Patterns of Cortical Oxygen Saturation Changes During CO$_2$ Reactivity Testing in the Vicinity of Cerebral Arteriovenous Malformations

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Background and Purpose—The aim of this study was to test the hypothesis that patterns of cerebrovascular reactivity (CVR) in the vicinity of cerebral arteriovenous malformations (AVMs) before and after resection are not specific for this disease.

Methods—With a microspectrophotometer, cortical oxygen saturation ($S_O^2$) was measured under steady-state conditions (Paco$_2$, 33 mm Hg) before and after removal of 22 AVMs and in 30 control subjects before and after transsylvian amygdalohippocampectomy. Intraoperative vasoreactivity tests were performed by induced changes of end-tidal CO$_2$ (25, 45, and 25 mm Hg) with simultaneous recording of local $S_O^2$ in all patients. CVR patterns were established by linear regression analysis ($P<0.05$) to define parallel (positive) versus inverse (negative) behavior, and reactivity indexes were calculated to define their degree.

Results—Cortical oxygenation under steady-state conditions increased significantly ($P<0.05$) from preoperative to postoperative levels equally in both groups (preoperative AVM, 54.8±10.4%$S_O^2$; postoperative AVM, 73.1±10.1%$S_O^2$; preoperative control, 52.7±9.1%$S_O^2$; postoperative control, 73.6±8.9%$S_O^2$). The rate of inverse CVR patterns increased significantly ($P<0.05$) from before to after resection without showing statistically significant differences between groups.

Conclusions—Local CVR patterns in presumably normal human cortex of control subjects are heterogeneous, including inverse behavior, and are similar to those of AVM patients before surgery. After surgery, cortical hyperemia is present in both groups, and a significant increase in inverse reactivity patterns interpreted as microvascular steal is noted. An AVM-specific CVR pattern could not convincingly be proved. (Stroke. 2003;34:938-944.)

Key Words: cerebral arteriovenous malformations • cerebrovascular circulation • oxygen

The literature on the topic implies that specific patterns for cerebrovascular reactivity (CVR) exist in the presence of cerebral arteriovenous malformations (AVMs) and after their resection. Some authors even speculate that these patterns might be predictive of the occurrence of neurological deficits or the so-called postoperative hyperperfusion injury syndrome.1–6 “CVR overshoot” and impaired reactivity have been noted and were rather arbitrarily interpreted as being AVM specific and/or predictive.1–3 The results of other studies, however, speak for a uniformly preserved vasoreactivity in the brain surrounding AVMs before and after their obliteration.7–9 Thus, the question remains as to whether CVR patterns in the presence of AVM are unique to this disease.

Recently, it was shown that spectroscopic techniques are suitable for measuring the responses of Hbo$_2$ during induced alterations of CO$_2$ for the assessment of CVR in a clinical setting.10,11 We adopted this algorithm for intraoperative studies in AVM patients and control subjects by using a previously described experimental method of high-resolution remission spectrophotometry to answer the above question.

Subjects and Methods

This study was approved by the local ethics committee (protocol 121/96). All patients gave informed consent for participation.

Measurements of Intracapillary Oxygen Saturation

Values of intracapillary $S_O^2$ were measured with the Erlangen Microlightguide Spectrophotometer (EMPHO II, Bodenseewerk Geräteotechnik GmbH, BGT), which was introduced in 1989.12 It was designed for fast, diffuse remission spectrophotometry by flexible micro light guides in small tissue volumes of moving organs in situ. Light in the visible domain illuminates tissue via the illuminating fiber, and backscattered light is transmitted via 6 detecting fibers (Ø, 70 µm) arranged in a hexagonal pattern around the illuminating fiber to a rotating bandpass interference filter disk. This serves as a monochromating unit in the spectral range of 502 to 628 nm in 2-nm steps. Spectra of 64 wavelengths per rotation are transmitted to a photomultiplier, an AD converter, and a computer, in which 1 $S_O^2$ value per spectrum (1 single raw data point) is calculated by algorithms described elsewhere.12 Under unchanged O$_2$ consumption, $S_O^2$ changes reflect changes in regional cerebral blood volume. These are linearly correlated with regional cerebral blood flow (rCBF) changes, and the obtained $S_O^2$ values indicate tissue oxygen-
ation and nutritive capillary flow. The high temporal (100 spectra/s) and spatial (75 × 75 × 250 μm) resolution permits a scanning procedure of superficial cortical capillaries by moving the light guide above the brain.

**Study Groups and Protocol**

Twenty-two patients (9 female, 13 male; mean age, 35 years; range, 11 to 64 years; median clinical assessment according to the American Society of Anesthesiologists (ASA score), 2; range, 1 to 3) who underwent elective removal of a supratentorial AVM (Spetzler/Martin grades: I, n=5; II, n=7; III, n=7; IV, n=3) were included in the study.

SO₂ distributions were measured by scanning 31 cortical areas (~5 × 5 mm²) located ≥2 cm from the AVM nidus before and after resection. All areas were numbered and photographed for postoperative probe relocation. Approximately 700 SO₂ values per area and measurement were obtained to assess cortical oxygenation under steady-state moderate hypocapnia (PaCO₂, 33 mm Hg).

After each steady-state assessment before and after AVM resection, behavior of SO₂ after induced changes in CO₂ was tested by modification of ventilation parameters within a range of 25 to 45 mm Hg end-tidal CO₂ (etCO₂) and vice versa with the light guide probe held steady on the cortical areas. The observed behavior was interpreted as a measure of local CVR.

Thirty patients (15 female, 15 male; mean age, 35.5 years; range, 16 to 67 years; median ASA score, 2; range, 1 to 3) with chronic seizure disorder resulting from Ammon’s horn sclerosis were included as control subjects. None had evidence of intracranial cerebrovascular or neoplastic disease. All underwent microsurgical transsylvian selective amygdalohippocampectomy (AH) in which self-retracting spatula are applied on the frontal and temporal opercula to gain access to the inferior temporal horn.

With a protocol identical to that used for the AVM group, steady-state cortical oxygenation was assessed on frontal and temporal opercula ≥2 cm distant from the sylvian fissure before and after dissection (after spatula release). Preoperative and postoperative vasoreactivity was tested on 30 areas as described above.

All patients were operated on under total intravenous anesthesia: 1.5 mg/kg propofol (maintenance dosage, 5 to 10 mg · kg⁻¹ · h⁻¹), 15 μg/kg alfentanil (maintenance dosage, 0.1 to 0.2 mg · kg⁻¹ · h⁻¹), and 0.1 mg/kg vecuronium (maintenance dosage, 30 to 60 μg · kg⁻¹ · h⁻¹) under inhalation of O₂ and N₂O at a ratio of 40:60. Mean arterial blood pressure was monitored continuously via the radial artery. Arterial (PaO₂, PaCO₂, pH) and venous blood (hematocrit) were taken at the times of SO₂ measurements.

**Data Analysis**

SO₂ values obtained under steady-state hypocapnic conditions were calculated as means (%SO₂) per patient and pooled according to

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**Example of CO₂ Reactivity Test after Transsylvian Amygdalohippocampectomy**

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**Figure 1.** Example of inverse CVR interpreted as microvascular steal in 1 patient in the control group (top). Illustrated is the inverse behavior of SO₂ on etCO₂ during vasodilatation and vasoconstriction. Linear regression analysis was performed for these 2 parts of the test separately (bottom). From the sign of the slopes, the behavior was categorized as parallel (+) or inverse (−). Slope of the linear regressions (−1.451 and −0.544 in this case) was then considered a measure for the RI.
groups (AVM versus control subjects) and times of measurements (before versus after). Physiological variables and \( SO_2 \) data were compared via analysis of variance (ANOVA) with a level of significance set at \( P<0.05 \). All values are given as mean±SD.

For analysis of \( SO_2 \) reactivity as a measure of CVR, linear regression analysis of \( SO_2 \) on et\( CO_2 \) was performed for increasing and decreasing et\( CO_2 \), with et\( CO_2 \) as an independent variable. Regressions not reaching statistical significance were excluded from further analysis. If the slope of the regression line was positive, the behavior of \( SO_2 \) was categorized as parallel; in cases of a negative slope, the behavior was categorized as inverse (see Figure 1). The ratios in which these CVR patterns occurred within groups and/or times of measurements were calculated and compared via \( \chi^2 \) and Fisher’s exact test (\( P<0.05 \)).

To further quantify the degree of positive or negative CVR, a reactivity index (RI) was introduced. For each test, the slope of the linear regression of \( SO_2 \) on et\( CO_2 \) within exactly corresponding time intervals was considered an appropriate measure for this reactivity (Figure 1) because the dynamic component of the response was included, as opposed to previously described end-point calculations for RIs.\(^{10,11} \)

ANOVA was used for comparison of RIs among groups and times of measurements (eg, AVM before versus AVM after or AVM before versus control subjects before) separately for inverse and parallel CVR. In 9 AVM patients in whom \( >1 \) area was assessed, the mean RI was calculated.

**Results**

Physiological variables showed no significant differences among groups (AVM versus control subjects) and times (before versus after) in measurements, except for hemoglobin and hematocrit, which were higher in the AVM group before surgery, and postoperative temperature, which was higher in control subjects than in all other groups (Table 1).

Comparison of \( SO_2 \) data from measurements under steady-state conditions of moderate hypocapnia (Paco\(_2\), 33 mm Hg) showed that baseline values before AVM resection or transylvanian dissection were identical (AVM, 54.8±10.4%\( SO_2 \); control subjects, 52.7±9.1%\( SO_2 \)). In both groups, a significant increase in cortical oxygenation occurred after surgery (AVM, 73.1±10.1%\( SO_2 \); control subjects, 73.6±8.9%\( SO_2 \)), without showing a significant intergroup difference among the postresective values (Table 2).

The ratio of parallel to inverse behavior of CVR in groups and times is displayed separately for the vasodilatory and vasoconstrictive parts of the tests in Figure 2. In both groups, after the vasodilating and vasoconstricting stimuli, a comparable percentage of patients with inverse behavior existed before surgery. After surgery, the proportions of parallel versus inverse CVR patterns are practically reversed, becoming significantly different from the preoperative situation.

The mean±SD group values of the RIs derived from the slopes of the regression lines are displayed in Table 3 and Figure 3. No statistically significant intergroup differences were seen, except for the lower postoperative RI for parallel behavior under induced vasodilation in AVMs, which was significantly lower than preoperatively in the AVM group.
and in control subjects but not significantly lower than for postoperative control subjects.

Discussion

Our study provides evidence for similarly heterogeneous CVR patterns on supposedly normal frontal and temporal cortex in patients with Ammon’s horn sclerosis and cortex in the vicinity of cerebral AVM.

Methodology

One problem arises from the fact that CVR is traditionally defined as changes in CBF to vasodilating or vasoconstricting stimuli. The inability to measure CBF quantitatively with sufficient temporal and spatial resolution in a clinical setting has resulted in the use of substitutes such as blood flow velocity or HbO2 with nearly infrared spectroscopy (NIRS). We have adopted the latter approach because Smielewski et al have shown that HbO2 changes after induced alterations in CO2 allow valid assessment of CVR. This algorithm is based on the assumption that SO2 changes under constant conditions of O2 consumption reflect changes in regional cerebral blood volume, which are linearly correlated with rCBF changes. This linearity is eventually violated under ischemic conditions, which was ruled out in our patients by the rSo2 measurements under steady-state hypocapnia. Our apparatus differs from NIRS systems with respect to the catchment volume. Unlike NIRS, ours measures So2 in smaller supply units, which explains some counterintuitive results in our control group (see below).

The second concern is whether our control patients were normal with regard to cerebrovascular status. We thought the best approach to control for potential confounders was to select a homogeneous cohort of patients with isolated Ammon’s horn sclerosis. They are best matched regarding age, comorbidities, etc, to the AVM group and harbor a non-space-occupying lesion remote from the measuring site. Workup and operative procedures are standardized, enabling us to isolate the influence of a uniform surgical trauma. Patients with chronic seizures may have altered vasoreactivity because abnormalities in rCBF/metabolism and morphological capillary alterations in resected tissue may occur. These findings, however, are confined to the epileptogenic focus. Highly sensitive MRI sequences, PET or single photon emission CT, and EEG define those patients with structural, metabolic, and electrophysiological abnormalities extending into the lateral cortex, which will then undergo a temporal lobe resection instead of selective AH. The assumption of normality in our control subjects seems more reasonable than in patients with unruptured aneurysms, which harbor a local phenomenon of a mostly generalized vascular disorder.

With a primarily negative finding reported in this paper (no proof of AVM-specific CVR patterns), the question remains as to whether this lack of significant intergroup differences indicates equivalence. For group sizes ≥20, a statistical power of 80% was reached. This was not always the case in subgroup comparisons of RIs for parallel and inverse behavior under different etCO2 curves. We are well aware that statistical nonsignificance does not necessarily imply equivalence and therefore discuss suggestive but insignificant findings below.
CVR in AVM Patients and Control Subjects

Preoperative Situation

Results of CVR testing in AVM patients reported in the literature are inconclusive. This may be explained by the variety of methods applied and by arbitrary interpretations of results. For example, in studies using transcranial Doppler sonography, one has to take into account which vessels were insonated. In one study, the results were considered indicative of pathological vasoreactivity without clearly stating whether these arteries were involved in AVM supply, whereas other authors found evidence for intact CVR in nonfeeding arteries with transcranial Doppler sonography or intraoperative micro-Doppler.

Other authors found impaired CVR and hyperresponsiveness to vasodilative stimuli and thought that they were predictive of the occurrence of postoperative hyperemic complications. The results of xenon CT studies after acetazolamide challenges were found to indicate a compromised vascular reserve capacity in up to one third of the regions. Arteriolar exhaustion resulting from a shunt-induced, chronically reduced cerebral perfusion pressure was thought to be the underlying cause.

In contrast, Young et al, applying intraoperative xenon CBF measurements, described regional CVR intact in all AVM cases. They could further demonstrate that arteriolar dilatation compensates for reduced cerebral perfusion pressure but never to a maximum extent. In conjunction with the results of studies showing intact pressure autoregulation in all cases, we thought it unlikely that the myogenic response to vasodilatation or vasoconstriction is disturbed in an AVM-specific manner. To test this hypothesis, we compared the distribution of parallel versus inverse CVR patterns between AVM and control patients and also tested whether the degree of vasoreactivity is different.

The fact that 40% (with increasing etCO₂) and 17% (with decreasing etCO₂) of patients in the AVM group showed a propensity for inverse behavior after both stimuli could be interpreted as being AVM specific. But a similar distribution of CVR patterns in control subjects before surgery prohibits this interpretation and contradicts the notion of uniqueness. The identical degree of “responsiveness” to either stimulus underlines this point. To accept that CVR in AVM patients is normal, one would have to be positive that the results in the control group are representative of normal cerebrovascular behavior. This poses a problem at first glance, because a ratio of 23% (with increasing etCO₂) and 18% (with decreasing etCO₂) of impaired CVR, appears counterintuitive for “healthy” patients. One may still consider our control group as harboring some form of vascular compromise, but we would rather propose a different explanation.

This discussion resembles the one that has taken place with regard to resting CBF and AVM. Here, a so-called patchy hypoperfusion has been considered AVM specific until proved otherwise and now is well explained by theories regarding regulation of capillary circulation. Compared with other modalities, the spatial resolution of our methods is higher. Because it measures erythrocytic capillary flow, the inverse CVR behavior corresponds to a predominantly plasmatic capillary flow in the assessed area during a challenge. As such, it represents a physiological rather than a pathophysiological phenomenon and makes its interpretation as “disturbed” at least questionable. It is probably better defined as a form of microvascular steal.

One result may be considered suggestive for being AVM dependent: Despite occurring in an equal proportion in both groups, the inverse response after a vasoconstrictive stimulus (the relative increase in nutritive capillary flow at the measuring site with decreasing CO₂) seems to occur to a lesser degree in AVM patients (Figure 3 and Table 3). Yet, more likely, it is a difference by chance because, according to the data on parallel behavior to decreasing CO₂, this cannot be caused by a hyperresponsiveness for vasoconstriction in other areas surrounding AVM.

Postoperative Situation

After the treatment of AVM, the CVR findings in various studies were interpreted as “impaired” vasoreactivity.
whereas others thought it to be “preserved.”7,9 The postoperative increase in oxygenation under steady-state conditions confirms that AVM resection leads to reactive hyperemia and tissue hyperoxia in the surrounding brain.20,25,27 Therefore, it is not surprising that two thirds of patients showed an inverse CVR pattern after an increase in CO2 in the AVM group. The degree of reversibility was lower after surgery, reaching a degree of responsiveness was almost identical to those of the control group after surgery (Figure 3 and Table 3).

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In conclusion, CVR patterns on supposedly normal frontal and temporal cortices in patients with Ammon’s horn sclerosis and cortex in the vicinity of cerebral AVM before surgery are similarly heterogeneous and include inverse behavior of SO2 to changes in CO2 in approximately one third of the examined patients. After surgery, inverse CVR patterns indicative of microvascular steal increase significantly because of the presence of reactive hyperemia in both groups. Apart from postoperatively lowered reactivity under induced vasodilation in the AVM group, no AVM-specific pathological CVR pattern could be proved. Yet, after surgery, the reduced capacity for vasoconstriction seems to be better confined regionally in control subjects than in AVM patients.

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References


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