No Intracerebral Steal Phenomenon In The Ischemic Brain Following Papaverine Administration

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SUMMARY The steal phenomenon due to a vasodilator was investigated in 6 cats in which cerebral ischemia had been produced by left middle cerebral artery (MCA) occlusion. The photoelectric method was employed for continuous recording of the cerebral blood volume together with frequent determinations of the cerebral blood flow (CBF) through the ischemic cerebral tissue at the following four stages: 1) before MCA occlusion, 2) 2 hours after MCA occlusion before the injection of papaverine, 3) after the injection of papaverine, and 4) when the systemic arterial blood pressure (SABP) was adjusted non-pharmacologically to the control level using a "vasculator". The administration of the vasodilator produced conflicting results for the CBF changes in the ischemic area with a decrease in SABP as reported previously in the literature. However, when the SABP was corrected to the control level, the CBF in the ischemic region became increased in all 6 cases to above the control ischemic flow values. It is concluded that the decreased CBF in the ischemic tissue after vasodilator administration was not due to the steal phenomenon, but simply to a fall in SABP.

CEREBRAL VASODILATING AGENTS have not been recommended for use in the therapy of patients with acute stroke.1-3 However, the pioneer opinion proposed by Browne and Poskanzer in 1969 that cerebral vasodilators were of no value or even harmful to the patient with acute stroke, was based on observations of the steal phenomenon.5-6 The decrease in cerebral blood flow (CBF) to the ischemic tissue by CO₂ inhalation was studied extensively in laboratory animals,7-10 but the issue still remained controversial. Since it has been observed that the pharmacological sites of CO₂ and vasodilating agents in the cerebral arteries are different,11 the findings for the former cannot be extended to the effect of the latter. In the literature, the reported changes in CBF due to vasodilators, e.g., papaverine, in ischemic regions of patients with acute stroke and of animals with acute cerebral arterial occlusion, have been diverse and inconclusive.12-18 Even when CBF was demonstrated to decrease with papaverine, as in the cases reported by Olesen and Paulson19 and Regli et al,20 the decrease could not necessarily be attributed to the intracerebral steal phenomenon. It might be simply due to the influence of a concomitant decrease in SABP.

This paper attempts to re-evaluate the effect of vasodilators on the CBF of an ischemic area produced acutely by middle cerebral artery (MCA) occlusion in cats, under conditions where any decrease in SABP, after papaverine administration, was adjusted to the control level.

METHODS Six cats of both sexes weighing 2.5-4.2 kg were used. All cats were anesthetized with 50 mg/kg body weight of alpha-chloralose and 500 mg/kg body weight of urethane and immobilized with alcuronium chloride. Tracheal intubation was performed and respiration was controlled with a Harvard respirator. The left femoral artery and femoral vein were catheterized to monitor SABP and to administer papaverine (papaverine hydrochloride, Dainippon Pharmaceutical Co. Ltd., Japan). A thin polyethylene catheter was inserted into the left carotid artery via the lingual artery and used for repeated manual injection of 0.5 ml of saline to produce tissue hemodilution curves. For measurement of the cerebral blood volume (CBV) and mean transit time (T), the photoelectric method was employed. This method was designed to measure changes in the optical density of the cortical tissue in the bilateral sylvian opercula in situ, respectively. Details of the surgical technique and validity of the method have been reported elsewhere.21 The recordings of the optical density were scaled for changes in CBV, assuming that the control value of CBV was 6.3 vol% and that the influence of aggregate formation by red cells was negligible. The value of T was obtained by the area-over-height method from the dilution curves and further used for the calculation of 1/T and CBF according to the Stewart-Hamilton principle: CBF = 60 × CBV/ T. The cerebrovascular resistance (CVR) through the vascular channels in the measured tissue was calculated according to the equation: CVR = MABP/CBF. Transorbital occlusion of the left MCA at its origin was performed with a miniature Mayfield clip during continuous recording of CBV from the ipsilateral (i) brain region and simultaneously from the corresponding contralateral (c) region of the same brain. Papaverine hydrochloride at a dose of 1.5 mg/kg body weight was administered intravenously after 2 hours of MCA occlusion. The decrease in SABP induced by the papaver-
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FIGURE 1. An actual protocol of continuous recordings of CBV and CBF, before and after MCA occlusion, during and after papaverine injection and during SABP control with the vasculator. Small arrows denote tissue hemodilution curves used for calculating the mean transit time (1) of blood through the cerebral tissue.

Papaverine administration was adjusted to the control level by using a "vasculator" (Model AT 202, Amano & Co. Ltd., Hamamatsu, Japan). For the experimental maneuver, the lower part of the cat’s body was encased in the plastic cylindrical chamber of the vasculator so that a positive pressure ranging from 0 to 200 mmHg could be applied. A rubber flap was installed between the body of the cat and the rim of the vasculator chamber inlet to prevent leakage of air from the chamber. The changes in several hemodynamic parameters such as CBV, I, CBF and CVR were obtained from both the ischemic (i) and contralateral (c) cortices at the following four stages: 1) control or before MCA occlusion, 2) in the ischemic state, 2 hours after MCA occlusion just before papaverine administration, 3) after papaverine injection, and 4) in the ischemic state during control of SABP by means of the vasculator. The results were expressed as the arithmetical mean ± the standard error of the mean (SEM). Statistical significance was evaluated by Student’s t-test and the Wilcoxon’s signed rank test.

Results

A typical record of the sequential changes in CBV, CBVi, I and SABP recorded simultaneously before MCA occlusion, 2 hours after clipping of the MCA, after injection of papaverine and during control of SABP with the vasculator, is shown in figure 1. Occlusion of the MCA produced a rapid decrease in CBVi accompanied by a prolongation of the indicator dilution curve as reported previously.22 CBVi then gradually increased to the stage of low perfusion hyperemia.22 Injection of papaverine produced a remarkable increase in both CBVi and CBFi of the healthy side and a concomitant decrease in CBVi and slight increase in CBF of the occluded side. When SABP had recovered, both CBVi and CBFi were increased. The mean values of CBVi, CBVi, I/Ti, I/Tc, CBFi, CBFi, CVRi, CVRc, MABP and SABP during the four stages are summarized in table 1. Papaverine produced a decrease of MABP in all cases. The CBVi in the ischemic cortex was decreased in 4 animals, and slightly increased or unaltered in 2. It should be noted that CBFi was decreased in 2 animals, although the mean CBFi was increased on the average. The CBVi in the nonischemic cortex was increased following papaverine administration and CBFi was increased in all cases but one. The recovery of SABP effected by the vasculator produced increases in CBVi and CBFi of both the ischemic and nonischemic hemispheres in all animals of this series. The increase in CBFi from the values at the MCA occlusion level was statistically significant (p < 0.05). The mean CVRi, after clipping of the MCA was increased almost 3 times on the occluded side, whereas it was decreased slightly on the healthy side. Injection of papaverine produced a fall in CVRc, which remained decreased in spite of the recovery of SABP effected by the vasculator. A summary of the changes in CBVi and CBF is presented in figure 2 and figure 3, respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before MCAO (control)</th>
<th>2 hours</th>
<th>2 hours + papaverine</th>
<th>2 hours + papaverine + recovery of SABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBVi (vol%)</td>
<td>c</td>
<td>—</td>
<td>−0.38 ± 0.38</td>
<td>+0.67 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>i</td>
<td>—</td>
<td>+1.12 ± 0.57</td>
<td>−0.43 ± 0.79</td>
</tr>
<tr>
<td>I/T (sec⁻¹)</td>
<td>c</td>
<td>0.14 ± 0.02</td>
<td>0.13 ± 0.03</td>
<td>0.16 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>i</td>
<td>0.14 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>CBF (% of control)</td>
<td>c</td>
<td>100</td>
<td>79 ± 11.5</td>
<td>100.3 ± 16.8</td>
</tr>
<tr>
<td></td>
<td>i</td>
<td>100</td>
<td>30 ± 4.2</td>
<td>40 ± 7.9</td>
</tr>
<tr>
<td>CVR (mmHg/ml/100g/min)</td>
<td>c</td>
<td>2.23 ± 0.37</td>
<td>1.94 ± 0.30</td>
<td>1.36 ± 0.61</td>
</tr>
<tr>
<td></td>
<td>i</td>
<td>2.25 ± 0.43</td>
<td>6.18 ± 1.39</td>
<td>3.18 ± 0.70</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>—</td>
<td>107 ± 11</td>
<td>69 ± 8</td>
<td>99 ± 7</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 6); MCAO = middle cerebral artery occlusion; c = contralateral side; i = ipsilateral side.

*p < 0.05, control versus 2 hours MCAO.

*p < 0.005, control versus 2 hours MCAO.

*p < 0.05, 2 hours MCAO versus 2 hours MCAO + papaverine + recovery of SABP.

*p < 0.005, 2 hours MCAO versus 2 hours MCAO + papaverine + recovery of SABP.

*p < 0.005, 2 hours MCAO + papaverine versus 2 hours MCAO + papaverine + recovery of SABP.

*p < 0.01, 2 hours MCAO + papaverine versus 2 hours MCAO + papaverine + recovery of SABP.
Discussion

For the sake of simplicity, it is assumed that there is a conduit artery which divides into two branches, one of which goes to the ischemic tissue and the other to the surrounding normal area. Following vasodilator administration, the intracerebral steal phenomenon may occur if the artery to the ischemic region is non-responsive to the vasodilator, while the artery to the surrounding area dilates, increasing CBF greatly. The blood pressure at the branching site must decrease, since the pressure drop ($\Delta P$) in the conduit artery is predicted to be increased by $\Delta P = R\Delta Q$, where $\Delta Q$ is the increased blood flow through the conduit artery, and $R$ is the segmental vascular resistance which is assumed to be constant. Combination of the decrease in blood pressure head at the orifice of the ischemic microvasculature and constant peripheral vascular resistance in the ischemic region, causes a decrease in CBF to the region (ischemic CBF), while the blood flow to the intact cerebral tissue is increased following vasodilator administration. The fact that the decrease in ischemic CBF aggravates tissue ischemia, is a principal reason for refraining from the use of vasodilators in the therapy of acute stroke. However, a decrease in SABP commonly occurs concomitantly with vasodilator administration. Because the "autoregulatory" response of the vessels in the ischemic region is known to be abolished, it seems likely that the ischemic CBF decreases passively with the decrease in SABP. A differentiation between the two processes for the decrease in ischemic CBF induced by a vasodilator, i.e. the intracerebral steal phenomenon or a SABP decrease, was made in the present experiment. A decrease in ischemic CBF by papaverine was observed in 2 animals. This was, generally speaking, in accordance with the results reported by Olesen and Paulson,19 and Regli et al.20 Olesen and Paulson attributed their findings to the intracerebral steal phenomenon produced by papaverine. However, the present data for the increase in ischemic CBF during recovery of SABP to the level before papaverine administration, are contradictory to the steal phenomenon. The increase in ischemic CBF by papaverine under conditions of constant SABP can be explained in two ways. The first is that the artery in the ischemic tissue is still responsive to papaverine, and the dilated vessels result in the increase in ischemic CBF. The second possibility is that the conduit artery is dilated more by papaverine than the peripheral arteries supplying blood to the healthy tissue. The segmental vascular resistance ($R$) decreases, and the blood pressure at the branching site increases. Tomita et al measured the blood pressure in 150 µ pial arteries of cats before and after papaverine administration using a sphygmomanometric tech.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Summary of changes in CBV in the healthy (c) and ischemic (i) areas at the following four stages: 1) before MCA occlusion, 2) 2 hours after MCA occlusion before the injection of papaverine, 3) after the injection of papaverine, and 4) when the SABP was adjusted to the control level. Different symbols are used for each experimental case.

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Summary of changes in CBF in the healthy (c) and ischemic (i) areas. Explanations for the abbreviations are the same as in figure 2.
We are uncertain whether the carotid arterial system which forms a large portion of the conduit artery, dilated to increase the ischemic CBF as in the case of the "autoregulation" reported by McIedlishvili et al.24

A comment should be made concerning the intracerebral steal phenomenon produced by CO₂ inhalation as reported by Waltz,2 and Symon et al.9 Using the photo-electric method in 3 cats, Tomita found that the CO₂ responsiveness of cerebral vessels in the ischemic region estimated from the CBV increase during CO₂ inhalation began to decline approximately 10 min after MCA occlusion, completely disappeared at 2 hours of ischemia, and was restored at ca. 20 min after reopening of the MCA, while the responsiveness of cerebral vessels in the nonischemic area remained unchanged.25 If one considers the fact that CO₂ dominantly dilates the smaller part of intact cerebral arteries,1,11 the occurrence of the intracerebral steal phenomenon by CO₂ inhalation in spite of slight rise in SABP is likely according to the mechanism mentioned above.

In conclusion, it can be said that no intracerebral steal phenomenon due to papaverine took place in the ischemic brain in the present experiments. Vasodilators may tend rather to increase the cerebral blood flow in the ischemic region, if only the systemic arterial blood pressure can be maintained. Whether the increase in cerebral blood flow under conditions of constant systemic arterial blood pressure is due to the remaining responsiveness of the cerebral vessels in the ischemic tissue to vasodilators, or due to marked dilation of the conduit artery remains to be studied. Vasodilators which dilate cerebral vessels specifically may thus have a beneficial effect in selected patients with cerebral arterial occlusive disease.

References

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