ASOSPASM is a major source of morbidity and mortality following cerebral aneurysm rupture, and it is the most common cause of delayed ischemic deficits. Approximately 30% of patients who survive the initial cerebral hemorrhage are affected. A diagnosis of symptomatic vasospasm is made when patients develop new neurological deficits or a decreased level of consciousness after exclusion of hydrocephalus, cerebral edema, infection, or metabolic disturbances as possible causes. After treatment by means of coil or clip placement, most patients with symptomatic vasospasm are treated with hypertensive hypervolemic hemodilution (triple-H) therapy and calcium channel blockers in the intensive care unit. Endovascular treatment with papaverine infusion or angioplasty is usually reserved for patients whose symptoms are resistant to these medical measures.

The optimum endovascular strategy for treatment of symptomatic vasospasm is unclear. Patients have been treated with papaverine alone, angioplasty alone, or by a combination of papaverine and angioplasty. In this study, we examine the effects of papaverine on cerebral arteries to help understand the site of action (proximal compared with distal arteries), the duration of effect, and the effect of treatment timing on the vasodilatory response. Analysis of arteriographic data may thus help us form improved endovascular treatment strategies for individual patients.

The size of the internal carotid arteries (ICAs), anterior cerebral, and middle cerebral arteries on angiograms has been measured in the past using cut film angiography. In this investigation we have applied measurement techniques adapted from Gabrielsen and Greitz to determine relative arterial diameters by using digital subtraction angiography (DSA).

Clinical Material and Methods

This is a retrospective analysis of patients who received intraarterial papaverine therapy for treatment of vasospasm between November 1992 and August 1995. All patients developed cerebral vasospasm following subarachnoid hemorrhage (SAH) from a ruptured aneurysm. Patients receiving papaverine in the same treatment session with or following angioplasty in the ipsilateral territory were excluded from this study.

We measured 81 carotid territories in 34 patients before and after papaverine therapy. We studied 22 females and 12 males whose mean age was 54.1 years.

Of the ruptured aneurysms, 14 were located at the ante-
Intraarterial papaverine infusion after vasospasm

![Image](36x609 to 276x715)

**FIG. 1.** Left: Histogram showing the number of papaverine treatments administered at each time interval post-SAH. Right: Scatterplot showing the average arterial diameter change at each day post-SAH.

terior communicating artery, eight at the posterior communicating artery, four at the middle cerebral artery bifurcation, three at the ophthalmic segment, two at the ICA bifurcation, and one each at the basilar tip, pericallosal artery, and anterior choroidal artery. Of the 34 patients, seven were categorized as Hunt and Hess Grade I, seven were Grade II, 14 were Grade III, and six were Grade IV at presentation. On admission computerized tomography scans, two patients were designated Fisher Grade 1, five were Grade 2, 14 were Grade 3, and 13 were Grade 4.

The usual papaverine dose was 300 mg infused over 15 to 60 minutes into the ICA at the C1–2 level. Intracranial pressure (ICP) was monitored continuously, and the rate of infusion was adjusted to maintain cerebral perfusion pressure greater than 60 mm Hg by slowing the infusion if a rise in ICP compromised cerebral perfusion pressure. All angiograms were obtained using DSA techniques. We also evaluated the initial diagnostic angiograms obtained on admission in 26 of these patients for comparison to the pre- and postpapaverine results. The initial angiograms in the remaining eight patients were unavailable for review.

Measurements were made at 12 predetermined sites chosen to represent proximal, intermediate, and distal arteries. On the lateral views, measurements were made in the supraclinoid ICA, in the A1, M1, and P1 segments. The supraclinoid ICA was the representative proximal artery. Measurements were made in a blinded manner by a single observer. All identifying data were obscured on the film by using a sharp soft lead pencil to improve the image when viewing with the loupe, and the vessel diameters were recorded to the nearest 0.1 mm. Because DSA was used and there was variability in magnification between angiograms, skull diameters were measured in the anteroposterior and lateral projections. The arterial diameters were then divided by the skull diameters to achieve relative values. The measurement reproducibility was evaluated using test–retest analysis by repeating the measurements at 35 computer-generated random arterial sites. Based on our random repeated measurements, the average difference was $-3.5\%$ with a standard deviation of $9.3\%$. The Pearson correlation coefficient for the original and repeated measurements was $r = 0.99$.

The data were grouped into proximal, intermediate, and distal artery categories and the adjusted arterial diameters were compared. Distal arteries included the A2, A3, M2, M3, angular, P2, and P3 segments. Intermediate arteries included the A1, M1, and P1 segments. The supraclinoid ICA was the representative proximal artery.

To evaluate change through time we constructed quartile plots comparing the relative corrected diameters on presentation, pre-, and postpapaverine angiograms. Evaluation of the distributions and correlations of the changes were accomplished by first calculating the percentage change in size from presentation to vasospasm and vasospasm to posttreatment. The percentage changes were averaged for all, distal, intermediate, and proximal arteries. Distributions were depicted with histograms, and associations were examined with scatterplots. Pearson correlation coefficients, and simple regression analysis. In

![Image](276x715 to 332x594)

**FIG. 2.** Histogram depicting the average arterial diameter change for the patient population after administration of papaverine.

<table>
<thead>
<tr>
<th>Time Interval Between DSA Sessions</th>
<th>Proximal Artery</th>
<th>Intermediate Artery</th>
<th>Distal Artery</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dx to prepapaverine</td>
<td>0.001</td>
<td>0.003</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>pre- to postpapaverine</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>dx to postpapaverine</td>
<td>0.911</td>
<td>0.786</td>
<td>0.367</td>
<td></td>
</tr>
</tbody>
</table>

* Dx = diagnosis (admission).
nine cases, the patient underwent repeated angiography on the day after papaverine treatment. We compared arterial diameters on each day in these patients to estimate the duration of the papaverine effect.

**Results**

The distribution of the timing of our treatments post-SAH is shown in Fig. 1 left. The largest number of treatments were performed on Day 8, and they ranged from Days 3 to 19. In all 81 treatments there was an increase in arterial diameters following infusion of papaverine (Fig. 2). The increase in diameter ranged from 2.8 to 73.9%, with a mean increase of 26.5%, and 95% confidence limits of 23.3% and 29.8%. The relationship between arterial responsiveness and the time after hemorrhage is shown in a scatterplot (Fig. 1 right). There was no relationship between the timing of treatment and subsequent responsiveness to papaverine in this series ($r = 0.06, p = 0.60$).

The relative diameters of vessels seen on angiograms on admission and pre- and postpapaverine for proximal, intermediate, and distal arteries are shown in Fig. 3. All vessel sizes show consistent changes: there was a decrease in arterial diameters following admission to prepapaverine angiograms, followed by an increase in diameters from pre- to postpapaverine angiograms. Repeated-measures analysis of variance demonstrated that the differences between the three groups were statistically significant for all vessel sizes ($p < 0.001$). Paired t-tests showed that there were statistically significant differences in each group from admission to prepapaverine and from pre- to postpapaverine measurements (Table 1). For the paired t-tests the threshold for statistical significance was altered by using the Bonferroni correction for multiple tests. There was no statistically significant difference between diameters on admission and after papaverine treatment, indicating that the arteries were near their initial baseline diameters.

A decrease in vessel size from admission to prepapaverine angiograms in proximal, intermediate, and distal arteries was demonstrated in the majority of patients (Fig. 4). The percentage change in each vessel size from the pre- to postpapaverine angiograms is positive in most cases (Fig. 5), indicating that patients had a consistent increase in arterial diameters after papaverine administration. The percentage changes in vessel diameter following treatment tend to be inversely correlated to the percentage changes associated with vasospasm (Fig. 6). In other words, the greater the decrease in diameter due to vasospasm, the greater the increase in diameter associated with papaverine treatment.

In nine cases repeated DSA was performed on the day after papaverine therapy. In each case arterial size decreased from the postpapaverine angiogram on Day 1 to the prepapaverine angiogram on Day 2. This was followed by another increase in size with repeated treatment (Fig. 7). Paired t-test analysis showed that there was a significant difference between diameters from pre- to postpapaverine on Day 1 ($p = 0.002$), from postpapaverine Day 1 to prepapaverine Day 2 ($p < 0.001$), and again from pre- to postpapaverine on Day 2 ($p < 0.001$). The arterial diameters were statistically indistinguishable between

**Fig. 3.** Quartile plots showing the average corrected relative diameters (in millimeters) of proximal (left), intermediate (center), and distal (right) arteries as shown on presentation (present), prepapaverine (pre-pap), and postpapaverine (post-pap) angiograms. The middle bar represents the median, the top and bottom of the box represent the 75th and 25th percentiles, and the outer lines represents the 95th and 5th percentiles.

**Fig. 4.** Histograms showing the percentage change in arterial diameters in the region of vasospasm from the admission to the prepapaverine angiograms for proximal (left), intermediate (center), and distal (right) arteries. This is a measurement of the magnitude of vasospasm present in our patients before treatment.
prepapaverine on Days 1 and 2 (p = 0.526) and between postpapaverine on Days 1 and 2 (p = 0.203).

**Discussion**

Papaverine is a potent vasodilator that is an alkaloid of the opium group. It is known to have a direct action on smooth muscles, but its exact mechanism is not completely understood. It is thought to work in part by inhibition of cyclic adenosine monophosphate and cyclic guanosine monophosphate phosphodiesterase in smooth muscles to increase intracellular amounts of these substances. It also may work by blocking calcium ion channels in the cell membrane and inhibiting the release of calcium from the intracellular space.

Our study included papaverine infusions in 81 carotid territories. Treatments were performed from Days 3 to 19 post-SAH, with the largest number of patients treated on Day 8. This distribution is consistent with published reports on the timing of symptomatic vasospasm. There was no relationship between arterial responsiveness and the timing of treatments (Fig. 1 right). Other authors have described a papaverine-resistant phase with increasing duration of vasospasm caused by histological changes in arterial walls. However, our angiographic findings indicate that patients may respond to papaverine for up to 19 days post-SAH.

In our patients who received additional papaverine within 24 hours of the first infusion, each treated territory demonstrated an average decrease in arterial diameters from the time the postpapaverine angiogram was obtained on Day 1 to the angiogram obtained before additional papaverine was administered on Day 2. Although data from this subset of patients were biased because all were suspected of suffering recurrent vasospasm, the results support findings that the effects of papaverine are transient. These territories responded to repeated infusions with a similar degree of vasodilation on the 2nd day (Fig. 7).

The exact role of papaverine in relation to angioplasty in the treatment of patients with symptomatic vasospasm is not clear. Angioplasty is the primary method of treatment at many institutions and its effectiveness has been described by more than one author. However, treatment by angioplasty is limited to larger, more proximal arteries. We have shown that papaverine affects not only proximal arteries, but also distal vessels that are not treated by means of angioplasty. The duration of the papaverine effect appears to be transient based on our results, whereas angioplasty treatment may be more permanent. Both factors suggest that the ideal treatment strategy may combine both therapies.

The risks associated with endovascular treatment are significant and must also be considered. Angioplasty is associated with the risk of vessel rupture. Many authors also believe that systemic anticoagulation is necessary. Papaverine infusion can be associated with rapidly increasing ICP, transient neurological deficits, and...
mydriasis. Respiratory depression may also be seen with vertebrobasilar infusion of papaverine. Although studies have not been performed in which the complication rates of angioplasty and papaverine are compared, papaverine infusion into the cervical ICA may be safer than angioplasty. In addition, placement of a catheter in the cervical ICA is routinely performed and does not require extensive angiographic skills or equipment.

The goal of vasospasm treatment is to increase cerebral blood flow and prevent infarction. We have shown that papaverine causes vasodilation in proximal, intermediate, and distal cerebral arteries, which would be expected to improve blood flow. We have previously shown that papaverine causes a consistent decrease in cerebral circulation time, indicating improved cerebral blood flow. Papaverine probably has a complementary role with angioplasty for treatment of symptomatic vasospasm following subarachnoid hemorrhage: an update. J Neurosurg 14:599–608, 1983

Additional outcome studies are necessary to help determine the most effective treatment strategies.

References

Manuscript received January 28, 1997. Accepted in final form August 8, 1997.
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