Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage

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The effects of dopamine-induced hypertension on local cerebral blood flow (CBF) were investigated in 13 patients suspected of suffering clinical vasospasm after aneurysmal subarachnoid hemorrhage (SAH). The CBF was measured in multiple vascular territories using xenon-enhanced computerized tomography (CT) with and without dopamine-induced hypertension. A territorial local CBF of 25 ml/100 gm/min or less was used to define ischemia and was identified in nine of the 13 patients. Raising mean arterial blood pressure from 90 ± 11 mm Hg to 111 ± 13 mm Hg (p < 0.05) via dopamine administration increased territorial local CBF above the ischemic range in more than 90% of the uninfarcted territories identified on CT while decreasing local CBF in one-third of the nonischemic territories. Overall, the change in local CBF after dopamine-induced hypertension was correlated with resting local CBF at normotension and was unrelated to the change in blood pressure. Of the 13 patients initially suspected of suffering clinical vasospasm, only 54% had identifiable reversible ischemia.

The authors conclude that dopamine-induced hypertension is associated with an increase in flow in patients with ischemia after SAH. However, flow changes associated with dopamine-induced hypertension may not be entirely dependent on changes in systemic blood pressure. The direct cerebrovascular effects of dopamine may have important, yet unpredictable, effects on CBF under clinical pathological conditions. Because there is a potential risk of dopamine-induced ischemia, treatment may be best guided by local CBF measurements.

KEY WORDS • subarachnoid hemorrhage • ischemia • hypertension • dopamine • cerebral blood flow • vasospasm

DELAYED ischemic neurological deficits due to vasospasm complicate the course of 15% to 36% of patients after aneurysmal subarachnoid hemorrhage (SAH), and account for approximately 13.5% of inpatient mortality and morbidity. Various surgical approaches and pharmacological agents have been evaluated both experimentally and clinically to improve cerebral blood flow (CBF) in patients with vasospasm. Currently, the mainstay of medical management for established vasospasm is induced hypertension and volume expansion. The primary rationale for the use of induced hypertension is that raising cerebral perfusion pressure may increase CBF in high-resistance vascular beds and/or increase collateral flow to ischemic brain regions.

Induced hypertension was initially used as therapy for cerebral ischemia in patients with neurological deficits caused by ischemic cerebrovascular disease. Farhat and Schneider were the first to recognize the potential applicability of induced hypertension in patients with vasospasm after SAH. Induced hypertension combined with volume expansion ultimately evolved as a routine management strategy in patients with symptomatic vasospasm following the report of Kosnik and Hunt in which six of seven patients were neurologically improved or stabilized after initiating this treatment modality. Although these and subsequent studies were not controlled, induced hypertension in combination with volume expansion is now clinically accepted treatment for the reversal of delayed ischemic deficits after SAH. Despite these favorable clinical reports, hypertensive therapy is not always effective in reversing neurological deficits. Furthermore, vasopressor-induced hypertension may cause intracranial complications such as hemorrhage and aneurysmal rebleeding. Cardiac arrhythmias and myocardial infarction are also recognized complications of hypertensive therapy.
The safe and effective application of vaspressors to induce hypertension under pathological conditions such as vasospasm should be based on their known or directly measured effects on CBF. Rational choices for vaspressors, however, are hindered by the paucity of data on their cerebrovascular effects, resulting in indiscriminate use with ill-defined blood pressure endpoints. Dopamine hydrochloride is one of the more commonly used vaspressors in the management of vasospasm after SAH. The objective of this study was to evaluate the effects of dopamine-induced hypertension on CBF in patients suspected of having delayed ischemic deficits due to vasospasm.

Clinical Material and Methods

**Patient Population**

The medical records, CBF studies, and computerized tomography (CT) scans of 13 patients with aneurysmal SAH who had undergone physiological challenge studies with dopamine were reviewed retrospectively. Neurological status was graded on admission to the hospital according to the Hunt and Hess classification. The patient group was predominately female, with a mean age of 59 ± 16 years (range 24 to 77 years) (Table 1). In 12 of the 13 patients, CT scans showed cisternal blood. All patients underwent aneurysm clipping within 72 hours of the primary or secondary hemorrhage. Neurological deterioration that was remote from surgery and not readily explainable by metabolic, electrolyte, or infectious etiologies developed in all patients and was considered to represent clinical vasospasm. Vasospasm was documented angiographically or by transcranial Doppler ultrasound flow measurements in 12 of the 13 patients; the remaining patient (Case 12) had equivocal evidence of vasospasm on angiography.

**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Clinical Grade*</th>
<th>Aneurysm Location†</th>
<th>Vasospasm‡</th>
<th>Angiography</th>
<th>TCD</th>
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<td>1</td>
<td>72, F</td>
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<td>+</td>
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<tr>
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<td>+</td>
<td>+</td>
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<tr>
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<td>61, M</td>
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<td>+</td>
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<tr>
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<td>+</td>
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<tr>
<td>5</td>
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<td>rt ACA</td>
<td>+</td>
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<tr>
<td>6</td>
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<td>+</td>
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<tr>
<td>7</td>
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<td>+</td>
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<tr>
<td>8</td>
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<td>+</td>
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<tr>
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<td>60, M</td>
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<td>+</td>
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<td></td>
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<tr>
<td>11</td>
<td>67, F</td>
<td>I</td>
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<td>+</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>63, F</td>
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<td>+</td>
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<tr>
<td>13</td>
<td>33, F</td>
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</table>

* Grading according to the Hunt and Hess classification. † ICA = internal carotid artery; PCoA = posterior communicating artery; ACA = anterior communicating artery. ‡ TCD = transcranial Doppler ultrasound study; + = evidence of vasospasm present.

**CBF Measurements**

Patients underwent CBF measurement via xenon-enhanced CT using a scanner with software adapted for CBF imaging. Briefly, the scanning protocol for CBF imaging began with the selection of two scan slices acquired from standard CT images. The first of these scans passed through the basal ganglia (level 1), while the second was 20 mm higher, passing through the centrum semiovale (level 2). Following scan selection, two baseline images at each selected CT level were obtained, followed by six enhanced images at each CT level acquired during the inhalation of a 35% xenon/67% oxygen gas mixture. In intubated patients, the gas was delivered to the gas intake port of a portable mechanical ventilator. The total xenon inhalation period was approximately 4.5 minutes. Arterial blood pressure, end-tidal CO₂, and arterial saturation were monitored continuously throughout each study. Arterial blood gases were measured at the end of each CBF study.

Nineteen CBF studies were performed with and without dopamine-induced hypertension at a mean of 9.7 ± 5.6 days (range 1 to 22 days) after aneurysmal SAH. In 10 of the 19 studies, dopamine was already being administered prior to CBF measurement as treatment for suspected vasospasm. In these cases, the first CBF measurement was made while the patient was receiving dopamine. Following the first CBF measurement, dopamine infusion was reduced until mean arterial blood pressure (MABP) fell by at least 10 to 15 mm Hg, then the second CBF measurement was made at least 20 minutes later. In the remaining nine studies, dopamine was administered to increase MABP by at least 10 to 15 mm Hg after the first CBF measurement. Similarly, the second CBF measurement was made at least 20 minutes after the first. The dopamine dose was not available for all studies but ranged from 6.4 to 20 μg/kg/min to achieve blood pressure endpoints. Minute ventilation was kept constant.

After acquisition of CBF images, multiple circular regions of interest (2 cm in diameter), which included a mixture of gray and white matter, were placed about the cortical mantle for each CT/CBF level by vascular territory (Fig. 1). Local CBF was determined for each of these regions. The flow values for each region of interest within a vascular territory were averaged, providing a mean territorial flow value. For every CBF measurement, three vascular territories in each hemisphere at each CT level provided a total of 12 vascular territories for CBF analysis. Any vascular territory with an average flow value of 25 ml/100 gm/min or less was considered to be ischemic. Territories with acute CT-defined infarction or image artifact were noted. All six territorial flow values for level 1 were averaged with those of level 2 to provide a global CBF value for each CBF study. The CBF data for

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* XeScan gas mixture supplied by Prazair Pharmaceutical Gases, Danbury, Connecticut.

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FIG. 1. Schematic drawing of the level 1 (left) and level 2 (right) computerized tomography scan slices illustrating the placement of multiple circular regions of interest (2 cm in diameter) around the cortical mantle based on vascular territories for the calculation of local cerebral blood flow (CBF). Territorial local CBF was derived by averaging the flow values of all regions within a vascular territory. ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery. For definition of levels 1 and 2, see Clinical Material and Methods section.

selected patients were recalculated with CBF images presented in a color scale format.†

Statistical Analysis

Paired t-tests were used to compare CBF values at normotension to those obtained after dopamine-induced hypertension. Simple linear regression was used to examine the relationship between territorial CBF at normotension and the CBF response to hypertension. The data are presented as mean ± standard deviation, and differences were considered significant if the p value was less than 0.05.

Results

Dopamine infusion resulted in a significant increase in MABP from 90 ± 11 mm Hg (range 71 to 110 mm Hg) to 111 ± 13 mm Hg (range 95 to 150 mm Hg) (p < 0.05). Arterial pCO<sub>2</sub> was 34.2 ± 4.1 mm Hg during normotension and was unchanged during dopamine-induced hypertension. Hematocrit for the entire group was 32% ± 3%.

A total of 228 vascular territories were analyzed from the 19 CBF studies. Of these, 16 territories from four studies were eliminated because of image artifact, leaving a total of 212 territories available for analysis. Mean global CBF for the group was 38.4 ± 13.6 ml/100 gm/min at normotension and 39.3 ± 13.7 ml/100 gm/min during dopamine-induced hypertension (difference not significant). There was no correlation between either global or territorial CBF to changes in MABP induced by dopamine administration.

Of the 212 normotensive territorial flow measurements, 180 territories (on both levels 1 and 2) (85%) had CBF values greater than 25 ml/100 gm/min. Flow values of 25 ml/100 gm/min or less were identified in the remaining 32 territories (15%) and were considered to be ischemic. Flow values increased to more than 25 ml/100 gm/min in 22 of these ischemic territories after dopamine-induced hypertension; eight of the 10 remaining ischemic territories had CT-defined infarcted tissue contained within the territory. Mean CBF in these infarcted territories was 16.8 ± 5.5 ml/100 gm/min (range 7.2 to 22.2 ml/100 gm/min) at normotension. In ischemic territories that contained no infarcted tissue, mean CBF increased from 20.2 ± 4.4 ml/100 gm/min at normotension to 32.6 ± 11.5 ml/100 gm/min during dopamine-induced hypertension (p < 0.05). Figure 2 illustrates the favorable effect of dopamine-induced hypertension on low flow values in one patient (Case 10).

In the 180 nonischemic territories, mean CBF was 41.8 ± 11.8 ml/100 gm/min at normotension and 41.5 ± 13.0 ml/100 gm/min with dopamine-induced hypertension (difference not significant). Although overall mean CBF was unchanged during dopamine-induced hypertension in these territories, analysis of individual territorial responses revealed that local CBF increased by at least 5 ml/100 gm/min in 56 territories (31%), was unchanged in 59 (33%), and decreased by at least 5 ml/100 gm/min in 65 (36%). Of the 65 territories in which flow decreased, six fell below 25 ml/100 gm/min and none fell below 20 ml/100 gm/min. Figure 3 illustrates a “paradoxical” decrease in CBF with dopamine-induced hypertension in one patient (Case 9).

Simple linear regression was used to evaluate the relationship between CBF in noninfarcted territories at normotension and the change in CBF after dopamine administration (Fig. 4). The territorial CBF response to dopamine was negatively correlated with territorial CBF under normotensive conditions (r = −0.52, p < 0.001).

When individual patients were evaluated, four patients suspected of suffering clinical vasospasm had no evidence of ischemic flow under normotensive conditions. Ischemic territorial flow values were, however, identified in nine of the 13 patients at the time of CBF study; seven responded to dopamine administration with an increase in CBF out of the ischemic range. One of the remaining patients had ischemic flow identified only in CT-defined infarct zones, while the other patient had postsurgical changes in the ischemic territory that also did not respond to dopamine administration.

Discussion

Numerous clinical reports suggest that dopamine-induced hypertension effectively reverses neurological deficits associated with vasospasm after SAH.5,6,18,23,37,50,55,56 The dopamine-induced elevation in perfusion pressure presumably increases local CBF above ischemic thresholds, resulting in functional improvement. Although dopamine-induced hypertension has been shown to improve CBF in animal models of focal ischemia52 and SAH,61 data in patients with SAH are

† Color imager manufactured by Diversified Diagnostic Products, Inc., Houston, Texas.
limited. In addition, because most clinical reports are confounded by the concurrent use of other treatments, the direct effect of dopamine-induced hypertension on clinical response of CBF is unclear.

In the present study, global CBF was unchanged with dopamine-induced hypertension; however, evaluation of territorial responses demonstrated a significant increase in CBF in those territories that were ischemic but not infarcted. An increase in CBF above the ischemic range occurred in 92% of these ischemic territories. Mendelow, et al., measured hemispheric CBF ipsilateral and contralateral to aneurysm rupture with $^{133}$Xe during withdrawal of dopamine-induced hypertension in eight patients suspected of having vasospasm after SAH. Dopamine withdrawal decreased MABP from 113 to 85 mm Hg. The CBF also decreased significantly in both hemispheres, with CBF in the hemisphere affected by aneurysm rupture decreasing from a mean of 34 to 27 ml/100 gm/min. Beneficial effects on ischemic CBF were also shown using similar CBF methods after phenylephrine-induced hypertension. In four patients with vasospasm, CBF increased from 18.8 to 30.8 ml/100 gm/min in the hemisphere ipsilateral to the side of surgery and from 21.0 to 35.8 ml/100 gm/min in the contralateral hemisphere. These data support the concept that drug-induced hypertension is associated with an improvement of CBF in regions of ischemia in patients with SAH.

The observed CBF responses to dopamine-induced hypertension in nonischemic territories were variable. Either an increase or no change in local CBF was observed in about two-thirds of these territories, while in the remaining one-third, CBF paradoxically decreased in response to induced hypertension. The CBF in a small percentage of these territories decreased into the ischemic range. When the relationship between the change in blood pressure and change in territorial CBF was examined, CBF was unrelated to changes in blood pressure but was related to normotensive CBF values. The paradoxical negative flow response to hypertension in nonischemic territories was unexpected and is a potentially deleterious effect associated with dopamine-induced hypertension.

Several mechanisms may explain the observed increases in CBF with dopamine-induced hypertension. As autoregulation may be impaired after SAH, CBF may increase passively, following changes in cerebral perfusion pressure. The observed increases in CBF might also be caused by mechanical vasodilation or by an increase in collateral flow. Direct pharmacological effects of dopamine must also be considered. When applied to pial arteries, dopamine
infused at a low concentration causes vasodilation while higher concentrations cause vasoconstriction. The vasodilatory response to dopamine appears to be mediated by dopaminergic receptors, while the vasoconstrictor response is likely mediated by alpha-adrenergic and/or serotonin receptors. Studies using intravenous administration have also shown a dose-dependent response of CBF to dopamine, with lower doses causing flow to decrease or remain unchanged while moderate doses increase CBF and high doses decrease CBF. In animal models of focal ischemia and SAH, dopamine administration improved CBF with minimal effects on perfusion pressure. In clinical studies, hemispheric CBF increased by 10%, with focal areas of ischemia improving in response to low-dose dopamine (5 μg/kg/min) in patients with SAH, while MABP increased by only 5%. Similar effects on CBF were noted with low doses of dopamine in a group of patients with cerebrovascular and degenerative disease. Although we were unable to establish a dose-response relationship in our study, the foregoing data indicate that dose-related pharmacological effects are possible explanations for the lack of a direct relationship between changes in CBF and changes in perfusion pressure.

It is not generally recognized that dopamine-induced hypertension can decrease CBF when used in the treatment of vasospasm. Although the number of territories was small, the reduction of flow in nonischemic regions to below 25 ml/100 gm/min is worrisome. Several mechanisms might explain these observations. First, disruption of the blood-brain barrier, as can occur with SAH, may permit dopamine concentrations to...
reach levels sufficiently high to result in vasoconstriction and reduced CBF. In such circumstances, even low concentrations of dopamine might cause vasoconstriction because of denervation hypersensitivity.  

Second, the reduction in flow may represent a steal phenomenon. Vascular beds with increased flow in response to dopamine may steal flow from marginally perfused vascular beds that are known to exist in a state of compensated vasodilation. Finally, hypertension-induced localized increases in tissue pressure might result in localized decreases in perfusion pressure and decreased CBF. Although the mechanisms of the steal response after dopamine administration are speculative, these observations raise serious concerns about the potential for causing ischemia when dopamine is employed empirically.

An important consideration in the interpretation of our study is the flow threshold at which we chose to define ischemia. Thresholds for neuronal function and viability exist and are well described in animal models of ischemia. Although such flow thresholds have been identified experimentally, similar thresholds have been difficult to define in man. Interpretation of the available data in this regard is limited in that there may be regional selective vulnerability, and the available CBF methods measure large regions of tissue that contain a mixture of both gray and white matter. Nonetheless, recent investigations using positron emission tomography and xenon-enhanced CT in patients with ischemia and SAH suggest that local CBF values less than 15 to 20 ml/100 gm/min are associated with infarction. Flow values in the range of 15 to 19 ml/100 gm/min appear to be adequate to sustain tissue viability, while flow values greater than 19 ml/100 gm/min preserve function. Little data on functional CBF thresholds in patients with SAH exist. However, using the $^{133}$Xe method, Symon, et al., correlated mean CBF values less than 30 ml/100 gm/min with delays in somatosensory central conduction time in patients with SAH. In view of these data, we consider the threshold value of 25 ml/100 gm/min that we used in this study to be reasonable for assessing the effects of dopamine administration on CBF after SAH.

Many recent reports have suggested that CBF measurements are of value in the diagnosis and management of patients with vasospasm after SAH. Our CBF data, obtained using xenon-enhanced CT, further emphasize that clinical signs may not be reliable in identifying patients with reversible ischemia or (perhaps more importantly) which patients might benefit from therapeutic interventions such as induced hypertension. Nine of the 13 patients suspected of suffering vasospasm in this series had ischemic flow values identified, with seven demonstrating reversible ischemia. The difficulty in determining the presence of reversible ischemia on clinical grounds could explain the variability in response to such therapeutic interventions. The sensitivity of clinical signs as indicators of the presence of significant vasospasm is also a problem. Critical flow reductions may occur in clinically silent zones or may precede the onset of focal signs. By permitting the identification of regions of infarction and ischemia, methods such as xenon-enhanced CT that allow for high-resolution CBF measurements with direct anatomical correlation should provide accurate assessment of patients with suspected vasospasm and thus safer, more appropriate prescription and titration of therapeutic interventions.

**Conclusions**

In our study, only 54% of patients suspected of suffering vasospasm after SAH actually had dopamine-induced reversible ischemia identified by xenon-enhanced CT. Dopamine-induced hypertension was effective in improving ischemic territorial flow in noninfarced territories; however, dopamine administration may also paradoxically decrease flow with the potential to cause ischemia. Our experience further underscores the potential value of CBF measurements to confirm the presence of ischemia and to evaluate the response to therapeutic interventions employed in patients with suspected vasospasm after SAH.

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