Effect of α-adrenergic blockade on the cerebrovascular response to increased intracranial pressure after hemorrhage

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Object. In this study the authors tested the hypothesis that hemorrhagic hypotension and high intracranial pressure induce an increase in cerebrovascular resistance that is caused by sympathetic compensatory mechanisms and can be modified by α-adrenergic blockade.

Methods. Continuous measurements of cerebral blood flow were obtained using laser Doppler microprobes placed in the cerebral cortex in anesthetized pigs during induced hemorrhagic hypotension and high cerebrospinal fluid pressure. Eight pigs received 2 mg/kg phentolamine in 10 ml saline, and 13 pigs served as control animals. During high intracranial pressure occurring after blood loss, cerebral perfusion pressure (CPP) \( p < 0.01 \) and cerebral blood flow \( p < 0.01 \) decreased in both groups. Cerebrovascular resistance increased \( p < 0.05 \) in the control group and decreased \( p < 0.005 \) in the phentolamine-treated group. The cerebrovascular resistance was significantly lower in the phentolamine-treated group \( p < 0.05 \) than in the control group. Cerebrovascular resistance increased at lower CPPs in the control group (linear correlation, \( r = 0.39, p < 0.01 \)) and decreased with decreasing CPP in the phentolamine-treated group (linear correlation, \( r = 0.76, p < 0.001 \)).

Conclusions. This study shows that the deleterious effects on cerebral hemodynamics induced by blood loss in combination with high intracranial pressure are inhibited by α-adrenergic blockade. This suggests that these responses are caused by α-adrenergically mediated cerebral vasoconstriction.

Key Words • cerebral blood flow • hemorrhagic hypotension • high intracranial pressure • α-adrenergic blockade • pig

Although moderate hypotension does not impair cerebral blood flow (CBF), several studies suggest that cerebrovascular resistance may increase if blood loss is the cause of the hypotension.\(^5\) The cerebrovascular resistance in hemorrhagic hypotension could be affected both by vasodilating influences as part of autoregulation and by vasoconstricting influences as part of the sympathetic compensatory mechanisms to hemorrhage.\(^7,28\) Increased cerebrovascular resistance has also been observed during periods of high cerebrospinal fluid pressure.\(^7\) The catecholamine response to high intracranial pressure is greatly enhanced at perfusion pressures below 30 mm Hg.\(^8\) Our hypothesis was that combined hemorrhagic hypotension and high intracranial pressure induce an increase in cerebrovascular resistance that is caused by sympathetic compensatory mechanisms and thus can be modified by a sympathetic blockade. We have therefore studied the effect of α-adrenergic blockade on the cerebrovascular response to increased intracranial pressure after hemorrhage. For this purpose a model of high cerebrospinal fluid pressure combined with blood loss in pigs was used. Our results suggest that the combination of blood loss and high intracranial pressure increases cerebrovascular resistance and causes a dysfunction of autoregulation. These changes can be blocked by α-adrenergic antagonists, consistent with our hypothesis.

Materials and Methods

Animal Preparation and Operative Technique

The study was performed with the consent of the Norwegian Council of Animal Research Code for the Care and Use of Animals for Experimental Purposes.

Twenty-one juvenile Norwegian-bred landrace pigs of either sex, each weighing between 15 and 30 kg, were used. All animals were housed with veterinary supervision; they were denied food overnight but were allowed free access to water. The animals were anesthetized with an intramuscular bolus injection of ketamine (15 mg/kg) and anesthesia was maintained by continuous intravenous infusion of pentobarbital (15 mg/kg/hour), supplemented by occasional intravenous injections of 1 mg/kg pentobarbital and 1 mg/kg morphine to maintain the absence of pain reactions. After intubation, ventilation was established with 70% nitrous oxide/30% oxygen by a servventilator at 20 breaths/minute and 5 to 7 L/minute, adjusted to maintain normocapnia according to repeated blood gas measurements. Muscular paralysis was achieved by intravenous administration of pancuronium (0.1 mg/kg in repeated doses) after the surgical preparation had been completed. With the animal supine, an
indwelling bladder catheter was inserted. Fluid-filled catheters were inserted into the aorta through the femoral arteries for monitoring of the arterial pressure and for controlled hemorrhage. Cardiac output was measured using standard thermodilution techniques. Blood temperature was measured through the thermistor probe of the Swan-Ganz catheter. Ringer’s acetate solution was administered intravenously at a rate of 10 mL/kg/hour throughout the experiment.

After these preparations had been made, the animal was turned to the prone position and a longitudinal midline incision was made, extending from the glabella to C-7. The atlantooccipital membrane and held in position by a rubber membrane and rapidly setting methylmethacrylate glue.

Three 5-mm diameter holes were made using a twist drill in the frontoparietal area of the skull, 10 mm from the midline on both sides, 10 mm in front of the coronal suture on one side, and 10 mm behind the coronal suture on both sides. Laser Doppler microprobes were positioned 3 to 5 mm into the cerebral cortex through small incisions in the dura. To achieve mechanical stability, the probes were stabilized in relation to the skull by inserting them through a cork that fit the hole and by gluing them to the bone with rapidly setting methylmethacrylate glue. The probes were connected to master probes with screw couplings. The catheters were connected to pressure transducers and the zero reference was leveled at mid-chest. Recordings were transferred to a computer by an analog digital conversion system at a sample rate of 10 per second.

**Laser Doppler Flowmetry**

Laser Doppler measurements of CBF were obtained using one-channel and two-channel laser Doppler flowmeters. The flowmeters have a 2-mW helium-neon laser light with wavelength of 632.8 nm that is led by an optical fiber to a microprobe with a diameter of 0.5 mm. The magnitude and frequency distribution of the Doppler-shifted light is proportional to the number and velocity of blood cells moving through the illuminated area of the tissue. It is independent of the movement direction of the individual blood cells and, therefore, directional blood flow is not measured. A portion of the light is backscattered from the tissue. Photodetectors convert backscattered light into electrical signals, measured in millivolts. The flowmeters are used to measure backscattered light from tissue within 1 to 1.5 mm of the probe; they provide relative, not absolute, values of blood flow.26,27 Postmortem signals were considered to be zero blood flow and were subtracted from the flow values. The instruments were calibrated against a standardized latex solution, as recommended by the manufacturer. The analyzing band width of the flowmeters was set at 12 kHz, the gain at 1, and the time constant of the output amplifier at 0.2 second. The movement artifact filters of the flowmeters were never used. The laser Doppler technique demands a stable probe to avoid movement artifacts. Blood around hydrogen clearance electrodes have not revealed damage.33

Sources of Supplies and Equipment

The servoventilator (model 900B) was manufactured by Siemens (Solna, Sweden) and the Swan-Ganz catheter (model 93A-1311-74) by American Edwards Laboratories (Santa Ana, CA). The laser Doppler flow probes (model PF3199 L120, diameter 0.5 mm), screw couplings (model PF 318), and laser Doppler flowmeters (Periflux P28B [one channel] and Periflux 4000 [two channels]) were manufactured by Perimed AB (Stockholm, Sweden). The pressure transducers (model AE840) were obtained from Sensonor (Horten, Norway); and the pressure amplifiers, the Biopac analog digital conversion system (model M100WS), and Acknowledge software from Biopac Systems Inc. (Santa Barbara, CA). Phentolamine (Regitine) was manufactured by Ciba-Geigy (Basel, Switzerland) and the histoacryl methylmethacrylate glue was manufactured by Braun Melsungen (Melsungen, Germany).

**Results**

There were no significant differences observed between the two groups in any variable at baseline. Phentolamine caused small decreases (p < 0.05) in blood pressure, CPP, and systemic vascular resistance but no change in cardiac output, CBF, or cerebrovascular resistance (Table 1).

Acute responses to hemorrhage were decreases in blood pressure (p < 0.001), CPP (p < 0.01), CBF (p < 0.05), and systemic vascular resistance (p < 0.05). The response was of similar magnitude in phentolamine-treated animals and in controls (Table 2). Cerebrovascular resistance decreased (p < 0.01) in treated animals, but did not change significantly in controls. Thirty minutes after hemorrhage was induced, the blood pressure and the CPP had increased in both groups, but both pressures were still lower.
than at baseline (p < 0.05). Cerebral blood flow and systemic vascular resistance had normalized in both groups. In treated pigs cerebrovascular resistance was no longer significantly different from baseline before intervention.

When high intracranial pressure was applied in this setting, blood pressure increased in both groups, so that it was no longer significantly different from the baseline values (Table 2). Cardiac output and systemic vascular resistance remained unchanged from baseline in the phentolamine-treated animals, but systemic vascular resistance was higher than baseline (p < 0.05) in the controls. Cerebral perfusion pressure was considerably decreased from baseline in both groups (p < 0.01 in treated pigs; p < 0.001 in controls) and CBF was similarly decreased (p < 0.01 in treated pigs; p < 0.001 in controls). Cerebrovascular resistance, however, was decreased in phentolamine-treated animals (p < 0.005) and increased in control animals (p < 0.05).

### Discussion

This study shows that hemorrhage combined with high intracranial pressure increases cerebrovascular resistance considerably. The increase could be prevented by an α-adrenergic blockade, indicating that increased sympathetic activity induced by the combination of hemorrhage and high intracranial pressure is responsible for this undesirable effect on the cerebral circulation.

Barbiturate anesthesia causes a reduction in the cerebral metabolic rate and decreases the functional activity of the brain, however, flow and metabolism remain coupled

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td><strong>Effects of α-adrenergic blockade in eight pigs</strong></td>
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<tr>
<td>Variable</td>
</tr>
<tr>
<td>Cmicrocirc (AU)</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
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<tr>
<td>CVR (CPP/Cmicrocirc)</td>
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<tr>
<td>MABP (mm Hg)</td>
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<tr>
<td>CO (L/min)</td>
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<tr>
<td>SVR (MABP/CO)</td>
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</table>

* Values are expressed as means ± standard deviations. Abbreviations: AU = arbitrary perfusion unit; Cmicrocirc = cerebral microcirculation as measured with laser Doppler flowmetry; CO = cardiac output; CVR = cerebral vascular resistance; MABP = mean arterial blood pressure; SVR = systemic vascular resistance.
† p < 0.05.

### Table 2

<table>
<thead>
<tr>
<th>Effects of high intracranial pressure during arterial hypotension in pigs*</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td><strong>controls (13 animals)</strong></td>
</tr>
<tr>
<td>Cmicrocirc (AU)</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
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<tr>
<td>CVR (CPP/Cmicrocirc)</td>
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<td>SVR (MABP/CO)</td>
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</table>

| **α-adrenergic blockade (8 animals)** | | | | |
| Cmicrocirc (AU) | 94 ± 47 | 65 ± 27† | 98 ± 53 | 34 ± 20‡ |
| CPP (mm Hg) | 97 ± 16 | 47 ± 17‡ | 81 ± 10† | 24 ± 23‡ |
| CVR (CPP/Cmicrocirc) | 1.29 ± 0.67 | 0.87 ± 0.50§ | 1.18 ± 0.93 | 0.76 ± 0.82§ |
| ICP (mm Hg) | 7 ± 5 | 6 ± 4 | 7 ± 5 | 73 ± 19§ |
| MABP (mm Hg) | 104 ± 19 | 53 ± 16† | 88 ± 12† | 93 ± 17 |
| CO (L/min) | 3.1 ± 0.85 | 2.54 ± 0.91 | 2.77 ± 0.68 | 2.83 ± 0.77 |
| SVR (MABP/CO) | 33 ± 8 | 22 ± 5§ | 32 ± 5 | 34 ± 8 |

* Values are expressed as means ± standard deviations. Abbreviations: AU = arbitrary perfusion unit; Cmicrocirc = cerebral microcirculation as measured with laser Doppler flowmetry; CO = cardiac output; MABP = mean arterial blood pressure; ICP = mean intracranial pressure; CVR = cerebral vascular resistance; SVR = systemic vascular resistance.
† p < 0.05 compared to baseline.
‡ p < 0.01 compared to baseline.
§ p < 0.005 compared to baseline.
α-Adrenergic blockade, high intracranial pressure, and hemorrhage

TABLE 3
Changes from baseline in 13 controls and α-adrenergic receptor-blocked pigs during high intracranial pressure following hemorrhage*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>α-Adrenergic Blockade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmicrocirc (AU)</td>
<td>0.37 ± 0.31</td>
<td>0.42 ± 0.31</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>0.34 ± 0.21</td>
<td>0.26 ± 0.26</td>
</tr>
<tr>
<td>CVR (CPP/Cmicrocirc)</td>
<td>2.0 ± 1.9</td>
<td>0.51 ± 0.37†</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>1.1 ± 0.15</td>
<td>0.84 ± 0.21</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>0.9 ± 0.18</td>
<td>0.8 ± 0.18</td>
</tr>
<tr>
<td>SVR (MABP/CO)</td>
<td>1.42 ± 0.32</td>
<td>0.92 ± 0.24†</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard deviations. The change in each animal was calculated separately by dividing the value obtained during high intracranial pressure with baseline value. See Table 1 for list of abbreviations.
† p < 0.05 compared with controls.

during pentobarbital anesthesia. The result is an increase in cerebrovascular resistance, with a decrease in CBF and cerebral blood volume. The animals in our study received approximately 2 g of pentobarbital during the total study. It is likely that this dose would cause a general reduction in CBF in our animals as compared with CBF in conscious animals. Pentobarbital also causes a reduction in the peripheral vasoconstriction and reduces the increase in blood levels of norepinephrine that follows hemorrhage. Pentobarbital tends to depress the sympathetic nervous system and inhibit its role in the maintenance of arterial pressure with hemorrhagic hypotension. It is therefore likely that the use of pentobarbital anesthesia in our study attenuated the effect of hormones acting on α-adrenergic receptors and that differences between α-adrenergic receptor–blocked animals and controls would probably be greater in conscious animals.

Laser Doppler flowmetry has shown a good correlation with radioactive microsphere and hydrogen clearance measurements of CBF measurements. A correlation coefficient of 0.92 between laser Doppler flowmetry and radioactive microspheres for measuring CBF in rabbits has been reported, and excellent agreement between the two techniques for measuring spinal cord blood flow in rabbits has also been found. We have previously shown, in a model similar to the present one, that measurements of the intracerebral microcirculation made by laser Doppler flowmetry correlate with radioactive microsphere measurements. Laser Doppler flowmetry has been used for numerous blood flow studies in the central nervous system when the most important variable for study was the relative change in tissue perfusion over time, although no current laser Doppler instrument can present absolute perfusion values (such as milliliters per 100 g tissue per minute), and measurements are expressed in arbitrary units. The calculated cerebrovascular resistance based on laser Doppler flowmetry, therefore, also has arbitrary units, but relative changes in cerebrovascular resistance based on laser Doppler flow values and microsphere measurements are highly correlated.

Our results, which suggest that high intracranial pressure following an episode of bleeding increases cerebrovascular resistance, are compatible with those of previous studies showing that, when hypotension is combined with some other kind of insult to the brain such as trauma, focal lesions, or vasospasm, hypotension causes a disproportionate decrease in the cerebral circulation. Even mild hemorrhagic hypotension is poorly tolerated by the brain when combined with some other kind of injury. The results of the present study indicate that generalized high intracranial pressure causes a similar vulnerable situation for the brain and that the tolerance to hemorrhage is probably small, not only in head injury victims but in many other neurosurgical patients suffering

FIG. 1. Graphs displaying changes in CPP plotted against changes in cerebrovascular resistance after blood loss and high intracranial pressure (all measurements included). A: Control animals. When CPP is very low, cerebrovascular resistance increases. (Line of best fit is second-order polynomial regression line, r = 0.49, p < 0.005.) B: α-Adrenergic receptor–blocked animals. When CPP decreases, cerebrovascular resistance also decreases. (Line of best fit is second-order polynomial regression line, r = 0.78, p < 0.001.) Both cerebrovascular resistance and CPP are shown as change from baseline.
from high intracranial pressure. Increased cerebrovascular resistance with decreasing CPP has been found in a high cerebrospinal fluid pressure model in rabbits, and it has been shown that the sympathetic response to high intracranial pressure increases sharply when the CPP falls below 30 mm Hg.\textsuperscript{15}

That low blood pressure combined with head injury is detrimental for the brain has been shown both clinically and experimentally by several groups.\textsuperscript{6,17,20,39,40} Autoregulation is impaired after head injury.\textsuperscript{20} Wei, et al.,\textsuperscript{39} found that pial vessel dilation with hemorrhagic hypotension disappeared after injury, and increased cerebrovascular resistance after head injury has been found.\textsuperscript{39} It has been suggested that increased cerebrovascular resistance after brain injury is an effect of increased sympathetic tone because these alterations can be attenuated by $\alpha$-adrenergic blockade.\textsuperscript{39} The increase in cerebrovascular resistance after head injury is therefore most probably caused by sympathetic compensatory mechanisms to blood loss.

The most important implication of this study is that a blockade of sympathetic $\alpha$-adrenergic receptors might result in higher levels of CBF in patients with the frequent combination of high intracranial pressure and hemorrhage. The normal reaction to hypotension is cerebral vasodilation.\textsuperscript{27} During hemorrhage, however, the CBF is probably affected both by autoregulatory vasodilation and neurogenic vasoconstriction. Loss of intravascular volume causes hypotension but also an increase in sympathetic nerve activity.\textsuperscript{28} It has been shown that sympathetic nerves affect the cerebral vessel tone via $\alpha$-adrenergic receptors and that sympathetic nerves are responsible for shifting the autoregulation toward higher CPP levels.\textsuperscript{27} When the sympathetic tone is high, as in hemorrhagic hypotension, the upward shift of the lower limit of the autoregulation is not advantageous for the brain but, rather, related to the general regulatory mechanisms of the body in response to blood loss. It has also been shown previously that in experimental hemorrhagic hypotension, blockade of sympathetic $\alpha$-adrenergic receptors can result in higher levels of CBF.\textsuperscript{6,12,15}

Even if phentolamine reduced cerebrovascular resistance, it did not improve CBF very much because $\alpha$-adrenergic blockade also reduced the CPP. Whether $\alpha$-adrenergic blockade might be used clinically to reduce the cerebrovascular resistance in situations in which the endogenous $\alpha$-adrenergic receptor stimulation is high (such as in hemorrhagic hypotension) while the blood pressure is maintained by agents not acting on $\alpha$-adrenergic receptors demands further study.

Conclusions

This study shows that blood loss in combination with high intracranial pressure has deleterious effects on the cerebral hemodynamics. The observed hemodynamic responses were strongly inhibited by $\alpha$-adrenergic blockade, suggesting that these effects are caused by activation of the sympathetic nerves to the cerebral vessels and a consequent $\alpha$-adrenergically mediated cerebral vasoconstriction.

References

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