A Paradoxical Cerebral Hemodynamic Effect of Hydralazine

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Abstract:
A Paradoxical Cerebral Hemodynamic Effect of Hydralazine

Hydralazine is shown to have a very complex cerebral hemodynamic effect. It raises the intracranial pressure which, together with its effect upon systemic blood pressure, reduces the cerebral perfusion pressure. In spite of this and a concomitantly induced hyperventilation by hydralazine, CBF increases with some delay. The conclusion is that hydralazine is a cerebral vasodilator acting immediately upon cerebral capacitance vessels but later upon the resistance vessels as well.

Methods
Regional cerebral blood flow (rCBF) was measured in 35 areas of the hemisphere by the $^{133}$Xe intra-arterial injection method. During each measurement an arterial blood sample was drawn for determination of carbon dioxide tension ($P_{aco_2}$) using a Severinghaus electrode. The arterial blood pressure (MABP) was measured intra-arterially using an electromanometer connected to the carotid catheter. The logarithmically displayed clearance curves were used for evaluation of regional differences in flow. In the normal brain these curves are linear and it is then possible to calculate rCBF$_{initial}$ quantitatively. In damaged brain tissue the two-minute curves are often nicked, and, if so, a more quantitative estimation of flow values is impossible by this method. As this situation occurred in most of the patients in the present series, we preferred to calculate flow from the linearly recorded clearance curves averaging all 35 detectors over ten minutes. The calculation was done by the height over area method. These are the figures given in table 1 and figure 1. The reproducibility by this method is about 5% expressed as the coefficient of variation.²

The intraventricular pressure was measured through a Seletz cannula inserted into a lateral ventricle through a precoronal burr hole. The cannula was connected to an electromanometer (Elema 35) and recorded continuously on a paper writer. Recording included amplitude as well as mean intraventricular pressure (MIVP). Mean arterial pressure (MABP) and MIVP were recorded simultaneously and both registrations were calibrated to the same water column.

Autoregulation was tested either by increasing MABP by intravenous (I.V.) infusion of synthetic angiotensin (Hypertensin®), thereby inducing a short augmentation of MABP, or by I.V. infusion of trimethaphan (Arfonad®), effecting a short-lived decrease of MABP.

Case Reports
PATIENT NO. 1
A 62-year-old woman with arterial hypertension was treated during the last ten years. One month before the actual study she had a stroke. Angiography revealed an intracerebral hematoma in the right parietal region which was evacuated on the eleventh day. The postoperative condition was unchanged with somnolence and a pronounced left hemiplegia. Blood pressure in this period was about 250/145 mm Hg and monitored MIVP about 30 mm Hg at a slight hypocapnia ($P_{aco_2}$ 31 to 34 torr). Following hydralazine (6.5 mg I.V.), blood pressure decreased to 190/90 mm Hg but MIVP rose to 50 mm Hg. The CBF study was done 19 days after operation. The autoregulation was tested before hydralazine was given and was found impaired. One minute after infusion of 12.5 mg hydralazine I.V. the intracranial pressure began to rise, and after another five minutes, a plateau was reached. Simultaneous to the change of MIVP the amplitude was doubled. The plateau continued the next 14 minutes until it promptly decreased when $P_{aco_2}$ was lowered to 24 torr by artificial hyperventilation. The MABP decreased at a slower rate than the MIVP rose, and not until seven minutes after the injection did it reach the lowest value.

PATIENT NO. 2
A 16-year-old boy was admitted nine hours after a traffic accident. A huge epidural hematoma was evacuated and the clinical condition was, on the whole, unchanged for the next weeks, i.e., coma and decerebrate rigidity. The first CBF study was performed on the fourth day. The autoregulation was impaired. Half a minute following infusion of hydralazine (12.5 mg I.V.), the intracranial pressure began to rise and also the amplitude to three times the resting value. Repeated infusion of 6.5 mg and again 6.5 mg hydralazine did not induce any further change of this intracranial pressure pattern. MABP started to decrease 90 seconds after the first 12.5 mg infusion of hydralazine, but...
A PARADOXICAL CEREBRAL HEMODYNAMIC EFFECT OF HYDRALAZINE

**TABLE 1**

<table>
<thead>
<tr>
<th>Case</th>
<th>MABP (mm Hg)</th>
<th>MIVP (mm Hg)</th>
<th>Paco₂ (torr)</th>
<th>CBF₁₀ (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>196</td>
<td>180</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>144</td>
<td>115</td>
<td>10</td>
<td>40</td>
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<td>106</td>
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</tr>
<tr>
<td>6</td>
<td>120</td>
<td>98</td>
<td>23</td>
<td>33</td>
</tr>
</tbody>
</table>

The lowest value was reached two minutes later and kept nearly constant for the following 24 minutes. The second CBF study was done on the tenth day, when the patient was still comatose with atypical decerebrate rigidity. Aurorregulation was tested with trimethaphan. Both blood pressure and intraventricular pressure decreased during this test and aurorregulation was impaired. Following 12.5 mg of hydralazine I.V., MIVP started to rise after one minute. A plateau was reached in ten minutes and this level remained unchanged for the next hour. The amplitude stayed more than doubled during the same period. MABP was unchanged after the initial two minutes after hydralazine injection and then slowly decreased, but not until ten minutes later did it reach the lowest level, which was steady for the next 50 minutes. CBF showed a decrease at 18, 30, and 50 minutes after the drug administration.

The second CBF study was done ten days after the stroke. Four-vessel angiography and ventriculography did not disclose an intracranial lesion but a certain degree of arteriosclerosis. During the interval between the investigation MIVP had been monitored continuously with values 30 to 40 mm Hg at moderate hypcapnia. Following infusion of 12.5 mg hydralazine I.V., MIVP reached a plateau with an approximately 50% increase in five minutes. After this it slowly increased a few torr but the amplitude was still doubled. The blood pressure began to decrease three minutes after the drug, and a plateau was reached after another four minutes and then kept at that level for the next hour. CBF measured 17 minutes after the administration of hydralazine showed a slight tendency to increase.

**Results**

Table 1 and figure 1 illustrate the well-known effect of hydralazine (12.5 to 18.5 mg I.V.) upon systemic blood pressure with an average reduction of 20%. From the continuous monitoring it appears that the decrease in blood pressure does not start until two to four minutes after the injection.

At the same time the intracranial pressure is raised about 110% and it is worth mentioning that this increase has a shorter delay after the administration of hydralazine, as it is manifest already about one minute after the injection. Not only is intracranial pressure increased, but the amplitude as well, up to two to three times the values at rest as illustrated in figure 2.

**Discussion**

In the present series the most striking effect of hydralazine was the increased intracranial pressure, in
average 110%, which appears before the decrease in systemic blood pressure. The combination of higher intracranial pressure and the lower systemic blood pressure means a decreased perfusion pressure. In spite of this and a pronounced tendency to hyperventilation by the administration of hydralazine, CBF increases. An increased CBF during administration of hydralazine has been suggested before. In 1953 McCullough reported that hydralazine in a series of controls and patients with hypertension due to pre-eclampsia had an increasing effect upon CBF. The author used the Kety-Schmidt nitrous oxide method and, judging from their CBF values, none of their patients seemed to have had any severe brain damage and probably an intact autoregulation although neither this nor the intracranial pressure was measured.

Most surprising in the present series is the fact that even in cases with an abolished autoregulation where CBF passively should be expected to follow the systemic blood pressure, CBF increases in spite of decreased perfusion pressure. The only exception is case 5, characterized by the highest intracranial pressure measured in these series and the steepest fall in MABP leaving a perfusion pressure as low as 46 mm Hg.

Concerning the early and persistent raise in intracranial pressure in spite of hyperventilation, the explanation must be that hydralazine initially has a more pronounced effect upon capacitance vessels than upon cerebral resistance vessels. A discrepancy of this kind is known from a few other drugs: histamine, isoprenaline, and hydergine. The clinical significance of these phenomena is difficult to evaluate. It may explain the headache which is a known side effect during the use of hydralazine. Later, hydralazine affects the resistance vessels as well, and to an even higher degree as CBF increases in spite of the decreased perfusion pressure.

In the pathogenesis of acute hypertensive encephalopathy an increased intracranial pressure plays a certain role. We have good evidence to believe that the first step in acute hypertensive encephalopathy is the breakthrough of cerebral autoregulation with a sudden all-over increase in CBF and with a raise in intracranial pressure of nearly the same proportion. A persistent hyperperfusion results in extravasation of albumin and water, i.e., a cerebral edema with increased pressure, reduced CBF, and ischemia. From this model it seems logical to presume that drugs increasing intracranial pressure should be avoided, but when on the other hand hydralazine improves CBF in spite of the increased intracranial pressure, the evaluation of this drug against others, e.g., certain sympatholytica which have been proved not to affect cerebral hemodynamics, can be based only upon clinical series.

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