Effect of Intra-Arterial Papaverine on Regional Cerebral Blood Flow in Hemodynamically Relevant Cerebral Vasospasm

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Background and Purpose—It remains controversial whether the intra-arterial administration of papaverine (IAP) is effective in reversing vasospasm-associated cerebral hypoperfusion after aneurysmal subarachnoid hemorrhage. The aim of the present study was to continuously assess regional cerebral blood flow (rCBF) during and after IAP with the use of quantitative, bedside thermal diffusion flowmetry.

Methods—Eight patients with cerebral vasospasm after subarachnoid hemorrhage (mean flow velocity $>120$ cm/s; angiographic vessel constriction $>33$%; hemispheric cerebral blood flow [CBF] $<32$ mL/100 g per minute) were prospectively entered into the study. Before IAP, thermal diffusion microprobes were implanted into the white matter of each affected vascular territory ($n=10$) for rCBF monitoring. During and after IAP (300 mg papaverine/50 mL saline over 1 hour), mean arterial blood pressure, intracranial pressure, cerebral perfusion pressure, thermal diffusion rCBF (TD-rCBF), and cerebrovascular resistance (CVR) were recorded continuously.

Results—IAP significantly increased TD-rCBF from $7.3\pm1.6$ to $37.9\pm6.6$ mL/100 g per minute (mean±SEM), indicating reversal of cerebral hypoperfusion. This TD-rCBF response was dependent on the degree of cerebral vasospasm and reduced perfusion within the vascular territory. Long-term analysis of TD-rCBF, however, demonstrated that this beneficial effect of IAP on cerebral hypoperfusion was only transient: within 3 hours after treatment, TD-rCBF and CVR returned to baseline values. Furthermore, a lack of correlation between transcranial Doppler sonography and thermal diffusion flowmetry suggested that transcranial Doppler sonography is not suited for CBF-based neuromonitoring after IAP.

Conclusions—IAP is not effective in permanently reversing cerebral hypoperfusion in patients with cerebral vasospasm. The need to validate alternative therapeutic strategies that seek to improve cerebral perfusion in vasospasm warrants continued development of CBF-based neuromonitoring strategies. (Stroke. 2001;32:498-505.)

Key Words: cerebral circulation • ischemia • microcirculation • stroke

Severe cerebral vasospasm remains a leading cause of morbidity and mortality in patients suffering from aneurysmal subarachnoid hemorrhage (SAH). Current strategies for preventing and treating cerebral vasospasm include calcium channel blocker treatment, hypertensive/hypervolemic/hemodilution (triple-H) therapy, early surgery with clot removal, and local thrombolysis of cisternal blood. For those patients who are refractory to these medical/surgical measures, endovascular strategies such as balloon angioplasty or the intra-arterial administration of papaverine (IAP) have been advocated.

Although balloon angioplasty seems to be superior to IAP, the procedure is associated with significant drawbacks: it demands an experienced endovascular surgeon or radiologist, is limited to proximal vessel segments, and is associated with significant risks. Therefore, IAP has remained a mainstay in the endovascular treatment of cerebral vasospasm.

Several clinical reports have suggested efficacy for IAP in reversing cerebral vasospasm, both in the acute setting, ie, during papaverine infusion, and in the long-term setting, ie, hours or days after treatment. Accordingly, IAP has been shown to reverse or improve both angiographic and transcranial Doppler (TCD) sonographic vasospasm. Furthermore, it has been shown to improve reduced cerebral oxygenation, at least in the short-term setting. In contrast to these encouraging results, clinical studies focusing on outcome have failed to reveal a beneficial effect of IAP in the treatment of cerebral vasospasm. One reason for this discrepancy might be that only little is known about the direct effects of IAP on the key parameter during hemodynamically
relevant cerebral vasospasm, ie, reduced cerebral blood flow (CBF).

This lack of knowledge is in part due to the fact that most techniques that are currently used to assess cerebral perfusion in patients do not allow for a continuous and quantitative analysis of CBF at the bedside. Recently, a novel intraparenchymal thermal diffusion microprobe has been developed and validated for the continuous, quantitative, bedside assessment of regional cerebral blood flow (rCBF) in patients. Therefore, the objective of the present study was to apply this novel technique to prospectively study the direct short-term and long-term effects of IAP on reduced rCBF in patients suffering from hemodynamically relevant cerebral vasospasm. To reliably distinguish patients with angiographic and/or sonographic vasospasm only from those with concomitant vasospasm-related hypoperfusion, diagnosis of vasospasm was additionally based on functional blood flow studies using stable xenon-enhanced CT (sXe-CT), as previously described.

**Subjects and Methods**

**Patient Population**

The prospective study was approved by the local research ethics committee. The study comprised 8 patients with hemodynamically relevant cerebral vasospasm after aneurysmal SAH. Patient characteristics are summarized in Table 1. Mean age was 48±12 years (range, 32 to 68 years). All patients had undergone early surgery within the first 48 hours after hemorrhage and were monitored daily for vasospasm by TCD assessing mean flow velocities in the middle cerebral artery (V_m MCA) and ipsilateral extracranial internal carotid arteries (V_m ICA). In addition, awake patients were assessed for the development of delayed neurological deficits.

**Diagnosis of Vasospasm**

The diagnosis of hemodynamically relevant cerebral vasospasm was based on sonographic, angiographic, and functional CBF studies. Accordingly, inclusion criteria were as follows: (1) V_m MCA >120 cm/s or increase in V_m MCA >50 cm/s within 1 day; (2) V_m MCA/ V_m ICA ratio (Lindegaard index14) >3; (3) angiographically proven vascular constriction of M1/M2 segments of the middle cerebral artery (V_m MCA) or A1/A2 segments of the anterior cerebral artery (ACA) >33%; and (4) rCBF <32 ml/100 g/min per territory within the vascular territory of the constricted artery as assessed by sXe-CT (sXe-rCBF), indicating significant vasospasm-related reduction of cerebral perfusion. By this means, 10 anterior circulation vessel territories of interest (6 MCA, 4 ACA) with vasospasm-related hypoperfusion could be identified in the 8 reported patients (Table 1). At the time when the patients were included into the study, none of them showed signs of infarctions in the CT scan.

**Stable Xenon-Enhanced CT**

The sXe-CT technique (DDP Inc) is accepted as one of the clinical gold standard techniques for rCBF measurements. The method is based on the Kety-Schmidt principle, which assumes that the rate of uptake and the rate of clearance of an inert substance, such as xenon, are proportional to the blood flow in the tissue. At the beginning of the investigation a baseline CT scan was performed. For determination of sXe-rCBF, a 4.5-minute wash-in protocol was used. Patients received a Xe/O2 mixture (30% Xe), and a 3-level investigation (slice thickness, 10 mm) was performed. The end-tidal carbon dioxide level was adjusted to approximately 35 mm Hg throughout the study. Next, the baseline scans were subtracted from the corresponding enhancement images to derive a curve of enhancement over time. Finally, a CBF map was calculated from the arterial and tissue xenon time curves by using the Kety-Schmidt equation. For diagnosis of hemodynamically relevant cerebral vasospasm, sXe-rCBF was separately evaluated within the vascular territories of the MCAs and ACAs by placing the region of interest such that it outlined the complete vascular territory as described.

**Monitoring of CBF**

After diagnosis of cerebral vasospasm, thermal diffusion microprobes (Thermal Technologies Inc) were implanted into each hypoperfused vascular territory through a 3.2-mm burr hole at a depth of 20 mm below the level of the dura (ie, white matter) and were tightly fixed with a 1-way bolt (DD Medical), as previously described. For implantation into the ACA territory and MCA territory, a coronal burr hole was placed 15 and 60 mm from the midline, respectively. Correct probe position was confirmed radiographically during angiography. The probes were kept in place during the study period and were removed as soon as the patients were allowed to wake up.

**Papaverine Treatment**

IAP was started immediately after microprobe implantation and obtention of reliable baseline TD-rCBF readings. To decrease the risk of technical complications, treatment was performed with all patients sedated and intubated. All patients were equipped with arterial and venous lines for cardiac monitoring as well as with an external ventricular drainage for intracranial pressure (ICP) monitoring and ICP-directed treatment. Triple-H therapy was induced as soon as vasospasm was confirmed and was maintained during the endovascular treatment as well as throughout the postinterventional study period. After selective positioning of the microcatheter within the distal internal carotid artery (ICA) (CI/C2 segment), papaverine hydrochloride was infused continuously at a concentration of 300 mg/50 mL saline (0.6%) over 1 hour per territory. After IAP, the...
patients remained sedated and ventilated and were treated following a standardized ICP-directed management protocol.

**Study Protocol**
During IAP, mean arterial blood pressure (MAP; mm Hg), ICP (mm Hg), cerebral perfusion pressure (CPP = MAP − ICP; mm Hg), regional thermal diffusion CBF (TD-rCBF; mL/100 g per minute), and cerebrovascular resistance (CVR = CPP/TD-rCBF) were recorded continuously at a sampling rate of 1 Hz. In parallel, sonographic and angiographic vasospasm was assessed intermittently before and after IAP. After endovascular treatment, MAP, ICP, CPP, Vm MCA, TD-rCBF, and CVR were assessed by 10-minute intervals of continuous registration at 1, 3, 6, and 12 hours after IAP.

**Patient Outcome**
Radiological and clinical outcome was assessed at the time of discharge from the hospital. Radiological outcome was assessed by evaluating the development of cerebral infarctions within the affected vascular territories after IAP. The extent of infarctions was categorized into none, incomplete, or complete. Clinical outcome was assessed according to the Glasgow Outcome Scale.

**Statistical Analysis**
Quantitative values are given as mean ± SEM. MAP, ICP, and CPP values are calculated as mean values of the 8 patients, and sXe-rCBF, Vm MCA, and TD-rCBF values are calculated as mean values of the 10 vascular territories of interest. For each reported time point, continuously recorded values were averaged over 1 minute. To study the relationship between the degree of vasospasm and the efficacy of IAP, the vascular territories were subgrouped according to their baseline TD-rCBF value into territories with moderate vasospasm (TD-rCBF ≥10 mL/100 g per minute) and severe vasospasm (TD-rCBF <10 mL/100 g per minute). To analyze the dose-response relationship during IAP, the time intervals necessary to reach 25%, 50%, 75%, and 100% of the maximum (ie, final) TD-rCBF value were evaluated. Comparisons of dependent variables were tested with the paired Student’s t test and Bonferroni probabilities for repeated measurements. A value of P < 0.05 was considered significant. To correlate Vm MCA and TD-rCBF after endovascular treatment, we performed univariate linear regression analysis.

**Results**
All patients underwent IAP within 6 hours after critical elevation of TCD values or onset of ischemic symptoms and within 1 hour after final diagnosis by sXe-CT and angiography. Thus, all patients were within the critical time frame for successful papaverine treatment. Probe-related complications after implantation were not observed. Dislocation of the probes did not occur. Before IAP, mean sXe-rCBF and TD-rCBF were 27.4 ± 1.6 and 7.3 ± 1.6 mL/100 g per minute, respectively. In parallel, mean Vm MCA was 207.3 ± 22.0 cm/s. On the basis of the baseline TD-rCBF measurements, 3 vascular territories revealed moderate vasospasm (TD-rCBF = 13.0 ± 1.0 mL/100 g per minute) and 7 severe vasospasm (TD-rCBF = 4.8 ± 1.3 mL/100 g per minute).

**Short-Term Effects of IAP**
IAP ameliorated angiographic and sonographic vasospasm in all patients. At the end of the treatment, Vm MCA was significantly reduced to 152.2 ± 25.3 cm/s (P < 0.05 versus baseline), although it failed to reach normal levels. Figure 1 illustrates the short-term effect of IAP on angiographic vasospasm and TD-rCBF in a patient with hemodynamically relevant vasospasm within the territory of the ACA on day 5 after rupture of an anterior communicating artery aneurysm. After 10 minutes of IAP, TD-rCBF started to increase from 11 mL/100 g per minute and plateaued after 50 minutes at approximately 55 mL/100 g per minute.

The quantitative analysis of all assessed territories demonstrated that IAP significantly improved TD-rCBF from 7.3 ± 1.6 to 37.9 ± 6.6 mL/100 g per minute, indicating reversal of cerebral hypoperfusion (Figure 2A). This increase in cerebral perfusion was attributed to an 85% reduction of CVR (Figure 2B), while CPP remained constant during the treatment (103.4 ± 1.7 versus 104.4 ± 2.5 mm Hg before and after IAP, respectively).

The individual TD-rCBF responses to IAP, however, varied significantly (Figure 3A). For instance, the time to reach 50% of the maximum TD-rCBF value varied between 2.4 and 59.5 minutes. Subgroup analysis between vascular territories with moderate and severe vasospasm revealed that this variable TD-rCBF response was in part dependent on the degree of cerebral vasospasm and reduced perfusion (Figure 3B). Consequently, patients with a baseline TD-rCBF ≥10 mL/100 g per minute responded much more quickly to IAP than those with a TD-rCBF <10 mL/100 g per minute.
Long-Term Effects of IAP

Long-term analysis of TD-rCBF for up to 12 hours after treatment demonstrated that the beneficial effect of IAP on cerebral vasospasm and hypoperfusion was only transient. Figure 4 illustrates a lack of long-term efficacy of IAP on TD-rCBF in a patient with hemodynamically relevant vasospasm within the territory of the right MCA on day 3 after rupture of an supraclinoid ICA aneurysm. Within 1 hour, TD-rCBF as well as CVR returned to baseline values, finally resulting in delayed cerebral infarction. In accordance with this observation, overall analysis of TD-rCBF and CVR after treatment confirmed this inefficacy of IAP in long-term reversal of hemodynamically relevant vasospasm (Figure 5). In contrast to the TD-rCBF response in the acute setting, long-term reperfusion failure was independent of the degree of vasospasm.

Use of TCD Versus TD-rCBF to Monitor Papaverine Treatment

TCD has been advocated as the gold standard bedside technique for postinterventional surveillance of the efficacy of IAP in reversing vasospasm-associated cerebral hypoperfusion. Its successful application, however, might be limited in that TCD does not allow direct assessment of cerebral perfusion. To test whether TCD is suited for adequate CBF-based neuromonitoring after endovascular treatment of cerebral vasospasm, we directly compared TCD with thermal diffusion flowmetry, which yielded no correlation between $V_{\text{m,MCA}}$ and TD-rCBF in assessing the course of cerebral perfusion after IAP (Figure 6).

Patient Outcome

The lack of long-term efficacy of IAP on cerebral hypoperfusion finally resulted in the development of infarctions within 8 of 10 affected vascular territories (Table 2). At the time of discharge, 4 patients had succumbed to their refractory vasospasm (Glasgow Outcome Scale score of 1), and 4 patients were severely disabled (Table 2).

Discussion

In the present study we have characterized the direct effects of IAP on reduced rCBF in patients with hemodynamically relevant vasospasm after aneurysmal SAH using continuous rCBF monitoring by thermal diffusion flowmetry. The principal novel findings of the study are (1) the characterization of the acute rCBF response to IAP and (2) the proof that IAP lacks long-term efficacy in reversing reduced rCBF beyond a few hours after treatment.

Endovascular treatment of vasospasm is usually reserved for patients who have failed medical treatment. The ideal endovascular treatment strategy, however, has remained unclear thus far. Therefore, angioplasty and IAP have been performed alone or in combination.

At many institutions angioplasty has advanced to become the primary method of endovascular treatment of vasospasm. Still, there are significant drawbacks associated with this
technique. First, angioplasty is technically demanding, which limits its successful use to highly skilled and experienced endovascular specialists. Second, angioplasty is only applicable to proximal, segmental vasospasm within the ICA or M1 portion of the MCA. Therefore, more distal vasospasm or vasospasm in vessels that are difficult to assess remains unaffected. Third, angioplasty is associated with significant risks, such as occlusion or rupture of major vessels or displacement of aneurysm clips off the neck. Consequently, IAP alone has remained an attractive approach in the endovascular treatment of cerebral vasospasm.

Papaverine is known as one of the most potent nonspecific vasodilators with relaxing action on the smooth musculature of larger vessels. Its dilatory potency on large vasospastic cerebral vessels has been repeatedly documented in various clinical studies. Kassell and coworkers reported a 66% success rate in reversing angiographic vasospasm after IAP. In accordance, Kaku et al presented data on successful dilation of 92% of all treated vascular territories after superselective catheterization of the affected vessel. In both reports, improvement of angiographic vasospasm was accompanied by an improvement of the clinical condition in the majority of the patients studied. One major advantage of IAP, compared with angioplasty, is that it is not only effective on the vessel segments located proximally to the catheter tip but also affects the more distal cerebral arteries that can be identified on conventional arteriograms (eg, A2/A3 segments of the ACA, M2/M3 segments of the MCA). Besides its effect on angiographic vasospasm, IAP has been demonstrated to have a beneficial effect on sonographic vasospasm as well, significantly reducing mean blood flow velocities within the affected vessel segments during infusion. It is important to note that all these previous reports assessed the effect of IAP on vasospasm-related cerebral hypoperfusion only by indirect, qualitative, or discontinuous means. The same is true
for a recent study\(^1\) studying jugular bulb venous oxygen saturation, which again is an indirect and often unreliable indicator for hemispheric CBF.\(^{26,27}\)

The present study complements these findings in that it additionally examines the direct effects of IAP on reduced cerebral perfusion in hemodynamically relevant vasospasm using thermal diffusion flowmetry, a technique that enables a continuous and quantitative bedside assessment of rCBF.\(^1\) In parallel to improved angiographic and sonographic vasospasm, rCBF increased acutely from ischemic levels beyond normal white matter flow values during IAP. The continuous assessment of rCBF provided detailed dose-response curves to IAP, demonstrating that even the most severe vasospasm in our study could be reversed by the applied treatment protocol. Furthermore, the rCBF response to IAP has been shown to be dependent not only on the dosage of papaverine but also on the individual degree of vasospasm.

Although most investigators today feel that these antivasospastic effects of IAP are only transient, long-term efficacy for angiographic and sonographic vasospasm has been repeatedly reported with a frequency of 46% to 80%\(^{6,8,21,25,28}\). These reports, however, are contrasted by a number of discouraging clinical outcome results. For instance, despite a 78% angiographic success rate, Firlik et al\(^2\) were only able to demonstrate significant clinical improvement in 26% of their patients suffering from severe vasospasm. In parallel, a large retrospective multicenter analysis of 31 patients treated with IAP failed to show any beneficial effect on clinical outcome compared with medical treatment of vasospasm.\(^1\) The results of this study suggest that this discrepancy is due to an inability of IAP to permanently reverse vasospasm-related hemodynamic insufficiency. Although this is a finding that many opponents of IAP may have anticipated, it is only the continuous bedside assessment of rCBF in this study that has provided proof for the first time that IAP lacks long-term efficacy in reversing cerebral hypoperfusion and increased cerebrovascular resistance in vasospasm. This applies even if well-monitored medical therapy (ie, triple-H therapy) is optimized before IAP and continued throughout the postinterventional period.

For the present study we have focused on patients with hemodynamically relevant vasospasm. In contrast to previous studies on the efficacy of IAP, diagnosis was not only based on TCD and angiographic findings but also on functional CBF studies demonstrating corresponding cerebral hypoperfusion. A perfusion limit of 32 mL/100 g per minute, as suggested by Clyde et al,\(^1\) excluded patients with morphological or sonographic vasospasm only, which is mandatory for high-grade SAH patients who must remain sedated and ventilated and thus cannot be assessed clinically. In parallel, by using the sXe-CT technique for functional CBF studies, causes for cerebral hypoperfusion other than vasospasm (eg, edema, hydrocephalus, hemorrhage) could be ruled out. It is important to note that in contrast to the territorial sXe-CT results, thermal diffusion flowmetry with microprobes implanted at a depth of 2 cm below the dura level assesses white matter flow, which will approximate 10 mL/100 g per minute in case of a mean global CBF of 32 mL/100 g per minute (in agreement with our study).\(^3\) For this compartment, critical thresholds for severe ischemia were recently redefined as rCBF values <6 to 8 mL/100 g per minute.\(^3,11,31,32\)

Although, maintenance of sedation and mechanical ventilation during IAP is controversial, there are several reasons that justify sedation/ventilation of these patients with hemodynamically relevant vasospasm. First, especially in patients undergoing repeated papaverine infusions for multiple spastic vessel segments with the microcatheter remaining in place, it is useful to perform these endovascular interventions with all patients sedated and intubated to minimize the risk of technical complications.\(^2\) Second, although the use of deep sedation in patients with severe vasospasm was abandoned by some authors in the 1980s,\(^3\) maintenance of sedation in patients with therapy-refractory vasospasm still seems to be justified on the basis of recent reports supporting the neuroprotective effects of barbiturate coma or deep sedation during vasospasm-related ischemia.\(^3,11,32\) However, it should be noted that the application of multimodality neuromonitoring is not limited to the sedated patient but can be also performed in awake patients to obtain continuous surveillance of hemodynamic, perfusion, and metabolic parameters in addition to the clinical assessment.

Should papaverine consequently be omitted from the treatment of refractory vasospasm? On the basis of the results of this study and the results of recent clinical reports,\(^1,29\) IAP

**TABLE 2. Radiological and Clinical Outcome of the 8 Patients Who Underwent IAP**

<table>
<thead>
<tr>
<th>Case</th>
<th>Radiological Outcome: Infarctions Within Vascular Territories</th>
<th>Clinical Outcome: Glasgow Outcome Scale(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.J.</td>
<td>Complete</td>
<td>1</td>
</tr>
<tr>
<td>W.W.</td>
<td>Incomplete</td>
<td>1</td>
</tr>
<tr>
<td>H.L.</td>
<td>Complete</td>
<td>1</td>
</tr>
<tr>
<td>L.T.</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>M.V.</td>
<td>Complete/complete</td>
<td>1</td>
</tr>
<tr>
<td>U.K.</td>
<td>Incomplete</td>
<td>3</td>
</tr>
<tr>
<td>B.B.</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>B.S.</td>
<td>Incomplete/incomplete</td>
<td>3</td>
</tr>
</tbody>
</table>

**Figure 6.** Comparison between TD-rCBF and \(V_{\text{mMCA}}\) after IAP by univariate linear regression analysis.
alone, as it is currently used, provides no additional benefit for patients with hemodynamically relevant vasospasm. Whether IAP in combination with angioplasty yields more favorable results remains to be determined, especially in the light of recent reports on the efficacy of angioplasty in reversing vasospasm.36 Neither will alterations in the timing of or indication for IAP likely improve its efficacy. In contrast, a useful modification of current IAP protocols could be the manner of drug administration; of interest here is a more continuous delivery of the drug, by either intra-arterial or intrathecal means.37,38

The present study advocates the need for refined neuro-monitoring strategies in the treatment of cerebral vasospasm. The efficacy of upcoming antivasospastic strategies, including the intrathecal delivery of nitric oxide donors or the systemic administration of endothelin antagonists, will improve by continuous surveillance of hemodynamic, perfusion, and metabolic parameters. Thus far, TCD is the accepted technique to assess the efficacy of antivasospastic therapy at the bedside. A comparison of TCD-calculated flow velocities and rCBF values in the present study, however, suggests that TCD is not suited for these means. This is in agreement with a recent study demonstrating unsatisfactory correlation between mean blood flow velocities and the degree of angiographic constriction in individual vessel segments in the course of papaverine treatment. This low reliability of TCD in the monitoring of cerebral perfusion during the treatment of vasospasm is due to the fact that it assesses flow velocity in major intracerebral vessels rather than tissue perfusion and microcirculation and is unpredictably influenced by hyperdynamic treatment strategies. As a consequence, thermal diffusion flowmetry currently represents a promising alternative to TCD in the bedside monitoring of cerebral perfusion. In conclusion, papaverine is a potent vasodilator with beneficial effects on vasospasm-related hypoperfusion in cerebral vasospasm. The improvement in cerebral perfusion and reduction of cerebrovascular resistance after IAP, however, are only transient and limited to a few hours after intervention. It is therefore doubtful whether current protocols of intermittent administration of papaverine have a significant impact on the treatment of hemodynamically relevant vasospasm. The need to validate alternative therapeutic strategies that seek to improve cerebral perfusion in patients with cerebral vasospasm warrants further development of CBF-based neuromonitoring strategies.

References


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