Alpha-Adrenoreceptor Antagonists and Pial Vessel Diameter During Hypercapnia and Hemorrhagic Hypotension in the Cat

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SUMMARY It has been proposed that sympathetic activation may prevent maximum dilatation of extraparenchymal cerebral vessels during hemorrhagic hypotension and hypercapnia. In the present study, the effect of alpha-adrenoreceptor antagonists (phenoxybenzamine 1.5 mg kg⁻¹ or phentolamine 8 mg kg⁻¹) on pial vessel diameter was studied in the cat during hypotension and hypercapnia alone or in combination. Two levels of hypercapnia were used (mean PaCO₂ 74 and 122 mm Hg respectively). Pial arterial vessels (resting diameter 46–184 μm) were observed by means of a closed cranial window technique using a Leitz intravital microscope, an image splitting eyepiece, and a videoangiometer, the latter giving continuous data on changes of the inspected vessel diameters. Alpha-adrenoreceptor antagonists did not further increase the arterial diameter in any of the situations studied.

REGULATION OF CBF by carbon dioxide is generally believed to be mediated via extracellular H⁺ concentration, but other possibilities have been discussed such as regulation via carotid chemoreceptors and interaction between H⁺ and other vasoactive components. Discrete lesions in the mesencephalic reticular formation have been reported to reduce or abolish the response to carbon dioxide, and to reduce the response obtained after pretreatment with indomethacin. Stimulation of the cervical sympathetic chain during hypercapnia has been reported to result in a decrease of cerebral blood flow (CBF), an effect possibly caused by constriction of the extracerebral, including pial, vessels. Hypercapnia may cause sympathoadrenal activation, although cervical sympathetic stimulation did not inhibit pial arteriolar dilatation during subsequent hypercapnia, although the hypercapnic CBF-increase was abolished.

Cerebral vessels have been reported to autoregulate at a lower level when the pressure is reduced by drugs than by bleeding in previously normotensive baboons but not in renal hypertensive baboons. As alpha-adrenoreceptor blockade improved the maintenance of CBF in hemorrhagic hypotension, it was suggested that the increased sympathetic activity during hemorrhagic hypotension leads to a vasoconstriction of the main inflow vessels to the brain. The present experiments were performed to evaluate a possible influence of the presumed increased sympathetic activity during hypercapnia and hemorrhage on pial vessels, i.e., to provide the answers to the following 3 questions:

1. Does alpha-adrenoreceptor blockade further dilate pial vessels during hypercapnia per se?
2. Do pial arterial vessels increase their diameter after alpha-blockade in hemorrhagic hypotension?
3. Does a sympathetic stimulation induced by bleeding reduce pial vessel dilatation during hypercapnia?

Materials and Methods

Seventeen cats were anesthetized with 40 mg kg⁻¹ pentobarbital, immobilized with 60 μg kg⁻¹ pancuroniumbromide, intubated endotracheally and respirated with a 3:1 mixture of N₂O:O₂, using a Loosco respirator (Hoek-Loos, Amsterdam, Holland). Both femoral arteries and one femoral vein were cannulated with Portex catheters for continuous monitoring of blood pressure (Hellige-unit, Hellige, Freiburg, GFR), withdrawal of arterial blood for frequent blood gas controls (AVL gas check type 937C, List, Graz, Austria) and intravenous administration of drugs, respectively.

Pial vessels were observed by means of a closed cranial window technique using a Leitz intravital microscope (Leitz, Wetzlar, GFR), an image splitting eyepiece and a videoangiometer, the latter giving continuous data on changes of the investigated vessel diameters. Alpha-adrenoreceptor antagonists did not further increase the arterial diameter in any of the situations studied.

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divided into 4 groups of 6, 5, 3 and 3 cats respectively.

Group 1. $\text{Paco}_2$ was increased from 29 to 117 mm Hg (mean values) by adding CO$_2$ to the respired gas mixture. CO$_2$ was withdrawn when maximum hypercapnic vasodilatation had been reached and after normalization of $\text{Paco}_2$. 1.5 mg kg$^{-1}$ phenoxybenzamine (3 cats) or 8 mg kg$^{-1}$ phentolamine (3 cats) was injected i.v. Thereafter, hypercapnia was again induced to a mean level of 115 mm Hg.

Group 2. The blood pressure was decreased by withdrawal of arterial blood. Alpha-adrenergic blockade was then induced by i.v. injection of 8 mg kg$^{-1}$ phentolamine. Continuous observation of arterial diameters as described above was carried out in order to detect any further dilatation.

Group 3. Phentolamine, 8 mg kg$^{-1}$, was injected i.v. during combined hypotension and hypercapnia ($\text{Paco}_2$ 122 mm Hg). Pial artery changes were simultaneously observed as described above. In these experiments, intracranial pressure (ICP) was monitored by inserting a needle into the cisterna magna to verify the effect of hypercapnia, i.e. the increase of cerebral blood volume and hence ICP.

Group 4. In these cats a moderate degree of hypercapnia was induced ($\text{Paco}_2$ 73.5-75.5 mm Hg) after lowering the blood pressure to 60 mm Hg by bleeding. As soon as a hypercapnic steady state was reached, 1.5 mg kg$^{-1}$ phenoxybenzamine was injected i.v. and mean arterial pressure (MAP) was kept stable on 60 mm Hg by reinfusion and bleeding. Statistical differences were evaluated by Student's t-test.

### Results

Mean arterial pressure, $\text{Paco}_2$, $\text{Pao}_2$ and pial arterial diameter variations during resting conditions and during the experimental procedure are given in Table 1.

**Table 1.** Mean Arterial Pressure (MAP), $\text{Paco}_2$, $\text{Pao}_2$ and Pial Arteriolar Diameter ($\phi$A) During Resting Conditions and Before and After Alpha-Adrenergic Blockade with Phenoxybenzamine (1.5 mg kg$^{-1}$) or Phentolamine (8 mg kg$^{-1}$) in Hypercapnia and in Hypotension. Mean values ± sd. n = number of animals.

<table>
<thead>
<tr>
<th>Group</th>
<th>$\phi$A μm</th>
<th>% of resting $\phi$</th>
<th>MAP mm Hg</th>
<th>$\text{Paco}_2$ mm Hg</th>
<th>$\text{Pao}_2$ mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 n = 6</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Resting</td>
<td>50.2 ± 7.9</td>
<td>100.0</td>
<td>152 ± 26</td>
<td>29 ± 1</td>
<td>107 ± 9</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>112.9 ± 24.4</td>
<td>225.5 ± 29.9</td>
<td>145 ± 17</td>
<td>118 ± 12</td>
<td>102 ± 16</td>
</tr>
<tr>
<td>Hypercapnia + α-blockade</td>
<td>108.2 ± 21.5</td>
<td>216.5 ± 28.1</td>
<td>79 ± 12</td>
<td>115 ± 12</td>
<td>106 ± 19</td>
</tr>
<tr>
<td><strong>Group 2 n = 5</strong></td>
<td></td>
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</tr>
<tr>
<td>Resting</td>
<td>103.9 ± 33.6</td>
<td>100.0</td>
<td>115 ± 29</td>
<td>28 ± 3</td>
<td>97 ± 14</td>
</tr>
<tr>
<td>Hypotension</td>
<td>107.2 ± 34.8</td>
<td>103.4 ± 2.9</td>
<td>67 ± 5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hypotension + α-blockade</td>
<td>106.6 ± 34.4</td>
<td>103.4 ± 7.5</td>
<td>67 ± 5</td>
<td>29 ± 7</td>
<td>96 ± 17</td>
</tr>
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<td><strong>Group 3 n = 3</strong></td>
<td></td>
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<tr>
<td>Resting</td>
<td>129.7 ± 62.1</td>
<td>100.0</td>
<td>143 ± 4</td>
<td>35 ± 1</td>
<td>123 ± 5</td>
</tr>
<tr>
<td>Hypotension</td>
<td>152.3 ± 50.7</td>
<td>126.3 ± 28.9</td>
<td>70 ± 0.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>183.3 ± 72.6</td>
<td>147.5 ± 10.3</td>
<td>161 ± 8</td>
<td>122 ± 26</td>
<td>105 ± 8</td>
</tr>
<tr>
<td>Hypotension + hypercapnia + α-blockade</td>
<td>169.0 ± 67.1</td>
<td>137.5 ± 27.1</td>
<td>50 ± 8</td>
<td>—</td>
<td>—</td>
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<tr>
<td><strong>Group 4 n = 3</strong></td>
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<tr>
<td>Resting</td>
<td>86.2 ± 41.6</td>
<td>100.0</td>
<td>142 ± 2</td>
<td>30 ± 1</td>
<td>105 ± 2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>118.7 ± 53.2</td>
<td>113.4 ± 10.6</td>
<td>63 ± 1</td>
<td>30 ± 1</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>147.9 ± 65.5</td>
<td>184.9 ± 51.6</td>
<td>63 ± 2</td>
<td>74 ± 1</td>
<td>—</td>
</tr>
<tr>
<td>Hypotension + hypercapnia + α-blockade</td>
<td>152.0 ± 66.9</td>
<td>189.6 ± 50.2</td>
<td>61 ± 2</td>
<td>73 ± 2</td>
<td>—</td>
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</tbody>
</table>
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Figure 1. Experiment from Group 1 showing mean arterial pressure (MAP, broken line, left ordinate) and arterial diameter (ΦA, solid line, right ordinate) during hypercapnia. The left half illustrates the parameters before, the right half after alpha-adreno-receptor blockade with phenoxybenzamine (Ph, 1.5 mg kg⁻¹). H = Hypercapnia.

Figure 2. Individual example of Group 2. Following hemorrhagic hypotension, phentolamine (8 mg kg⁻¹) does not induce further arterial dilatation (ΦA). MAP = mean arterial pressure. Further fall in MAP after phentolamine was compensated by reinfusion of blood.

Figure 3. Individual cat in group 3. The diameter of 2 pial arterial vessels (ΦA) increases during hemorrhagic hypotension and hypercapnia. Alpha-adrenergic blockade with phentolamine (8 mg kg⁻¹) does not increase the diameter further during this situation. Mean arterial pressure (MAP) increases during hypercapnia and a sharp pressure drop is induced by phentolamine to bring MAP back to the prehypercapnic hypotensive level. Intracranial pressure (ICP) rises as expected during hypercapnia.

Discussion
During sympathetic stimulation phentolamine has been reported to prevent the constriction of pial arteries and to prevent the decrease in cerebral blood flow. There is controversy in the literature regarding the influence of the peripheral sympathetic nerves on
CO₂-induced cerebrovascular reactivity. This data, indicating an unresponsiveness of pial arterioles to alpha-adrenergic blockade during hypercapnia, is supported by several reports. Stone et al.77 and Waltz et al.80 observed unchanged CO₂-induced vasodilatation following cervical sympathetic ganglionectomy. Eidelman et al.9 reported even a reduced CBF-response following chemical sympathectomy with intracisternal 6-hydroxydopamine. The same group10 observed equally decreased CBF-response to hypercapnia following excision of the carotid chemoreceptor bodies, thus excluding the possibility of the CO₂-response being purely chemoreceptor-mediated. James et al.95 and Kawamura et al.80 found an enhanced increase in blood flow following section of the cervical sympathetic nerve and alpha-receptor blockade, respectively.

The discrepancy between single studies may be derived from different degrees of hypercapnia. As no information is available on the possible influence of the peripheral sympathetic system on different levels of carbon dioxide tension the data are difficult to compare. Different anesthetic agents and levels of anesthesia may also play a role. In the present study 2 levels of PACO₂ were chosen representing moderate and pronounced hypercapnia (PACO₂ around 70 and 120 mm Hg, respectively). The fact that alpha-adrenergic blockade was without effect at both levels of hypercapnia is evidence against the possibility that failure to show any adrenergic influence during pronounced hypercapnia was due to a toxic effect on adrenergic receptors.

It is likely that the slight decrease in pial vessel diameter following phentolamine in Group 3 is due to the parallel fall of blood pressure since the phenomenon was missing in the phenoxybenzamine-treated animals in Group 4 where MAP remained constant. Phentolamine passes the blood brain barrier to a lesser extent than phenoxybenzamine which was the reason for using the considerably higher dose of phentolamine. The lack of effect on pial artery diameter in Group 2 and 3 animals where phentolamine was used alone is not likely to be explained by poor drug penetration in light of the results from Group 1 and 4.

The failure to demonstrate any alpha-adrenoceptor influence on pial arterial tone in our study could be related to the anesthesia used. Although pentobarbital was used to initiate anesthesia the effect of this drug was considered to be low at the time pial arterial diameters were measured when anesthesia was maintained with a mixture of N₂O:O₂. A recent study confirms that pial vessels react to sympathetic activation during conditions corresponding to those in the present study.11 All experiments concerning neurogenic influences on anesthetized animals must be interpreted with some caution. Our results do not support the hypothesis of neurogenically induced vasoconstriction of pial arteries during hypercapnia and/or hemorrhagic hypotension.

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References

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