Cerebral Blood Flow During Dihydralazine-Induced Hypotension in Hypertensive Rats

David I. Barry, Svend Strandgaard, David I. Graham, Ulrik G. Svendsen, Otto Braendstrup, and Olaf B. Paulson

SUMMARY The cerebrovascular effects of graded, controlled dihydralazine-induced hypotension were studied in rats with renal hypertension (RHR) and spontaneous hypertension (SHR). Repeated measurements of cerebral blood flow (CBF) were made using the intraarterial \(^{133}\)Xenon injection technique in anaesthetised normocapnic animals. Dihydralazine was administered in single increasing i. v. doses (0.1 to 2 mg/kg), and CBF measured after each dose when a stable blood pressure had been reached. From a resting level of 145 ± 7 mm Hg in RHR and 138 ± 11 mm Hg in SHR, mean arterial pressure (MAP) fell stepwise to a minimum of around 50 mm Hg. CBF was preserved during dihydralazine induced hypotension, and remained at the resting level of 79 ± 13 ml/100 g min in RHR and 88 ± 16 ml/100 g min in SHR. Following 2 hours hypotension at the lowest pressure reached, the rats were sacrificed by perfusion fixation and the brains processed for light microscopy. Evidence of regional ischaemic brain damage was found in 4 of 11 animals: in 2 cases the damage appeared to be accentuated in the arterial boundary zones. Although the lower limit of CBF autoregulation in these rats is around 100 mm Hg during haemorrhagic hypotension, dihydralazine brought MAP to around 50 mm Hg without any concomitant fall in CBF. This was interpreted as being due to direct dilatation of cerebral resistance vessels. The combination of low pressure and direct dilatation may have resulted in uneven perfusion, thus accounting for the regional ischaemic lesions.

EPIDEMIOLOGICAL STUDIES have established a clear pathogenic relationship between pre-existing hypertension and stroke morbidity and mortality. The importance of chronic antihypertensive therapy to the brain is emphasised by the resultant reduction in stroke incidence. In cases of malignant hypertension, and especially hypertensive encephalopathy, emergency blood pressure lowering is required, and may be life saving. Although this therapy is generally beneficial to the patient, recent concern has been expressed at the danger of inducing ischaemic brain damage by over-vigorous lowering of blood pressure. Central to this question is autoregulation of cerebral blood flow (CBF).

In the brain, blood flow is kept constant over a wide range of systemic pressure by autoregulatory changes in the diameter of resistance vessels; during a pressure increase they constrict and during a pressure decrease they dilate. The lower mean blood pressure limit of CBF autoregulation is about 70 mm Hg in normal man. At pressures below the lower limit autoregulatory vasodilatation is inadequate and CBF will fall in proportion to the fall in blood pressure. Maximal dilatation of cerebral blood vessels does not occur until an even lower blood pressure has been reached. Thus, there remains the possibility of pharmacological dilatation of cerebral vessels at pressures below the lower limit of CBF autoregulation, as demonstrated by the present study, and a similar study with nitroglycerine. In hypertensive patients, structural and functional adaptation of the cerebral circulation results in a shift in the lower limit of autoregulation to a higher pressure e.g. 100–120 mm Hg. The consequence of the autoregulatory shift is that if the blood pressure of a hypertensive patient is rapidly lowered to normotensive levels, CBF will fall. Chronic treatment restores normal autoregulation to the cerebral circulation in hypertensive rats, and seems to do so in patients. However, there is a paucity of information on the acute effects of antihypertensive drugs on the cerebral circulation.

Dihydralazine (and also hydralazine) is a vasodilator and an antihypertensive agent that has been widely used for emergency blood pressure lowering. In man, single intravenous doses of the drug may increase CBF and intracranial pressure. Dihydralazine has been shown to dilate pial arteries and increase intracranial pressure in normal cats. The aim of the present study in hypertensive rats was to determine the effect on the cerebral circulation of graded, controlled dihydralazine-induced hypotension, in particular at blood pressures below the lower limit of CBF autoregulation. Two types of hypertensive rats, renal and spontaneously hypertensive, were studied in case genetic or humoral factors might influence the outcome. The results were interpreted using a knowledge of the lower limit of CBF autoregulation during haemorrhagic hypotension.

Materials and Methods

The experiments were performed on male Wistar Kyoto rats (WKY, F24), and spontaneously hypertensive rats (SHR, F49) of the Okamoto strain (Møllegaard, Copenhagen). WKY were chosen for inducing renal hypertension as they are the control rat for SHR, being the strain from which SHR were bred. As both types of hypertension are based on the same strain of rat, the results are less likely to be obscured by inter-strain differences. Until the CBF study, all rats were housed in the same room, with free access to food and water. No salt or corticosteroids were added.
Chronic renal hypertension was induced in 1 month old WKY by a slight modification of the Loomis technique.13 Through a flank incision, one of the 2 branches of the left renal artery was ligated causing a partial infarction of the kidney. This was combined with contralateral nephrectomy. Systolic blood pressure (measured by the tail cuff method) then rose to about 200 mm Hg in one month, as compared to 130 mm Hg in unoperated rats of the same age.

CBF studies were performed when the rats were 4 months old, by which time the renal hypertensive rats (RHR) had been severely hypertensive for 2 months and the spontaneously hypertensive rats a little longer. At this stage, the cerebral circulation has adapted to the chronic hypertension as shown by a 20–30 mm shift in the lower limit of CBF autoregulation obtained during haemorrhagic hypotension.16 Only rats with a systolic tail pressure of 180–240 mm Hg were used for the CBF studies. 30–40% of the SHR obtained from the supplier were found to have a systolic pressure close to that of the normotensive WKY, and were therefore discarded.

CBF was studied using the 133Xenon injection technique,17 modified for rat studies.18, 19 Anaesthesia was induced with 4% halothane and maintained with 0.8% halothane in 30% O2:70% N2O. The rats were tracheotomised, paralysed with suxamethonium (40 mg/kg) and ventilated on a respirator. Both femoral arteries were cannulated, one for recording of arterial pressure (MAP) and heart rate (HR), one for sampling blood. A femoral vein was cannulated for blood or drug infusion. The skin and muscle overlying the right cerebral hemisphere were resected to expose the calvarium. All branches of the right common carotid artery (occipital, superior thyroid, external carotid and pterygopalatine arteries) were ligated in order to minimise extracerebral distribution of the injected 133Xenon. The animals were heparinised (5000 IU/kg) and a polyethylene catheter (size pp25) introduced retrogradely into the branches of the left renal artery was ligated causing a partial infarction of the kidney. This was combined with contralateral nephrectomy. Systolic blood pressure (measured by the tail cuff method) then rose to about 200 mm Hg in one month, as compared to 130 mm Hg in unoperated rats of the same age.

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Arterial tension of carbon dioxide (PaCO2) and oxygen (PaO2), together with pH (pHa), were measured at intervals during surgery/stabilisation, and at each CBF measurement, with conventional microelectrodes (Rädiometer, Copenhagen). The blood withdrawn for these measurements was substituted with blood from donor rats of the same strain. The rats were maintained at normocapnia (PaCO2 39–41 mm Hg) by adjustment of ventilation volume. Body temperature was maintained close to 37°C by means of a rectal-thermistor controlled heating table. Arterial blood pressure was recorded throughout the study, with mean arterial pressure (MAP) and heart rate (HR) being calculated from the recording.

The response of the cerebral circulation to graded, controlled dihydralazine-induced hypotension was studied in 6 SHR and 6 RHR. Following the 1 hour postoperative stabilisation period 2-4 baseline measurements of CBF were obtained at 8–12 min intervals. Dihydralazine mesylate (Nepresol®, Ciba Geigy) was then administered as repeated and increasing doses: 0.01, 0.2, 0.5, 1.0 and 2.0 mg/kg body weight i.v., at 15 min intervals. CBF was measured 4 min after each dose, at which time MAP had stabilised at its new level. At the same time, MAP, HR and body temperature were recorded, and 30 sec later, blood was sampled for determination of PaCO2, PaO2 and pHa.

When the lowest MAP had been reached, the rats were maintained in a stable condition for a further 2 hours. There was no spontaneous increase in MAP during that period. Except for one SHR, the animals were then sacrificed by perfusion with a fixative; 40% formaldehyde-glacial acetic acid-methanol, 1:1:8 by volume (FAM).22 The brains were left in situ for 24 hours, then removed and immersed in FAM for a further 48 hours before being processed for light microscopy. All brains were cut in a similar way into three coronal slices, which were embedded in paraffin wax. 7–8 μm sections were stained using a technique combining Luxol fast blue and cresyl violet, and also with haemotoxylin-eosin. All brains were coded with a random number such that the neuropathological examination could be performed blindly, with the code only being broken after completion of this and related studies.

A control study was made in 7 RHR and 5 SHR in order to verify the baseline stability of rats during prolonged halothane anaesthesia. CBF measurement was repeated at 15 min intervals over 2½ hours without manipulation of blood pressure. After a further 2 hours, the brains were prepared for neuropathological examination as described above.

Data are given as the mean ± 1 SD. Oneway analysis of variance, together with the Dunnett multiple-comparison test23 was used for statistical comparisons. Results were accepted as significant at p < 0.05.

Results

CBF Study

The CBF and MAP response to dihydralazine administration in these two types of hypertensive rats is given in table 1, alongside the corresponding HR,
TABLE 1  Cerebral Blood Flow (CBF), Mean Arterial Pressure (MAP) and Other Relevant Physiological Parameters, Prior to and following Administration of Dihydralazine to Rats with Renal Hypertension (RHR) and Spontaneous Hypertension (SHR)

<table>
<thead>
<tr>
<th>Dose mg/kg</th>
<th>CBF ml/100 g·min</th>
<th>% of baseline</th>
<th>MAP mm Hg</th>
<th>HR</th>
<th>PaCO₂ mm Hg</th>
<th>pHa</th>
<th>PaO₂ mm Hg</th>
<th>T °C</th>
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<tr>
<td>RHR (n = 6)</td>
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<tr>
<td>baseline</td>
<td>79 ± 13</td>
<td>—</td>
<td>145 ± 7</td>
<td>265 ± 28</td>
<td>38.8 ± 0.6</td>
<td>7.42 ± 0.05</td>
<td>129 ± 16</td>
<td>37.0 ± 0.2</td>
</tr>
<tr>
<td>0.05</td>
<td>72 ± 12</td>
<td>91 ± 7</td>
<td>123 ± 22</td>
<td>250 ± 33</td>
<td>38.8 ± 2.4</td>
<td>7.41 ± 0.06</td>
<td>118 ± 16</td>
<td>37.1 ± 0.2</td>
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<tr>
<td>0.1</td>
<td>73 ± 15</td>
<td>94 ± 14</td>
<td>89 ± 15*</td>
<td>260 ± 34</td>
<td>38.4 ± 2.2</td>
<td>7.41 ± 0.04</td>
<td>112 ± 16</td>
<td>37.2 ± 0.1</td>
</tr>
<tr>
<td>0.2</td>
<td>67 ± 15</td>
<td>86 ± 17</td>
<td>65 ± 13*</td>
<td>263 ± 44</td>
<td>39.3 ± 1.6</td>
<td>7.40 ± 0.05</td>
<td>129 ± 20</td>
<td>37.0 ± 0.3</td>
</tr>
<tr>
<td>0.5</td>
<td>65 ± 11</td>
<td>85 ± 21</td>
<td>56 ± 5*</td>
<td>282 ± 46</td>
<td>39.9 ± 2.0</td>
<td>7.36 ± 0.09</td>
<td>129 ± 16</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>73 ± 13</td>
<td>93 ± 19</td>
<td>52 ± 4*</td>
<td>282 ± 35</td>
<td>40.5 ± 2.9</td>
<td>7.34 ± 0.06</td>
<td>131 ± 20</td>
<td>37.0 ± 0.5</td>
</tr>
<tr>
<td>2.0</td>
<td>82 ± 19</td>
<td>106 ± 30</td>
<td>52 ± 4*</td>
<td>278 ± 51</td>
<td>39.6 ± 1.2</td>
<td>7.35 ± 0.06</td>
<td>125 ± 14</td>
<td>37.2 ± 0.5</td>
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<tr>
<td>SHR (n = 6)</td>
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<tr>
<td>baseline</td>
<td>88 ± 16</td>
<td>—</td>
<td>138 ± 11</td>
<td>296 ± 27</td>
<td>38.8 ± 6.2</td>
<td>7.41 ± 0.05</td>
<td>121 ± 10</td>
<td>36.9 ± 0.1</td>
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<tr>
<td>0.05</td>
<td>99 ± 18</td>
<td>104 ± 6</td>
<td>128 ± 15</td>
<td>290 ± 45</td>
<td>40.2 ± 1.3</td>
<td>7.36 ± 0.07</td>
<td>106 ± 12</td>
<td>37.2 ± 0.6</td>
</tr>
<tr>
<td>0.1</td>
<td>97 ± 23</td>
<td>104 ± 11</td>
<td>92 ± 9*</td>
<td>302 ± 31</td>
<td>39.4 ± 2.8</td>
<td>7.40 ± 0.07</td>
<td>122 ± 26</td>
<td>37.5 ± 0.2</td>
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<tr>
<td>0.2</td>
<td>101 ± 31</td>
<td>108 ± 20</td>
<td>73 ± 6*</td>
<td>292 ± 31</td>
<td>38.6 ± 3.3</td>
<td>7.39 ± 0.04</td>
<td>125 ± 18</td>
<td>37.2 ± 0.4</td>
</tr>
<tr>
<td>0.5</td>
<td>93 ± 42</td>
<td>104 ± 33</td>
<td>68 ± 12*</td>
<td>323 ± 35</td>
<td>38.6 ± 2.8</td>
<td>7.37 ± 0.02</td>
<td>125 ± 13</td>
<td>36 ± 1.4</td>
</tr>
<tr>
<td>1.0</td>
<td>84 ± 37</td>
<td>96 ± 33</td>
<td>58 ± 7*</td>
<td>347 ± 81</td>
<td>37.2 ± 2.3</td>
<td>7.36 ± 0.03</td>
<td>128 ± 19</td>
<td>37.0 ± 0.4</td>
</tr>
<tr>
<td>2.0</td>
<td>82 ± 27</td>
<td>94 ± 32</td>
<td>54 ± 8*</td>
<td>352 ± 67</td>
<td>39.0 ± 2.8</td>
<td>7.34 ± 0.04</td>
<td>118 ± 15</td>
<td>37.5 ± 0.8</td>
</tr>
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</table>

Values are mean ± 1 SD (n = 6). *p < 0.01. CBF, HR, PaCO₂, pHa, PaO₂ and T were not significantly different from baseline (p > 0.05).

PaCO₂, pHa, PaO₂, and body temperature. The results are illustrated by figures 1 and 2, which also show the corresponding CBF autoregulation curve obtained by haemorrhagic hypotension in identical rats (described in detail by Barry et al., 1982).

Baseline CBF was similar in RHR and SHR, being 79 ± 13 and 88 ± 16 ml/100 g·min respectively, at resting MAP of about 140 mm Hg. Dihydralazine caused a gradual fall in blood pressure, the dose response being slightly greater in RHR than SHR. In both groups MAP reached a minimum of about 50 mm Hg and was significantly lower than baseline (p < 0.01) at all doses above 0.1 mg/kg. On average, CBF was preserved at the resting level during dihydralazine-induced hypotension in both the RHR and SHR group. In individual animals, at different doses, CBF either increased or decreased. (In the RHR group, although the changes were nonsignificant, CBF tended to be below baseline at doses up to 0.5 mg/kg, and then increased slightly at 1 and 2 mg/kg). As is illustrated by figures 1 and 2, dihydralazine brought MAP well below the lower limit of CBF autoregulation seen during bleeding, without any concomitant fall in CBF. There were no changes in blood gases and pH, or...
body temperature that could have influenced the results. There was a slight increase in HR at the higher doses of dihydralazine.

Control Study

This revealed that CBF remained stable during the 2½ hour period in both the RHR group and SHR group, although CBF fluctuated in individual rats. MAP and HR remained stable in RHR, as did HR in SHR, whereas MAP fell slightly but insignificantly (10 mm Hg, p > 0.05) toward the end of the study in SHR. These results have been given in detail elsewhere.16

Neuropathology

As judged by uniform blanching and hardness of the specimens, satisfactory fixation was achieved in all animals. The well known cytological artefacts such as ‘dark cell’ and ‘hydropic cell’24, 25 were not found in any of the sections. The ischaemic lesions found in some of the rats, usually small foci, were similar to those reported previously in FAM fixed material.24, 26 A full description of the cellular changes which occur in the early stages of anoxic-ischaemic damage in the rat brain has been made elsewhere.24, 26, 27 In brief, these changes involve microvacuolation of the cells, followed by incrustation and shrinkage of the cytoplasm and nucleus, with a gradual transition to classic ischaemic cell change. The lesions reported in the present study were small areas of irreversible anoxic-ischaemic damage of this type.

In none of the control animals was there microscopic evidence of ischaemic brain damage. Of the animals given dihydralazine, evidence of ischaemic brain damage was found in 2 of 6 RHR and 2 of 5 SHR. In 2 of these animals there were 1 and 3 small ischaemic foci in the right cerebral hemisphere. In the other 2 animals the lesions were bilateral. In one of these, an RHR, there were 19 ischaemic foci that appeared to be accentuated in the arterial boundary zones; CBF had fallen to 60% of baseline after the intermediate doses of dihydralazine, and increased markedly to 120% of baseline after the highest doses. In the second animal, an SHR, in addition to ischaemic damage in the distribution of the right middle cerebral artery there were several lesions in the left hemisphere that appeared to be accentuated in the arterial boundary zones; CBF in this rat had remained at the resting level down to an MAP of 50 mm Hg and thus the ischaemic lesions did not appear to result from global ischaemia. In one SHR in which CBF did fall at the higher doses of dihydralazine, no lesions were found.

Discussion

Most vasoactive drugs have no pharmacological action on the cerebral circulation in vivo, mainly because of the protective effects of the blood-brain barrier located in the vascular endothelium. Thus, when angiotensin or noradrenaline is infused into the internal carotid artery in man, cerebral vasconstriction is not induced.23 With regard to antihypertensive drugs, the literature is particularly sparse.

CBF Autoregulation in Hypertension

Central to an understanding of the effects of antihypertensive drugs on the cerebral circulation are the changes in CBF autoregulation that occur during chronic hypertension. In hypertensive patients2, 6 and experimental animals,16, 29 structural and functional adaptation of the cerebral circulation results in a shift in the lower and upper limits of CBF autoregulation toward a higher blood pressure. This change in autoregulation can be reversed by chronic antihypertensive treatment, as has been shown in renal hypertensive rats11 and as appears to be the case in man.7, 8 Regarding acute treatment, however, the shift in the lower limit, which may be 30–50 mm Hg in both man7, 8 and animals,11, 16, 29 is particularly important. The consequence of this shift is that if a severely elevated blood pressure is suddenly normalised, the patient may experience a fall in CBF and perhaps manifest symptoms of brain ischaemia. This has been the subject of a number of clinical reports.6, 30, 31

The lower limit of CBF autoregulation is the point at which, during a fall in blood pressure, autoregulatory vasodilatation of cerebral vessels becomes inadequate to maintain flow, which then falls. The lower limit should not be equated with maximal dilatation of cerebral vessels as it has clearly been shown that pial vessels will continue to dilate as blood pressure is brought below the lower limit of autoregulation, i.e. whilst CBF is falling.6 It is possible, therefore, to dilate cerebral vessels pharmacologically at blood pressures below the autoregulatory lower limit.

Acute lowering of blood pressure by antihypertensive drugs may have two types of effect on the cerebral circulation. First, the blood pressure may be brought below the lower limit of CBF autoregulation, and second, there may be a direct pharmacological action of the drug on cerebral vessels. As an example of the first type of effect, diazoxide administration to hypertensive rats (a similar study to the present) caused a 30–40% reduction in CBF secondary to a blood pressure fall to below the lower limit of CBF autoregulation.32 In contrast, a drug with a direct pharmacological action (vasodilative), nitroprusside, will preserve CBF at low blood pressure.10

Dihydralazine and CBF Autoregulation

Dihydralazine, which lowers blood pressure by peripheral vasodilatation, may increase CBF in man.12, 13, 33, 34 In neurosurgical patients with intraventricular pressure monitoring, the drug caused a marked increase in intracranial pressure, leading to a smaller perfusion pressure than could be estimated from the fall in blood pressure alone. An elevation of intracranial pressure has also been observed in normal cats, in which dihydralazine caused a marked dilatation of pial arteries, but had no effect on cerebral veins.14 Furthermore, dihydralazine will dilate human pial arteries — in an in vitro-study of K+-constricted vessels, a vasodilatative log-dose response was observed (Barry, unpublished observation). Thus, dihydralazine seems to exert a direct vasodilatory effect on cerebral resis-
tance vessels which may occur in addition to the autoregulatory dilatation that accompanies the dihydralazine-induced blood pressure lowering.

In the present study in hypertensive rats, intravenous administration of dihydralazine caused a graded lowering of blood pressure down to a minimum of about 50 mm Hg without any change in CBF. The lower limit of CBF autoregulation determined during haemorrhagic hypotension in SHR and RHR of a similar age, and degree and duration of hypertension, is at a MAP of 90–100 mm Hg. The latter study was conducted under the same experimental conditions i.e. CBF method, anaesthesia etc. During dihydralazine induced hypotension, at blood pressures below the lower limit of autoregulation seen during bleeding, CBF was higher than would be expected if CBF were determined by perfusion pressure alone (figs. 1 and 2). This is interpreted as being due to direct dilatation by dihydralazine of cerebral resistance vessels. There was a tendency for RHR to show a more pronounced effect than SHR when given the highest doses of dihydralazine. The difference may be due to a lower degree of vascular structural adaptation in RHR than SHR. The resistance vessel walls are probably thicker in SHR as they are more resistant to acute hypertensive blood-pressure lowering.4-5 Patients with atheromatous encephalopathy,2-3 the benefit of emergency blood-pressure lowering is immediately obvious and may be life-saving. Despite this, recent concern has been expressed over the potential hazards of emergency blood-pressure lowering.4-5-32 The results of the present study indicate that at pressures below the lower limit of CBF autoregulation, when CBF would otherwise have fallen, drugs with direct cerebrovascular vasodilatory properties may, in addition to their blood-pressure effect, increase CBF to the resting level. Thus, CBF appears to be preserved as blood pressure falls. This situation, i.e. low blood pressure and direct cerebrovascular dilatation, may possibly lead to uneven brain perfusion, and the concomitant rise in intracranial pressure may further compromise the cerebral circula-

Clinical Implications

One of the main benefits of antihypertensive therapy, as has been emphasised by many reports, is the resultant reduction in stroke incidence. In the case of malignant hypertension, and especially hypertensive encephalopathy,6-7 the benefit of emergency blood-pressure lowering is immediately obvious and may be life-saving. Despite this, recent concern has been expressed over the potential hazards of emergency blood-pressure lowering.4-5-32 The results of the present study indicate that at pressures below the lower limit of CBF autoregulation, when CBF would otherwise have fallen, drugs with direct cerebrovascular vasodilatory properties may, in addition to their blood-pressure effect, increase CBF to the resting level. Thus, CBF appears to be preserved as blood pressure falls. This situation, i.e. low blood pressure and direct cerebrovascular dilatation, may possibly lead to uneven brain perfusion, and the concomitant rise in intracranial pressure may further compromise the cerebral circula-

Neuropathology

Uneven regional perfusion, although not demonstrated, may have been responsible for the ischaemic lesions found in some of the animals. These ischaemic foci were areas of irreversible anoxic-ischaemic damage of the type described previously in normotensive rat brain.24-26-27 Similar ischaemic lesions have been found in RHR and SHR subjected to haemorrhagic hypotension16 and diazoxide-induced hypotension.32 As in the latter two studies, there was a tendency for the lesions to occur mainly in the right hemisphere, although they were bilateral in 2 of the present rats. The possibility was considered that the lesions could be partly an artefact, such as embolism, associated with repeated CBF measurement. However, this was discounted as not a single lesion was found in the animals of the control study, in which repeated measurements of CBF were made over a 2½ h period. It is possible though that surgical intervention and carotid cannulation could render the right side of the brain more susceptible to hypotensive insult.

As the number of animals with ischaemic lesions was small (2 of 6 RHR and 2 of 5 SHR), it is difficult to relate the degree of damage with a particular CBF response to dihydralazine. Furthermore, it must be remembered that the CBF and pathology studies are not strictly comparable: CBF was measured in only one hemisphere whereas the neuropathological examination was of the whole brain. Furthermore, as the lesions were small it is quite unlikely that the reduced or negligible flow in these areas will significantly change the measured CBF, which in any case is derived from the initial slope index i.e. as flow is given in ml/100 g-min rather that absolute flow, small areas of no-flow not receiving 133Xe will not be registered. Although the RHR with the most severe bilateral lesions had a CBF fall after intermediate doses and a marked CBF increase after the higher doses of dihydralazine, the SHR with severe lesions did not have a CBF fall. Also, a second SHR which did have a CBF fall, did not have lesions. Thus the lesions do not seem to be provoked by a global CBF fall. In two of the rats, the lesions were more severe than in any of the RHR and SHR in which blood pressure was lowered to similar levels by diazoxide25 or haemorrhage.16

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tion. These conditions, if encountered clinically, may be potentially harmful to the brain. It is noteworthy that several of the patients in which emergency blood pressure lowering resulted in neurological damage, blindness or death were given dihydralazine or hydralazine (in addition to other antihypertensive drugs, notably diazoxide). 6, 39, 40

It is concluded that whereas dihydralazine may be well suited for inducing small decrements in blood pressure, acute lowering of blood pressure with large doses should only be undertaken with caution and the patients observed carefully for signs of cerebral dysfunction.

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Note added in proof
We have recently found that in SHR given 1 mg/kg dihydralazine i.v., CBF autoregulation was abolished and CBF pressure passive, indicating near maximal cerebrovascular dilatation: when MAP was raised stepwise from the post-dihydralazine level of 60 mm Hg to 140 mm Hg, CBF increased stepwise from 100% to around 200% of resting CBF. When MAP was lowered to 40 mm Hg, CBF fell to 70%. Furthermore Auer et al. found that although dihydralazine dilates small pial arteries in SHR (by 35% after 1 mg/kg and 55% after 2 mg/kg), recurring periods of marked arterial spasm lasting about 8 min occurred in half the rats given 2 mg/kg. These observations may have bearing on our finding of ischaemic lesions and give further reason for large doses only to be used with caution.

References
15. Loomis D. Hypertension and necrotizing arteritis in the rat following renal infarction. Arch Path Lab Med 41: 231, 1948
36. Eklof B, MacMillan V, Siesjö BK: The effect of hypercapnic acidosis upon the energy metabolism of the brain in arterial hypo-
Local Vascular Response to Change in Carbon Dioxide Tension. Long Term Observation in the Cat’s Brain by Means of the Hydrogen Clearance Technique

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SUMMARY Thirty six small hydrogen sensitive electrodes were inserted into the brains of 6 cats to evaluate the local vascular response to change in PaCO₂ of cortex, subcortical white matter, and caudate nucleus. Repeated measurements (617) of local cerebral blood flow (ICBF) were performed over a period of 12 weeks. Within a PaCO₂ range from 19 to 96 mmHg the local response of CBF was linear in most of the regions measured. The absolute local CO₂ reactivity (CO₂-R) showed a positive correlation to ICBF at PaCO₂ = 40 mmHg (ICBF₄₀) with the regression line: absolute CO₂-R = 0.02 ICBF₄₀ + 0.22, r = 0.71 (p < 0.01). Therefore relative ICBF change was calculated in relation to ICBF₄₀ to make comparisons between the CO₂ response of different measuring days and of different regions examined. No significant change in relative CO₂-R was observed during the 12 weeks interval. Differences of relative CO₂-R between investigated regions were insignificant. The uniformity of relative CO₂ response might support the hypothesis of a direct effect of PaCO₂ or pH on the vessel wall. For comparison of CBF, the individual determination of CBF₄₀ and relative CO₂-R would be necessary.

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Although arterial carbon dioxide tension (PaCO₂) has often been confirmed as a prominent factor of circulatory control in the central nervous system (CNS) since regional CBF measurements were performed, the quantitative relationship between local cerebral blood flow (ICBF) and PaCO₂ is not yet clear. Within physiologic ranges of PaCO₂, the vascular response has been described to be linear but also as an exponential function. This has led to uncertainty in calculations of CBF when adjustments for changes in PaCO₂ are necessary. It is also uncertain whether CO₂-reactivity (CO₂-R) in different regions of the CNS is uniform or not. Recently Meyer et al. stated from stable xenon-CT measurements that ICBF of both gray and white matter decreased "diffusely and homogenously throughout the brain," although they registered a 3.9% flow reduction/mmHg PaCO₂ change in occipital cortex but only a 2.6% flow reduction/mmHg PaCO₂ change in occipital white matter.

For these reasons the present study was designed to determine the quantitative response of ICBF to PaCO₂ change in gray and white matter as well as in the deep nuclei of the brain. The hydrogen clearance technique was chosen for ICBF-determination because this method enables direct and repeated measurements. As previous observations and preliminary data of this study showed, the vascular reactivity is not impaired by small hydrogen sensitive electrodes. To minimize and measure any possible influence of tissue trauma, in this study the electrodes were implanted chronically and the CO₂-R was repeatedly determined over a period of 12 weeks.

Methods

The experiments were carried out in 6 cats of either sex within the weight range of 2.4 to 3.7 kg. Anesthesia was induced with sodium pentobarbital (30 mg per kg) and maintained with 70% N₂O-30% O₂ gas via an endotracheal tube. The animals were paralyzed with pancuroniumbromide administered intravenously, repeated as necessary. Ventilation was maintained by a Schuler pump. Where the PaCO₂ was to be raised, this was done by adding CO₂-gas to the input of the pump. Systemic arterial blood pressure and central venous pressure were recorded continuously via polyethylene catheters inserted into a femoral artery and vein and connected to Statham pressure transducers. PaO₂,
Cerebral blood flow during dihydralazine-induced hypotension in hypertensive rats.
D I Barry, S Strandgaard, D I Graham, U G Svendsen, O Braendstrup and O B Paulson

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