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## The Anæsthetist's Effect upon the Cerebral Arteries

Changes in cerebral blood flow, by whatever method they are measured, are expressed in volumetric units, but the control of this volumetric cerebral blood flow must be achieved by changing the calibre of cerebral vessels.

The small pial arteries on the surface of the brain are open to inspection at operation and direct measurements may be made upon them in experimental animals. The main arterial trunks at the brain's base cannot be so directly observed in the intact animal; consequently less is known about their reactivity to physiological stimuli. Angiography offers a means of making such measurements, so that records obtained during routine angiograms under anæsthesia may be analysed to illustrate or even throw new light on the reactions of the arteries to anæsthetic manœuvres. As an extension of this method, angiography may be carried out under controlled conditions upon experimental animals. The most important single factor in setting the level of cerebral blood flow is the arterial $CO_2$ tension.

### *Hyperventilation*

The intracranial carotid artery and the main trunks of the middle cerebral and anterior cerebral arteries were measured in two groups of patients (Edmonds-Seal *et al.* 1967, du Boulay *et al.* 1968, 1970, du Boulay 1968) who had undergone carotid angiography under general anæsthesia in as nearly identical circumstances as could then be managed, except that in one group controlled respiration had been instituted at the beginning of the procedure (Series 2), while the others were breathing spontaneously (Series 1). The conditions of anæsthesia resulted in a mean $Paco_2$ of 30·8 mmHg (±7·5) for one group and of 51·6 mmHg (±8·7) for the other.

When measured, the mean diameters of the arteries were found to differ as shown in Table 1, which shows vasoconstriction with controlled respiration. The difference between the anterior cerebral arteries of the two groups (30%) is clearly significant (P=0·001), the difference between the middle cerebrals is borderline (P=0·1) and between the carotids is too small to be accepted as proved. It was a weakness of this study that halothane was employed, and it was difficult to make allowance for the possibly different concentrations of halothane in patients artificially ventilated and in those breathing spontaneously. This part of the work has therefore been repeated using nitrous oxide and oxygen only. The effects of ventilation with halothane have also been studied in the baboon. Details of anæsthetic and radiological techniques have been given in Edmonds-Seal *et al.* (1967) and du Boulay *et al.* (1968). In addition to the methods described there, direct monitoring of arterial and central venous pressure has been used in a number of patients using Statham P23 DE strain gauges.

This subsequent work in man without halothane (Table 2, Series 3 and 4) has confirmed the previous finding that lowering the $Paco_2$ from a mean of 45 mmHg to about 30 mmHg diminishes the calibre of the main intracranial arteries, including the internal carotid.

From this, however, a fresh fact has emerged. By comparing Series 4 with a third group of patients (Table 2, Series 5), it has been shown that those with $Paco_2$ below 25 mmHg have arteries which are not narrower than the group with $Paco_2$ of 25–35 mmHg, but wider. The statistical significance of the change is shown in Table 3. Several possible reasons must be considered.

It is well known that a reduction of $Paco_2$ is usually accompanied, as in these cases, by a

*Table 1*
**Effect of controlled respiration in man. Anæsthesia with halothane**

| | *Arterial diameter (mm)* | | | |
|---|---|---|---|---|
| | *Carotid* | *Middle cerebral* | *Anterior cerebral* | *Mean $PaCO_2$ (mmHg)* |
| Series 1: Spontaneous breathing | 4·1 | 3·32 | 3·02 | 51·6 |
| Series 2: Controlled respiration | 4·06 | 3·03 | 2·3 | 30·8 |

*Table 2*
**Effect of $CO_2$ and blood pressure in man. Nitrous oxide and oxygen only**

| | *Arterial diameter (mm)* | | | | |
|---|---|---|---|---|---|
| | *Carotid* | *Middle cerebral* | *Anterior cerebral* | *Mean $PaCO_2$ (mmHg)* | *Mean systolic blood pressure (mmHg)* |
| Series 3: Normal $PaCO_2$ | 4·31 | 3·2 | 2·83 | 45 | 103 |
| Series 4: Low normal $PaCO_2$ | 3·31 | 2·83 | 2·09 | 29·2 | 128 |
| Series 5: Subnormal $PaCO_2$ | 3·86 | 3·21 | 2·49 | 21·1 | 104 |

*Table 3*
**Significance of figures in Table 2**

| *Change in mean $PaCO_2$* | *Percentage change in arterial calibre* | | |
|---|---|---|---|
| | *Carotid* | *Middle cerebral* | *Anterior cerebral* |
| 45→29·2 mmHg | Diminish by: 23 ($P<0·01$) | 11·5 ($P<0·01$) | 26 ($P<0·01$) |
| 29·2→21·0 mmHg | Dilate by: 16 ($P<0·05$) | 12 ($P<0·05$) | 18 ($P<0·02$) |

lowering of the systemic blood pressure. The mean systolic blood pressure of Series 5 patients was 24 mmHg lower than the mean systolic pressure of Series 4. In order to test the possibility that the increase in diameter of the main cerebral arteries at subnormal level of $Paco_2$ may have been due to the drop in blood pressure, the results of a series of experiments upon baboons have been analysed.

Nine experiments were performed with 3 monkeys (2 *Papio doguere* of 7 and 10 kg, 1 *Papio cynocephalus* of 6 kg) in which the $Paco_2$ was altered but the blood pressure remained constant.

The baboons, after tranquillization by phencyclidine (2 mg/kg), were anæsthetized with an oxygen-halothane mixture in which both the proportion of halothane (1–1·5%) and the minute volume of the mixture were kept constant (usually 3 litres/min). The rate and depth of respiration (also constant) were controlled by means of a Carden Microvent. Arterial and central venous pressures were continuously monitored via catheters introduced into the femoral artery and vein, using Statham P23 DE and P23 BB strain gauges.

The common carotid artery was catheterized by a Seldinger technique with a polythene (PE 60) catheter with a single end-hole. The catheter was continuously perfused with heparinized normal saline and a series of arteriograms obtained by injecting 5 ml of urografin (methyl glucamine and sodium diacetyl, diamino-triiodo benzoic acid) and exposing 8 films at 2 per second in an AOT film changer. Focus- and object-film distances were always the same, namely 108 and 7 cm. The injections were made by a Cordis pressure injector set at 100 lb/in$^2$.

The arterial $CO_2$ tension, pH and $Po_2$ were obtained from samples drawn from the aorta via the femoral catheter and measured using the capillary pH electrode (Siggaard Andersen & Engel 1960) and the Severinghaus-Clark electrode assembly (Severinghaus & Bradley 1958).

In some experiments the $Paco_2$ fell spontaneously over a period of about one hour, providing opportunity for arteriograms at two levels. In other experiments 150–200 ml/min. of $CO_2$ was added to the inspired gases to raise the arterial $CO_2$ level.

Usually six arteries, occasionally seven and once four were measured in each experiment. They were the intracranial carotid, posterior communicating, posterior cerebral, middle cerebral, anterior cerebral (ascending portion), pericallosal and basilar arteries.

The method of measurement ensured an unbiased result. Each arteriogram consisted of 8 pictures, at least 4 of which usually showed any one artery. These pictures were given code numbers by an assistant, the true numbers being concealed. They were then shuffled with the pictures of other arteriograms (also coded) made during the experiment, and the arteries were measured at identical positions in all the pictures using a graticule marked to 0·1 mm. When all the measurements had been made they were reassembled into their correct series and for each arteriogram the mean value of the different measurements of the same artery was taken. In human arteriograms two measurements of an artery made by this method on two pictures after one injection have been found to vary by a mean of 1·3% (±3). In the baboons variations in arterial diameters from one arteriogram to the next under constant conditions of $Paco_2$ and blood pressure were very small (mean apparent vasoconstriction 1·6%±1·27).

The experiments have been divided into two kinds for comparison:

Series A: $Paco_2$ always above 28 mmHg:

| | Arteriogram 1 | | Arteriogram 2 |
|---|---|---|---|
| A1 | 28·0 mmHg | rising to | 48·0 mmHg |
| A2 | 38·4 mmHg | rising to | 52·5 mmHg |
| A3 | 35·4 mmHg | rising to | 59·0 mmHg |
| A4 | 48·0 mmHg | falling to | 33·0 mmHg |

Series B: $Paco_2$ rose from a level lower than 28 mmHg:

| | Arteriogram 1 | | Arteriogram 2 |
|---|---|---|---|
| B1 | 17·0 mmHg | rising to | 34·7 mmHg |
| B2 | 12·7 mmHg | rising to | 27·9 mmHg |
| B3 | 16·1 mmHg | rising to | 35·4 mmHg |
| B4 | 16·0 mmHg | rising to | 20·0 mmHg |
| B5 | 20·0 mmHg | rising to | 27·0 mmHg |

The results of these experiments may be presented in several ways:

(1) In some experiments, all, or nearly all, of the arteries appear to get larger, so that although the degree of change in each artery is small, there is very strong evidence of vasodilatation.
(2) The changes in diameter of smaller degree may be ignored and reliance placed only on large and easily recognized alterations. Since the various arteries differ in their original diameter, change may be expressed as a percentage and 10% has been taken as a significant change.

(3) The mean percentage change between one arteriogram and the next of all the measured arteries may be taken as an expression of mean vasodilatation or vasoconstriction, ignoring possible regional differences.

The purpose here is to compare the results of experiments A and B.

*Method 1:* In experiments in which the $Paco_2$ rose from 28 mmHg or more to a higher figure, there is very strong evidence that the arteries were wider at the higher $Paco_2$ in experiments A1 and A2 in which all the arteries measured (7 in one and 6 in the other) changed in the same direction. In experiment A3, 3 arteries became wider but 2 smaller, and in experiment A4, 4 arteries remained unchanged, one became narrower as the $Paco_2$ fell, but one became wider. Adding the results of these four experiments gives 17 arteries wider at higher $Paco_2$, 4 unchanged and 3 narrower. There is thus fairly strong evidence that within this range an increase in $Paco_2$ is accompanied by vasodilatation. In Series B, however, the conclusions are different: 7 arteries were wider at the higher level of $Paco_2$, 7 failed to change, but 13 were narrower.

*Method 2:* In Series A there were 4 arteries which were more than 10% wider at higher $Paco_2$, but one was more than 10% narrower. In Series B none of the arteries was more than 10% wider at higher $Paco_2$ but 6 were more than 10% narrower.

*Method 3:* In Series A the mean vasodilatation as $Paco_2$ rose was 3·4% ±1·44. In Series B there was a mean vasoconstriction of 3·9% ±1·68 as the $Paco_2$ rose.

Thus there is statistically significant evidence of a reactivity in differing directions in the A and B experiments consistent with the findings in humans that at subnormal $Paco_2$ further lowering of $Paco_2$ results in vasodilatation of the main arteries. At and above normal levels of $Paco_2$, rising $Paco_2$ causes vasodilatation.

It should be emphasized that these animal results were obtained in experiments in which the blood pressure remained constant. Blood pressure change is therefore excluded as a cause.

In other experiments, lowering the blood pressure rather profoundly in the baboon at constant $Paco_2$ causes not dilatation but constriction of these arteries. The extracranial, carotid and basilar arteries are most severely affected. Nevertheless, the anterior, middle and posterior cerebrals follow suit. Thus it again seems unlikely that widening of these cerebral arteries with falling $Paco_2$ at subnormal levels can be due to lowering of the arterial blood pressure.

Two other explanations have been considered: first, alteration in the central venous pressure. This has been excluded by monitoring the upper thoracic central venous pressure in a human series. There is no consistent relationship between the small variations in central venous pressure and the changes in arterial diameter. Secondly, that because of the very slow blood flow a degree of tissue hypoxia may occur and that a stimulus may be initiated which may override the vasoconstriction effect of low $Paco_2$ on the basal arteries. This explanation seems at the moment the more likely, but awaits experimental confirmation.

The effect of halothane has also been studied in the baboon and in our patients. Halothane is known to lower the systemic blood pressure. There has been an argument about its effect upon the cerebral circulation (McDowall 1965) but it now seems generally agreed that when the proportion in the inspired mixture is of the order of 1% or more, there is a rise in cerebral blood-flow (Wollman *et al.* 1965, Christensen *et al.* 1967). There is also a rise in intracranial pressure.

The suggestion has been made by Christensen *et al.* that the cerebral vasodilator effect of halothane may be potentiated by hypotension and/or hypercapnia. It has been further suggested that hyperventilation, by lowering the $Paco_2$, may overcome the cerebral vasodilator effect of halothane. This, however, is not borne out by a comparison of the sizes of major cerebral arteries in the previous and present series of human angiograms (Table 4). At the same low $Paco_2$ the arteries of patients anæsthetized with halothane were wider than those having nitrous oxide and oxygen alone.

Moreover, a series of baboons anæsthetized with an oxygen-halothane mixture when changed from spontaneous to more rapid controlled

*Table 4*
**Possible effect of halothane in man**

| | *Arterial diameter (mm)* | | | | |
|---|---|---|---|---|---|
| | *Carotid* | *Middle cerebral* | *Anterior cerebral* | *Mean $PaCO_2$ (mmHg)* | *Mean systolic blood pressure (mmHg)* |
| Series 2: With halothane | 4·06 | 3·03 | 2·3 | 30·8 | |
| Series 4: Without halothane | 3·31 | 2·83 | 2·09 | 29·2 | 128 |

respiration showed widening of cerebral arteries at normal $Paco_2$, presumably because of an increased level of halothane in the circulating blood.

In four experiments on baboons under oxygen-halothane anæsthesia, an increase in ventilation lowering the $Paco_2$ by a mean figure of 25 mmHg to a minimum of 32 mmHg, or a decrease in ventilation raising it by a mean figure of 11 mmHg from a minimum of 32 mmHg, caused vasodilatation as the $Paco_2$ fell and vasoconstriction as the $Paco_2$ rose, presumably because of the increased blood concentration of halothane produced by the hyperventilation. The figure for change in arterial diameter was 6·4%. Very wide variations occurred, some of the arteries dilating as much as 20%. Others, possibly because of a coincident blood pressure drop, constricted. Consequently the standard deviation is very large, ±8·9, and presented in this simple way the statistical significance is difficult to estimate.

*Conclusion*

The present work, following on that of Edmonds-Seal *et al.* (1967), has practical significance for cerebral angiography. It suggests that at very low levels of $Paco_2$ there is an unexplained phenomenon which begins to cause vasodilatation of the main cerebral arteries. Controlled respiration to maintain the level of $Paco_2$ at about 30 mmHg generally results in a very satisfactory angiogram, but perhaps lowering the $Paco_2$ further than this should be avoided until more is understood about its effects. It should, however, be stated that a great many patients have already undergone carotid angiography at levels of $Paco_2$ much lower than 30 mmHg and no ill effects have been observed in our series.

Some confirmation of the vasodilator effect of halothane on the cerebral circulation, even at low $Paco_2$, has been obtained.

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REFERENCES

**Christensen M, Høedt-Rasmussen K & Lassen N A** (1967) *Brit. J. Anæsth.* 39, 927
**du Boulay G** (1968) *Scand. J. clin. Lab. Invest.* Suppl. 102, VII:D
**du Boulay G, Edmonds-Seal J & Bostick T** (1968) *Brit. J. Radiol.* 41, 46
(1970) In: Recent Advances in the Study of Cerebral Circulation. Ed. J M Taveras *et al.* Springfield, Ill.; p 59
**Edmonds-Seal J, du Boulay G & Bostick T** (1967) *Brit. J. Radiol.* 40, 957
**McDowall D G** (1965) *Brit. J. Anæsth.* 37, 236
**Severinghaus J W & Bradley A F** (1958) *J. appl. Physiol.* 13, 515
**Siggaard Andersen O & Engel K** (1960) *Scand. J. clin. Lab. Invest.* 12, 177
**Wollman H, Alexander C, Cohen P J, Smith T C, Chase P E & van der Molen R A** (1965) *Anesthesiology* 26, 329

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## Regional Blood Flow in the Human Cerebral Hemisphere During General Anæsthesia, Studied at Normal and at Reduced Levels of Arterial $Pco_2$

A study was planned to investigate the state of regional perfusion of the normal hemisphere in the conscious state, during anæsthesia at normal levels of arterial $Pco_2$, and during anæsthesia at the time of arterial hypocapnia. The results of this study have been published in detail elsewhere (Wilkinson *et al.* 1969, Wilkinson & Browne 1970), but they may be reviewed collectively with profit to emphasize some of the salient findings of the investigation.

Regional cerebral blood flow was measured by simultaneous monitoring of the clearance of xenon-133 from 15 separate regions of the cerebral hemisphere, after injection of a small bolus of xenon-133 solution into the internal carotid artery. This was performed at the time of diagnostic carotid angiography; consequently none of the patients of the study was strictly normal. The criteria for 'normality' were that there were no abnormal physical signs referable to the cerebral hemisphere, and that the accompanying carotid angiogram subsequently proved to be normal.

Each regional clearance curve was analysed to give the perfusion rates in both the grey and the white matter of the region. In each patient, therefore, 15 regional values for the perfusion rate of grey and of white matter were obtained. From these 15 values a single mean value for the hemisphere for the perfusion rate of grey matter was determined, and similarly a single mean value for the rate of white matter perfusion in the hemisphere was obtained. The regional pattern of perfusion of grey matter throughout the hemisphere was demonstrated by making a topographical diagram of the 15 regional values on an outline of a lateral radiograph of the patient's skull. A similar diagram was constructed to show the regional pattern of white matter perfusion throughout the hemisphere.

Table 1 shows the results considered as mean values for the hemisphere. In the 10 conscious patients, studied at normal levels of arterial $Pco_2$ and blood pressure, values for grey and white matter perfusion were obtained which were very similar to those obtained by other workers (Høedt-Rasmussen 1967, Ingvar *et al.* 1965). Grey matter perfusion was numerically higher in the five conscious patients under 50 years of age than in those over 50, though this difference was not significant statistically. White matter perfusion was similar in the two age groups. In