Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures

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It is well known that the cerebral blood flow alters in response to changes in the arterial carbon dioxide tension. However, it is not yet clear whether there are upper and lower limits of $P_aCO_2$ beyond which the cerebral vessels do not react. In addition, there have been no reports on the response of cerebral blood flow to alterations in $P_aCO_2$ in hypotensive states.

The recent development by Lassen and Ingvar (1961, 1962) of a rapid, easily repeatable, and relatively untraumatic method of estimating the blood flow through the cerebral cortex has enabled us to make multiple estimations of blood flow in lightly anaesthetized dogs at varying tensions of arterial carbon dioxide and varying arterial blood pressures.

**METHOD**

Three hundred and two measurements of blood flow through the cerebral cortex were made on 41 unselected mongrel dogs. The animals were anaesthetized with thiopentone. A cuffed endotracheal tube was inserted and connected to a Starling respiratory pump, through which a 4:1 mixture of $N_2O$ and oxygen was delivered in open circuit. Suxamethonium chloride was administered at intervals. Repeated small doses of thiopentone were given during the actual operation. A cannula was inserted into the femoral artery and connected to a damped mercury manometer for the measurement of the systemic blood pressure. This cannula was also used for the withdrawal of arterial blood samples.

The thyroid branch of the common carotid artery was cannulated centripetally, the distal end being tied. The temporal muscle was excised and a trephine hole made over the parietal bone. A cruciate incision was made in the dura and the exposed brain cortex was covered with a plastic membrane (Melinex) 6μ in thickness. A thin lead shield was placed over the surrounding dura and bone, leaving exposed only the area of cortex covered by the membrane. An end window Geiger counter, mounted 1 mm. above the exposed cortex, was connected to a rate-meter and a direct writing recorder. After the operation was completed, thiopentone administration was dis-

continued and the preparation remained undisturbed for one hour before the first measurements of blood flow were made. Plasma substitute (Dextran), saturated with 85 Krypton, was injected, rapidly at first and then more slowly, into the carotid artery over two to three minutes. The blood flow through the brain cortex was calculated from the half-life of the initial slope of a semilogarithmic plot of the clearance curve using the formula of Lassen and Ingvar (1961, 1962). After each measurement of blood flow, blood samples were taken from the femoral artery for the measurement of $P_aCO_2$ and pH on the micro-Astrup apparatus. Arterial oxyhaemoglobin saturation was measured at intervals on a Kipp haemorefractor. Pharyngeal temperatures were measured with a mercury thermometer.

The experiments were divided into three groups.

**GROUP I: NORMOTENSIVE** The $P_aCO_2$ was gradually raised in 10 dogs by adding increasing quantities of carbon dioxide to the anaesthetic mixture, and lowered in nine dogs by increasing the volume delivered by the respiratory pump.

**GROUP II: HYPOTENSIVE** The mean arterial blood pressure was maintained at 100 mm.Hg by bleeding the animals into a reservoir flask held at this pressure. The $P_aCO_2$, was raised in seven dogs and lowered in five dogs.

**GROUP III: HYPOTENSIVE** The mean arterial blood pressure was maintained at 50 mm.Hg. The $P_aCO_2$ was raised in five dogs and lowered in five dogs.

**RESULTS**

**GROUP I** The effect of hypercapnia and hypocapnia on the blood flow through the cerebral cortex in normotensive dogs (mean initial blood pressure 150 mm.Hg) is shown in Figure 1. In each experiment there was a marked rise in blood flow as the $P_aCO_2$ increased and a fall in blood flow as the $P_aCO_2$ decreased. The rise in $P_aCO_2$ was accompanied by a fall in pH and vice versa.

As there was considerable variation in the initial control values for each experiment, the blood flow was plotted against the $P_aCO_2$ individually for each
FIG. 1. The effect of alterations in PaCO₂ in normotensive animals on the cortical blood flow. Zero reference line for blood flow is at PaCO₂ of 40 mm.Hg. (Tables giving the data from which this and subsequent figures were constructed will be sent by the authors on request.)

dog. A line giving the best fit for each experiment was drawn by hand and each dog's flow results expressed as a percentage of its blood flow at an arterial carbon dioxide tension of 40 mm.Hg as estimated from the individual graph. This enabled the results in each experiment to be expressed as a percentage change in blood flow from that occurring at a PaCO₂ of 40 mm.Hg. The points from all the experiments in this group have been plotted in Figure 1. A Deuce digital computer was used to fit a polynomial curve. A cubic curve was found to give the best fit. From Fig. 1 it can be seen that raising the PaCO₂ from 40 to 80 mm.Hg caused approximately a 100% increase in blood flow. Lowering the PaCO₂ from 49 to 20 mm.Hg caused a 40% decrease in blood flow. Reducing of the PaCO₂ below 20 mm.Hg caused no further decrease in blood flow.

GROUP II In the experiments in this group, the mean arterial blood pressure was held at 100 mm.Hg. The response of the blood flow to hypercapnia and hypocapnia is shown in Figure 2. The change in blood flow on altering the PaCO₂ is similar to, but less pronounced than, in group I. It can be seen from Fig. 2 that the percentage increase in blood flow when the PaCO₂ is raised from 40 to 80 mm.Hg is only 50% (compared with 100% increase in group I). Similarly, the reduction in flow when the PaCO₂ was lowered from 40 to 20 mm.Hg was only 25% (compared with a 40% decrease in group I).

GROUP III In this group the mean arterial blood pressure was held at approximately 50 mm.Hg. The effects of hypercapnia and hypocapnia on the cerebral blood flow are shown in Figure 3. It is evident that at this level of hypotension, neither raising not lowering the PaCO₂ had any significant effect on the blood flow.

DISCUSSION

Before assessing the results of these experiments, the importance of careful surgical technique, light anaesthesia, and control of respiration must be emphasized. Great care was taken to ensure that the brain was not injured in any way during surgery. If this happened, or if there was any persistent con-
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Patterson, Heyman, Battey, and Ferguson (1955) have suggested that the response of the cerebral blood vessels to hypercapnia is a threshold phenomenon and only occurs when the P_{CO_2} has risen by more than 4 mm.Hg. In our experiments the collected results from all dogs show a steady rise in blood flow with increased P_{CO_2}. As the coefficient of variation of repeated estimations under constant experimental conditions using the 85 Krypton clearance technique (Ingvar and Lassen, 1962; Harper, Glass, and Glover, 1961) is 8-10%, changes in blood flow of less than this figure would be difficult to detect. It would be interesting to know the coefficient of variation of repeated estimations with the N_2O technique (Kety and Schmidt, 1945) used by Patterson and his colleagues (1955). If it was of the same order fairly small increases in blood flow could be missed.

It has been suggested (Lassen, 1959) that the teleological implication of the cerebral vasodilatation produced by hypercapnia is to maintain a constant cerebral tissue tissue P_{CO_2} and that any increase in tissue P_{CO_2} (due to increased metabolism) will result in increased cerebral perfusion, and the disposal of the excess CO_2. However, in hypotensive conditions, this regulation of cerebral blood flow in response to changes in P_{CO_2} is impaired.

In Fig. 2, where the mean arterial blood pressure was reduced to and maintained at 100 mm.Hg, the increase in blood flow on raising the P_{CO_2} from 40 to 80 mm.Hg was only 50% compared with the 100% increase in the normotensive dogs. Similarly, there was considerably less reduction in flow with hypocapnia. This is even more strikingly shown in Fig. 3, where, at a mean arterial blood pressure of 50 mm.Hg, no change in flow occurred during either hypercapnia or hypocapnia. It has been shown (Forbes, Nason, and Wortman, 1937; Fog, 1938; Carlyle and Grayson, 1955; Rapela, Machowicz, and Freeman, 1963; Harper, 1965; Haggendal and Johansson, 1965) that the cerebral blood vessels are able to dilate to compensate for a fall in arterial blood pressure, and we would postulate that in severe hypotensive states the cerebral vessels, being already maximally dilated, are unable to dilate further in response to increased P_{CO_2}. The failure of the cerebral vessels to constrict when the P_{CO_2} is lowered could indicate that in severe hypotension the maintenance of cerebral perfusion takes precedence over the maintenance of a normal tissue P_{CO_2}. This ‘over-ride’ mechanism could be mediated through the tissue oxygen tension, which is presumably low due to the inadequate blood flow, and could counteract the vasoconstrictive effect of hypocapnia.

Finally, the clinical application of the finding...
reported in this paper would be that there is no advantage in the administration of CO₂ in an attempt to restore cerebral blood flow in severe shock. On the contrary, such an action might raise the cerebral tissue P₇CO₂ to dangerously high levels.

**SUMMARY**

Measurements of blood flow through the exposed cerebral cortex were made in lightly anaesthetized dogs, using the ⁸⁸Krypton clearance method of Lassen and Ingvar (1961). In normotensive animals, hypercapnia produced a marked increase, and hypocapnia a decrease, in blood flow. However, in hypotensive animals this effect was reduced or absent.

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