Abnormal Responses of the Human Cerebral Microcirculation to Papaverin During Aneurysm Surgery

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Background and Purpose—The role of the cerebral microcirculation in delayed ischemia after subarachnoid hemorrhage remains obscure. To test the hypothesis that cerebral arterioles have a reduced capacity to dilate after subarachnoid hemorrhage, we studied the microvascular responses to papaverine (PPV) in patients undergoing aneurysm surgery.

Method—In 14 patients undergoing aneurysm surgery, the diameter changes of cortical microvessels after topical application of PPV were observed using orthogonal polarizing spectral imaging.

Results—In control subjects, neither arterioles nor venules showed diameter changes in response to topical PPV. In patients operated <48 hours after subarachnoid hemorrhage, PPV resulted in vasodilatation of arterioles with a 45±41% increase in arteriolar diameter (P=0.012). In 2 of these patients, arteriolar diameter returned below baseline value. In patients undergoing late aneurysm clipping, the diameter increase of the arterioles after PPV was 25±34% (not significant). In 2 patients of this group, no vasodilatation but focal arteriolar narrowing occurred.

Conclusions—In patients with subarachnoid hemorrhage, unpredictable response patterns to PPV were observed with “rebound” vasoconstriction suggesting increased contractility of the microcirculation. Yet, diminished vasodilatory capacity of the cerebral microcirculation after subarachnoid hemorrhage was not confirmed by this study. (Stroke. 2009;40:317-320.)

Key Words: imaging technique ■ intracranial ■ microcirculation ■ neurosurgery ■ subarachnoid hemorrhage ■ vasospasm

Both the large conducting arteries and the cerebral microcirculation are involved in delayed cerebral ischemia after subarachnoid hemorrhage (SAH). Previously, we found increased contractility of the cerebral arterioles after SAH. We subsequently postulated that dilatory properties of the microcirculation are impaired with SAH.

Papaverine (PPV) elicits immediate relaxation of cerebral arteries and is used intraoperatively to reverse vasospasm. Furthermore, intra-arterial PPV improves cerebral blood flow and cerebral oxygenation, although its efficacy in improving neurological outcome remains inconclusive. We conducted this study to investigate the microvascular response to PPV in patients with SAH.

Patients and Methods

In 14 patients undergoing aneurysm surgery, the diameter changes of small cortical vessels were observed using orthogonal polarizing spectral imaging. Ten patients were operated on within 48 hours after the bleeding, whereas 4 underwent late surgery. Three other patients undergoing craniotomy for diseases not affecting the cortical blood vessels served as control subjects.

Patients were under general anesthesia with a 1.3% sevoflurane/O2 air mixture and an inspired oxygen fraction of 0.4. Mannitol was administered before opening the dura. Ventilation was adjusted to maintain a paco2 at 40 mm Hg and the mean arterial pressure was kept constant during the measurement period. After dura opening but before arachnoid dissection, the cortical microvessels were observed for a period of 20 minutes. After establishing a baseline diameter for 1 minute, 10 mL of 0.1 mmol/L PPV was applied to the brain surface. Subsequently, the change in microvascular diameter as well as the duration of the response was recorded.

The diameter of blood vessels was determined using image processing software specifically dedicated for analysis of the microcirculation (CapImage; Dr Zeintl Software Engineering, Heidelberg, Germany). The quality of the images allowed a resolution of 5 μm. Data are expressed as mean±SD. Comparison of mean diameter at baseline between groups was made using Mann–Whitney U test. Changes after PPV within each group were studied with the Wilcoxon signed rank test for related samples. Statistical significance was defined as P<0.05. The Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam approved this study, and written informed consent was obtained.

Results

In the normal brain cortex, the arterioles were regularly shaped and pulsating. The average diameter of arterioles was 91±49 μm (range, 61 to 147 μm). The venular walls were regularly shaped but not pulsating. The average diameter of...
venules was 75±35 μm (range, 31 to 113 μm). The erythrocytes in the venules showed a laminar flow pattern.

In patients undergoing early aneurysm surgery, the pulsatility of arterioles was attenuated. The arteriolar walls were regularly shaped in 7 cases but showed a multifocal constriction pattern resembling a bead string in 3 cases. The average arteriolar baseline diameter was 48±17 μm (range, 26 to 85 μm), significantly lower than in control subjects (P=0.028). The morphology and flow pattern of venules did not differ from control subjects. The average venular diameter was 97±36 μm (range, 34 to 225 μm). In patients undergoing late aneurysm surgery, the average diameter of arterioles (64±15 μm; range, 45 to 82 μm) did not significantly differ from control subjects. Venular diameter measured 95±55 μm (range, 25 to 156 μm).

In control subjects, neither arterioles nor venules showed a diameter change to topical PPV. In patients with SAH undergoing early surgery, PPV resulted in a significant vasodilatation of arterioles with 45±41% (range, 0% to 119%) increase in arteriolar diameter for a period of 8±2 minutes (P=0.012). Various patterns of constriction and dilatation were noted (Figure 1A–F). In patients undergoing late surgery, arteriolar vasodilatation of 25±24% (range, 0% to 49%) occurred in 2 of 4 patients (not significant). In 2 patients undergoing late surgery, subarachnoid blood was still present, and no vasodilatation but delayed focal arteriolar constriction occurred with a diameter decrease of −38% and −20%, respectively (Figure 2A–C). All results are shown in the Table.

**Discussion**

Using orthogonal polarizing spectral imaging, we found that SAH is associated with an abnormal, somewhat erratic vasodilatory response pattern to topical PPV with the occasional occurrence of an arteriolar bead string-like vasoconstriction. We detected multifocal microvascular vasospasm in 30% of patients with decreased arteriolar pulsatility. Similar observations were previously described.1,6

Topical application of PPV is known to have a dilating effect on cerebral arteries and arterioles.7,8 In our study, however, PPV surprisingly did not elicit a microvascular response in control subjects. Contrary to these observations, in patients with SAH, variable arteriolar dilation was seen for only several minutes during the early course of SAH after which most microvessels returned to their baseline diameters. Notably, 2 of 10 patients subsequently developed vasoconstriction. Arteriolar constriction in response to PPV may account for the clinical deterioration reported earlier due to
aggravation of vasospasm of primarily distal cerebral vessels with PPV infusion as well for lack of correlation between angiographic and clinical benefit after PPV infusion.4,7,9 Thus, in those cases in which delayed microcirculatory vasoconstriction would be the dominant effect, a paradoxical decrease in flow velocity as measured by transcranial Doppler ultrasound will be found. These unexpected findings thus stress the importance of measuring Lindegaard index rather than just flow velocity or, alternatively, monitoring of tissue pO₂.

In conclusion, we have shown that the cerebral microcirculation exhibits abnormal vascular responses to PPV in the presence of SAH (*).

Table. Summary of the Study Population’s Characteristics and Individual Measurement Results

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, Years</th>
<th>Clinical Grade</th>
<th>Fisher Grade†</th>
<th>Dbase, μm</th>
<th>Dpost, μm</th>
<th>Dend, μm</th>
<th>Percent Baseline Diameter Change After PPV</th>
<th>Percent Baseline Diameter Change After 20 Minutes</th>
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<td>III</td>
<td>38</td>
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M:F=1:1 57±13 | I-II=5 | I-II=3 | 48±17 | 67±21 | 47±14 | 45±41 | 0±25 |

III-IV=5 II-IV=7

SAH, late surgery | | | | | | | | |
| 1‡ | M | 61 | I | I | 65 | 65 | 40 | 0 | -38 |
| 2‡ | F | 49 | I | I | 82 | 90 | 66 | 10 | -20 |
| 3 | F | 46 | I | I | 45 | 64 | 43 | 42 | -4 |
| 4 | F | 56 | I | I | 63 | 94 | 86 | 49 | 37 |

M:F=1:3 53±7 | I-II=4 | I-II=4 | 64±15 | 78±16 | 59±22 | 25±24 | -6±32 |

III-IV=0 II-IV=0

Control subjects | | | | | | | | |
| 1 | M | 46 | N/A | N/A | 147 | 147 | 147 | 0 | 0 |
| 2 | M | 49 | N/A | N/A | 65 | 65 | 65 | 0 | 0 |
| 3 | F | 49 | N/A | N/A | 61 | 63 | 61 | 3 | 0 |

M:F=2:1 48±2 N/A N/A 91±49 92±48 91±49 1±2 0

*Clinical grade according to Hunt and Hess classification.
†Amount of blood on CT according to Fisher.
‡Subarachnoid blood still visible on orthogonal polarizing spectral image in late surgical group.
Dbase indicates baseline arteriolar diameter; Dpost, arteriolar diameter after topical PPV; Dend, arteriolar diameter at end of observational period; M, male; F, female; N/A, not applicable.
course of SAH compared with control subjects. Both dilation and constriction were observed. Vasoconstriction of microvessels in response to PPV has not been previously found and seems unique for the cerebral microcirculation.

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**Disclosures**
None.

**References**
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