity to acetazolamide challenge are more likely to depend on leptomeningeal anastomoses than on other extra-intracranial collaterals (contralateral carotid artery, circle of Willis, ophthalmic artery). ¹⁰

Unequivocally, there exists a subgroup of patients with carotid artery disease presenting neurologic symptoms primarily due to such a cerebral hemodynamic risk constellation. ²⁻⁴ However, this subgroup has not been well defined yet. Ringelstein ¹⁷ found an incidence of 1–2% in stroke patients. This may underestimate the true number, because in the series of Ruff et al., ⁵ 5.3% of patients suffering from TIs had symptoms preceded by hypotension. The incidence increased significantly to 44% in hypertensive patients with carotid artery stenoses. In 12 of 100 carotid operations in the current study, preoperative cerebrovascular reactivity in carbon dioxide was regarded impaired (<1.5%/mmHg). These numbers are comparable to the reports of Schroeder ³ and Gibbs, ⁴ who suggested a 10–20% incidence of carotid patients with cerebral hemodynamic risks (chronic hemodynamic failure due to markedly reduced perfusion pressure, delayed ischemic events ipsilateral to an occluded ICA).

It is well known that patients with contralateral ICA occlusion have a greater risk of EEG changes after clamping than patients with a patent or stenotic contralateral ICA. However, the need for temporary shunting is unpredictable by angiographic or clinical criteria. ²⁷ Assessment of cerebrovascular carbon dioxide reactivity gives a more dynamic look at cerebral hemodynamics and, therefore, may be helpful in identifying patients at risk for cerebral ischemia after ICA clamping. Our data support previous studies suggesting that cerebrovascular carbon dioxide reactivity is compromised especially in patients with high-grade stenoses or occlusions of the internal carotid artery (ICA), completed strokes, and permanent neurologic deficits. ⁷ Patients with carotid disease who present with ischemic symptoms show a significant correlation between clinical symptoms and a reduced carbon dioxide reactivity. ¹₆ In case of an occluded ICA, patients with an exhausted carbon dioxide reactivity predominantly present hemodynamic lesions in cranial computed tomography (CT) ⁹ and are at greater risk of ipsilateral ischemic events during follow-up than patients with sufficient reactivity. ¹₀ A diminished cerebrovascular response to carbon dioxide inhalation will significantly improve after carotid endarterectomy, ¹₆ ²₈ which also could be demonstrated in our study. One might suspect, therefore, that patients with impaired carbon dioxide reactivity undergoing carotid surgery may be the ones predominantly to suffer from cerebral ischemia after clamping. However, because intraoperative data are lacking in previous carbon dioxide reactivity studies, the current investigation is the first report on this special point of interest. According to our data, patients with compromised carbon dioxide reactivity, preoperatively, do not have an increased risk of cerebral ischemia after carotid clamping, when compared to subjects with unaltered carbon dioxide reactivity.

Some methodologic aspects of this study have to be discussed. The ability of TCD to assess cerebrovascular reactivity to carbon dioxide inhalation has been validated by CBF measuring techniques using radioactive tracers. ⁵ In 19 subjects without stenoses of the extracranial arteries as proven by ultrasonography and age-matched to our carotid patients, we found a mean 3.2%/mmHg carbon dioxide reactivity, which is comparable to the results of other investigators using TCD in awake subjects without cerebrovascular diseases. ⁹ It must be noted that carbon dioxide reactivity shows a wide scatter (fig. 1), which is in accordance with previous studies using TCD ¹⁶ or CBF methods. ⁵ This may represent considerable variations in cerebral collateral capacity but makes individual interpretation difficult. In addition, our approach to describe carbon dioxide reactivity by using four-data-point regression analysis may not be adequate in case of low carbon dioxide reactivity (n = 12 of the present study). Here, the carbon dioxide response was most likely shifted to the left, ¹⁹ and as a consequence, probability analysis failed to show a linear relation between PCO₂ and Vm-MCA (P > 0.30) in 7 of 12 patients.

Another point of criticism may be our definition of cerebral ischemia. In the current study, we used somatosensory evoked potentials after median nerve stimulation (SEP) to determine the onset of cerebral ischemia. There is consensus in the literature that SEP monitoring is both highly sensitive and specific in detecting cerebral ischemia during carotid surgery. ²¹ ³₀ ³₁ False-positive results (intraoperative SEP deteriorations without neurologic deficit after emergence from anesthesia) may be seen in a number of cases, whereas false-negative findings (new postoperative neurologic deficit despite unchanged SEP) have been reported in one study only. ⁵２ SEP criteria to precisely detect cerebral ischemia during carotid surgery are still under debate. The complete loss of cortical SEP (electrical silence),

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as proposed by Schweiger et al.,31 is unequivocally a highly specific criterion, but our group21 and Lam et al.30 found it less sensitive. In an attempt to achieve 100% sensitivity, we chose to define cerebral ischemia using the criteria N20P25 amplitude reduction > 50% of control or central conduction time prolongation > 20%, compared to the values immediately before carotid clamping.

There are numerous reports on TCD monitoring during carotid surgery with only few studies focusing on the relationship between MCA flow velocity changes and cerebral blood flow or cerebral function (EEG, SEP, respectively). Halsey et al.33 found a weak correlation (r = 0.52) between MCA blood flow velocity and rCBF during carotid surgery in 31 patients. The correlation was stronger (r = 0.66) in case of rCBF < 20 ml·100 g⁻¹·min⁻¹. After clamping, TCD waveforms disappeared (V-MCA = 0 cm/s) in four patients with accompanying ipsilateral EEG suppression and rCBF ranging between 6 and 9 ml·100 g⁻¹·min⁻¹. As rCBF and MCA blood flow velocity reflect perfusion in different regions of the brain (cortical vs. basal), it has been suggested that TCD may better demonstrate hemodynamics in the lenticulostriate arteries territory, and one method should not invalidate the other. This view is supported by our SEP findings in seven patients with complete absence of MCA flow velocity after ICA clamping. In five cases, SEP showed critical changes thereafter. However, SEP were unaffected in another two patients, and it may be speculated that leptomeningeal anastomoses maintained sufficient cortical blood supply undetectable by TCD.

Similar to previous findings of our group,34 the current study demonstrates a close relationship (P < 0.0001) between cerebral function (as reflected by SEP) and TCD changes (table 1), but these results must be interpreted with care. Regarding critical SEP alterations after carotid clamping, TCD was true-positive (post/preclamping Vm-MCA ratio ≤ 0.4) in 11 cases but revealed 10 false-negative. In three patients, cerebral ischemia as assessed by SEP was not reflected by TCD (false-negatives). Thus, sensitivity of critical TCD changes was only 78.6%, and specificity approached 88.0%.

A decreased or even absent cerebrovascular response to carbon dioxide inhalation, preoperatively, did not result in an increased incidence of critical SEP changes in the intraoperative course. The underlying cause cannot be extracted from our data. Although speculative, our findings give rise to the assumption that a highly stenosed ICA does not significantly contribute to CBF even in the presence of poor collateralization reflected by carbon dioxide reactivity < 1.5%/mmHg. In most of our patients, clamping of the ICA did not affect SEP parameters though blood flow velocity in the ipsilateral MCA decreased to a considerable extent. Thus, preoperative carbon dioxide reactivity assessment by TCD does not seem a reliable method to determine the risk of carotid cross-clamping of patients with carotid disease. Further studies using CBF measurements and/or neuroradiologic methods are needed to confirm our results.

In conclusion, our data suggest that an impaired cerebrovascular response to carbon dioxide inhalation in the presence of carotid artery disease is not a risk factor for the development of cerebral ischemia after carotid artery clamping.

References

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