Cerebral blood flow distribution during induced hypotension with haemorrhage, trimetaphan or nitroprusside in rats

T. TSUTSUI, T. MAEKAWA, C. GOODCHILD AND J. G. JONES

Summary
Local cerebral blood flow (CBF) during three types of profound hypotension were compared using the quantitative autoradiographic [14]-C iodo-antipyrine method. Rats were rendered hypotensive to a mean arterial pressure of 30 mm Hg for 30 min by haemorrhage, trimetaphan or nitroprusside during 0.8% halothane anaesthesia. During haemorrhagic hypotension, mean local CBF was reduced significantly in all except two pontine regions. This reduction in flow ranged from 83% to 41% compared with the normotensive control group, with the neocortex and telencephalon most affected. During trimetaphan-induced hypotension, local CBF was reduced to the same degree and in the same pattern as that during haemorrhagic hypotension. In contrast, during nitroprusside-induced hypotension, local CBF in many regions of the brain was well maintained (57-101%); although local CBF was significantly below control in all cortical and telencephalic regions, it was significantly greater in the majority of these regions than in the other two hypotensive groups. We conclude that local CBF was significantly reduced in the neocortex and telencephalon by hypotension of this degree induced by all three methods, but nitroprusside preserved local CBF significantly better than the other methods, in these, as in most other regions. (Br. J. Anaesth. 1995; 74: 686-690)

Key words

Regional distribution of CBF during several types of hypotension has been examined separately at different arterial pressures with various methods [6-8]. So far the different types of induced hypotension have not been compared for their effects on the distributions of CBF at a critical arterial pressure. The present study was designed to measure local CBF with [14]-C iodo-antipyrine (IAP) [9] during profound hypotension to a mean arterial pressure (MAP) of 30 mm Hg using nitroprusside, trimetaphan or haemorrhage.

Materials and methods
Twenty-four Wistar rats, weighing 280-400 g, were anaesthetized in a plastic box using 2.5-3.0% halothane and 50% nitrous oxide in oxygen. A tracheostomy tube was inserted and ventilation was controlled with the aid of intermittent injections of pancuronium 0.1 mg kg⁻¹. Anaesthesia was maintained with 1.0-1.5% halothane and 50% nitrous oxide in oxygen. Femoral arteries and veins and an axillary artery and vein were cannulated for pressure monitoring, withdrawal of arterial blood and infusion of drugs.

After surgical preparation, nitrous oxide was replaced with nitrogen and the inspired halothane concentration was reduced to 0.8% in 30-50% oxygen for at least 30 min for stabilization. A tracheostomy tube was inserted and ventilation was controlled with the aid of intermittent injections of pancuronium 0.1 mg kg⁻¹. Anaesthesia was maintained with 1.0-1.5% halothane and 50% nitrous oxide in oxygen. Femoral arteries and veins and an axillary artery and vein were cannulated for pressure monitoring, withdrawal of arterial blood and infusion of drugs.

The animals were allocated randomly to one of four groups. Hypotension was induced by haemorrhage, trimetaphan or nitroprusside.
CBF during induced hypotension

or hemorrhage, trimetaphan or nitroprusside combined with beta adrenergic blocking agents like propranolol, 0.2 mg kg⁻¹ i.v. Haemorrhagic hypotension was achieved by withdrawal of arterial blood. The total amount of blood removed was mean 10.4 (SD 1.4) ml. The trimetaphan group received trimetaphan (0.1% solution) to a maximum dose of 10 mg kg⁻¹ and the nitroprusside group received nitroprusside (0.01% solution) to a maximum dose of 1 mg kg⁻¹. Arterial pressure was lowered at a rate not exceeding 5 mm Hg min⁻¹ to an MAP of 28–30 mm Hg. This was accomplished in 15–20 min and then MAP was maintained for 30 min until the end of the study. In the trimetaphan and nitroprusside groups it was also necessary to withdraw arterial blood when the maximum dose of hypotensive drug had been given. The total amount of blood removed was 5.5 (0.6) ml in the trimetaphan group and 5.5 (1.4) ml in the nitroprusside group. This was the standard design to keep the doses of trimetaphan and nitroprusside the same and to adjust the degree of hypotension by removing blood. The control group of rats received neither drug nor blood removal and was exposed to 0.8% halothane for the same duration as the hypotensive groups. Physiological variables, except MAP, were taken immediately before measurement of CBF.

Local CBF was measured by the method of Sakurada and colleagues [9]. Briefly, IAP 75 μCi kg⁻¹ (specific activity 50–55 μCi ml⁻¹, Amersham, USA), dissolved in 0.5 ml of saline, was given through the axillary vein as a constant infusion over 60 s while 13–16 arterial blood samples were collected from the arterial catheter into 0.5-ml capillary tubes. Each local CBF measurement was made after a sustained period of hypotension of 30 min. At the end of these measurements, the rat was decapitated instantly and the brain was frozen in isopentane, chilled to –22 °C in a cryostat and dried on a hot plate at –22 °C in a cryostat and dried on a hot plate at 50 °C. The brain sections were exposed to an x-ray film (Kodak AR or Kodak SB-5, USA) with [14]-C standards for 10 days. The [14]-C radioactivity in arterial blood samples was measured by a liquid scintillation counter (Packard TRI-CARB 4530, Meriden, CT, USA) using the external standard method.

Local tissue concentration of the tracer was measured on the autoradiogram with the computer-assisted microdensitometer (UHG, Unique Medical, Tokyo). Each discrete brain region was identified according to the atlas of Konig and Klippel [10] and Craigie’s Neuroanatomy [11]. Local CBF at every region was calculated according to the equation described by Sakurada and colleagues [9].

Statistical differences were tested by one-way analysis of variance with the least difference test for multiple comparisons [12]. P < 0.05 was considered to be statistically significant.

Results

There was no statistically significant difference in PaO₂, PaCO₂ packed cell volume or rectal temperature between the groups (table 1). The combination of blood removal and hypotension caused acidemia (pH 7.1–7.2) in all hypotensive groups. After 15 min of hypotension, EEG activity in the nitroprusside group was well maintained compared with that in the haemorrhagic or trimetaphan groups. In contrast, after 30 min the EEG in the three hypotensive groups showed consistently slow-wave activity (5–7 Hz) with high amplitude waves (70–150 μV) (fig. 1).

Mean local CBF values in 37 discrete brain regions in the control group differed among the structures, from the lowest values of 59 ml 100 g⁻¹ min⁻¹ in the corpus callosum to the highest values of 205 ml 100 g⁻¹ min⁻¹ in the inferior colliculus (table 2).

During haemorrhagic hypotension, local CBF of the neocortex and telencephalon was lowered to 41–60% of control. Among the neocortices, the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 6)</th>
<th>Hypotensive groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Haemorrhage (n = 6)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>29 (1)*</td>
<td>30 (0.3)*</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>19.5 (0.8)</td>
<td>22.0 (4.0)</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>4.9 (0.3)</td>
<td>4.8 (0.3)</td>
</tr>
<tr>
<td>pH</td>
<td>7.10 (0.04)*</td>
<td>7.14 (0.04)*</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>41 (2)</td>
<td>36 (1)</td>
</tr>
<tr>
<td>Body temp. (°C)</td>
<td>37.2 (0.2)</td>
<td>37.3 (0.1)</td>
</tr>
</tbody>
</table>

Figure 1 Representative electroencephalograms before and 15 min and 30 min after the beginning of induction of hypotension. H = Haemorrhage, TMP = trimetaphan, NTP = nitroprusside.

Table 1 Physiological variables during induced hypotension (mean (SEM)). * P < 0.05 compared with control group
While flow to the neocortex and telencephalon was significantly reduced compared with control, it was control and to the telencephalon 69% of control. The mean reduction in flow to the neocortex was 64% of neocortex and telencephalon showed a significant reduction in local CBF to 57-82% of control. The maintained in most regions of the brain. However, the nitroprusside hypotension local CBF was well main-

The percentage changes in local CBF from control

The absolute values for local CBF during 0.8%

The absolute values for local CBF during 0.8%

Discussion

The absolute values for local CBF during 0.8% halothane anaesthesia were comparable with previous results obtained during 0.5% halothane with 70%, nitrous oxide anaesthesia [13]. The distribution of local CBF in the brain correlated well with that of local cerebral glucose utilization [14, 15].

Local cerebral blood flow was reduced significantly in most of the brain regions in the haem-
recently, Mendelow and co-workers [8, 21] reported that haemorrhagic hypotension to an MAP of 40-50 mm Hg produced no change in local CBF, however, a significant reduction in local CBF in the cortex was found at an MAP of 30 mm Hg. It was concluded that a critical arterial pressure with an MAP of approximately 30 mm Hg during haemorrhage or trimetaphan-induced hypotension could cause a significantly uneven reduction in local CBF in the brain, especially in the cerebral cortex and telencephalon.

Michenfelder and Theye [5] reported that cerebral metabolic derangement occurred during nitroprusside hypotension at an MAP of 40 mm Hg, although the dose was limited to the non-toxic range and they suspected that nitroprusside could cause maldistribution of local CBF. In the present study, administration of nitroprusside and trimetaphan was limited to the non-toxic range, and the three hypotensive techniques produced a similar uneven reduction in local CBF. The maldistribution of local CBF, which may imply the heterogeneous distribution of CBF uncoupled with local metabolism, could not be identified with local CBF measurement alone in this study. However, as EEG activity during nitroprusside hypotension could not be maintained after 30 min of insult even with relatively high local CBF, it was concluded that nitroprusside may cause an insidious metabolic derangement even with the recommended dose when arterial pressure is reduced to the critical level.

It is not easy to relate these findings to humans where the major concern is the preservation of normal cognitive function, which cannot be examined in animal studies. The combination of blood loss and pharmacological action may also differ from clinical applications. Clearly there is a need for further studies using isoflurane or propofol and we have begun to examine the role of propofol [22, 23].

In summary, nitroprusside maintained local cerebral blood flow in most of the brain regions during profound hypotension better than haemorrhage or trimetaphan, however, the pattern of CBF distribution was very similar even though profound hypotension was induced with different techniques.

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References


