Arterial P<sub>CO₂</sub> and cerebral hemodynamics<sup>1</sup>

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Reivich, Martin. Arterial P<sub>CO₂</sub> and cerebral hemodynamics. Am. J. Physiol. 206(1): 25-35. 1964.—The effect of arterial P<sub>CO₂</sub> in the control of cerebral hemodynamics over the full range of responsiveness of the cerebral vasculature was studied in the rhesus monkey. Cerebral perfusion pressure and arterial O₂ saturation were controlled so that they produced no significant effect on the cerebral circulation. Other possible sources of error, e.g., blood temperature, effect of anesthesia, development of metabolic acidosis, and validity of internal jugular measurements of cerebral blood flow were evaluated. Arterial P<sub>CO₂</sub> was varied from 5 to 418 mm Hg in eight animals. The minimum and maximum cerebral blood flows obtained were 18 and 140 ml/min 100 g, respectively. These values were approached when the arterial P<sub>CO₂</sub> was in the range of 10–15 mm Hg and 150 mm Hg, respectively. At these levels of arterial P<sub>CO₂</sub> the maximum and minimum cerebrovascular resistance occurred. These values were 4.78 and 0.63 mm Hg/ml/min per 100 g, respectively. A mathematical analysis of the data enabled equations relating arterial P<sub>CO₂</sub> to cerebrovascular resistance and to cerebral blood flow to be derived. Values predicted by these equations compare favorably with the actual measured data and with similar data in the literature.

METHODS

Cerebral Blood Flow

Cerebral blood flow was measured with two thermistor flowmeters, one in each internal jugular vein (R. Gelfand, personal communication). The flowmeter consists of a rigid plastic tube, 20 mm long with an inside diameter of 3 mm, into the wall of which are set two thermistors (32PB2, Thermistor Corp. of America). One thermistor is a flow probe, the circuit diagram for which is shown in Fig. 1, while the other is a temperature probe. The flowmeters were calibrated using blood flowing at a known volume per minute and at a known temperature. Since the calibration curves are temperature dependent, curves were obtained at various temperature levels in the range 33.0–39.5 C (Fig. 2). The temperature probe was calibrated against a standardized copper-constantan thermocouple (used with a Min-
were made for temperature and water vapor. Recorded at the time of each experiment to enable using a Liston-Becker infrared CO\(_2\) analyzer (6). The respiratory measurements

monkey blood (8).

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in a brachial vein and advanced into the superior vena

cation in which the \(O_2\) dissociation curve is shifted. Another contributing factor in the large variability of arterial \(O_2\) is the effect of changes in blood temperature, although this effect is much smaller than that of the \(P\) changes. A fall in blood temperature shifts the \(O_2\) dissociation curve to the left so that a given level of \(O_2\) saturation can represent an arterial \(P\) either higher or lower than the control \(P\), depending on the direction in which the \(O_2\) dissociation curve is shifted.

Arterial blood pressure was controlled and kept constant during the experiment by means of a pressurized reservoir system which contained heparinized monkey blood (8).

Respiratory Measurements

Tidal air was sampled continuously from a tracheotomy tube, and end-tidal \(P\) was recorded using a Liston-Becker infrared CO\(_2\) analyzer (6). The infrared analyzer was calibrated before and after each experiment using analyzed cylinders of mixtures of CO\(_2\) and \(O_2\). The gas analyses were performed by the Van Slyke method (58). The barometric pressure was

Hemodynamic Measurements and Control.

Arterial blood pressure was measured via a poly-

ethylene catheter inserted into a femoral artery and advanced into the thoracic aorta. The catheter was connected to a Statham pressure transducer which recorded on one channel of a six-channel Grass model 5 polygraph.

Venous pressure was measured via a catheter placed in a brachial vein and advanced into the superior vena cava. This catheter was connected to a second Statham pressure transducer which recorded on the Grass poly-

graph.

The animal's blood pressure was controlled and kept constant during the experiment by means of a pres-

surized reservoir system which contained heparinized monkey blood (8).

Blood Samples and Analysis

End tidal \(P\) equivalent to alveolar \(P\) (9), was used as a guide to the animal's arterial \(P\) level. This information was used in determining when to draw arterial blood samples from a catheter in the aorta. The \(pH\) and \(P\) of each sample was measured. The \(pH\) was determined using a McInnes-Belcher electrode system equilibrated to 37 \(C\) in a thermostatically con-
crolled, electrically shielded air bath, together with a Cambridge model R \(pH\) meter. Buffer checks were performed immediately before and after each blood \(pH\) measurement, using National Bureau of Standards buffers. Actual temperature of the blood \(pH\) measurement was determined to within \(\pm 0.1\) \(C\) with a calibrated thermistor thermometer, the thermistor being mounted within the lumen of the tubular glass electrode. Final \(pH\) values were corrected to the animal's measured blood temperature, using the coefficient 0.0147 per degree \(C\) (49), and were also corrected for glycolysis and for effects of whole blood on the glass electrode (55). Arterial \(P\) was determined electrometrically using the method described by Lowe (37). This latter method was compared with Van Slyke determinations of \(P\) on ten samples. The mean of the absolute differences was 1.54 mm Hg with a sd of \( \pm 0.00 \) mm Hg.

Arterial \(O_2\) saturation was recorded continuously using a Waters oximeter cuvette. The cuvette was inserted in an arteriovenous shunt from one femoral artery to vein. Arterial \(P\) was calculated from the \(O_2\) saturation, making corrections for blood \(pH\) and temperature using the nomogram of Severinghaus (54).

Even though the level of \(O_2\) saturation of the arterial blood was maintained within fairly narrow limits (Table 2), when the arterial \(P\) was calculated from these values a wide range of \(O_2\) resulted. This is partly due to the Bohr effect produced by changes in \(P\) and \(pH\) during the experiments. Because of this a given level of \(O_2\) saturation can represent an arterial \(P\) either higher or lower than the control \(P\), depending on the direction in which the \(O_2\) dissociation curve is shifted.

Another contributing factor in the large variability of arterial \(O_2\) is the effect of changes in blood temperature, although this effect is much smaller than that of the \(P\) and \(pH\) changes. A fall in blood temperature shifts the \(O_2\) dissociation curve to the left so that a given level of \(O_2\) saturation is produced by a lower arterial \(P\). During the experiments the maximum fall in blood temperature was 2.2 \(C\). This could produce a fall in arterial \(P\) of 9% of the control level without changing the \(O_2\) saturation from control levels. The changes in \(P\) due to changes of \(P\) and \(pH\) are of the order of 15 times this amount.

General Procedure

The experiments were performed in eight rhesus monkeys weighing between 12 and 15 lb and between 4 and 5 years of age. The animals were anesthetized with 20–30 mg/kg body wt. of Nembutal, intravenously,
arterial \( \text{PCO}_2 \) and cerebral hemodynamics

The mean cerebral blood flow obtained in these animals when their arterial \( \text{PCO}_2 \) was in the normal range (38.2–42.5 mm Hg with a mean of 40.7 mm Hg) was 49.3 ml/min/100 g. The value predicted by the fitted logistic curve shown in Fig. 3 (see Appendix for its derivation) is 48.8 ml/min/100 g at an arterial \( \text{PCO}_2 \) of 40.0 mm Hg. A maximum cerebral blood flow of 140 ml/min/100 g and a minimum flow of 18 ml/min/100 g was produced by the wide range of arterial \( \text{PCO}_2 \) attained. This represents an eightfold change in cerebral blood flow. The minimum value was approached at a \( \text{PCO}_2 \) of 15 mm Hg and the maximum cerebral blood flow at a \( \text{PCO}_2 \) of 150 mm Hg.

Cerebral vascular resistance varied from a maximum of 4.78 mm Hg/ml min per 100 g to a minimum of 0.64 mm Hg/ml min per 100 g. At normal control levels (i.e., when arterial \( \text{PCO}_2 \) was between 38.2 and 42.5 mm Hg) the mean cerebral vascular resistance was 1.80 mm Hg/ml min per 100 g.

Using the equation relating cerebral blood flow to arterial \( \text{PCO}_2 \) derived above and the following relationship:

\[
\text{CVR} = \frac{P}{\text{CBF}}
\]

where \( P \) = cerebral perfusion pressure, an equation relating arterial \( \text{PCO}_2 \) and cerebral vascular resistance (CVR) can be determined:

\[
\text{CVR} = \frac{P(1 + ce^f \log \text{PCO}_2)}{k + d(1 + ce^f \log \text{PCO}_2)}
\]

The value for the cerebral vascular resistance predicted by this equation at an arterial \( \text{PCO}_2 \) of 40.0 mm Hg is 1.78 mm Hg/ml min per 100 g.

Perfusion Pressure

Cerebral perfusion pressure was maintained within fairly narrow limits within any particular animal, the mean standard deviation being 2.3 ± 0.8 mm Hg. The over-all mean cerebral perfusion pressure was 85.6 mm Hg with a standard deviation of ±10.8 mm Hg. Thus the range of perfusion pressures studied between animals was somewhat wider.

Blood Measurements

It was difficult to maintain the arterial \( \text{O}_2 \) saturation constant within an animal as is shown by the larger mean standard deviation of 3.9 ± 3.0%. The over-all mean level of arterial \( \text{O}_2 \) saturation was 94.3 ± 6.2%.
The calculated values of arterial PO\textsubscript{2} showed a wide variability, as can be seen in Table 2 from their mean values and standard deviations. The arterial PO\textsubscript{2} varied from 60 to 380 mm Hg with an over-all mean of 150 ±

<table>
<thead>
<tr>
<th>TABLE 1. Cerebral hemodynamics and blood parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Art. PO\textsubscript{2}, mm Hg</strong></td>
</tr>
<tr>
<td>40.5</td>
</tr>
<tr>
<td>18.7</td>
</tr>
<tr>
<td>13.7</td>
</tr>
<tr>
<td>7.22</td>
</tr>
<tr>
<td>66.8</td>
</tr>
<tr>
<td>176.0</td>
</tr>
<tr>
<td>244.0</td>
</tr>
<tr>
<td>418.0</td>
</tr>
</tbody>
</table>

**Art. CO\textsubscript{2}, mm Hg** | **Art. pH** | **Venous Blood Temp., °C** | **Art. PO\textsubscript{2}, mm Hg** | **Perf. Press., mm Hg** | **CBF, ml/min** |
| 21.2 | 99.0 | 7.296 | 35.75 | 190 | 90.0 |
| 17.7 | 99.0 | 7.347 | 35.05 | 210 | 90.0 |
| 17.3 | 99.0 | 7.355 | 35.00 | 230 | 90.0 |
| 21.5 | 99.0 | 7.349 | 35.85 | 150 | 90.0 |
| 25.9 | 99.0 | 7.481 | 39.90 | 160 | 90.0 |
| 35.3 | 90.0 | 7.330 | 35.25 | 200 | 90.0 |
| 54.8 | 95.0 | 7.196 | 35.55 | 200 | 90.0 |
| 71.0 | 97.0 | 7.081 | 35.15 | 190 | 90.0 |
| 66.8 | 97.0 | 7.099 | 35.65 | 190 | 90.0 |

**CBF** = cerebral blood flow; **CVR** = cerebral vascular resistance.

80 mm Hg. Some of the reasons for this variation were discussed under METHODS.

Arterial PO\textsubscript{2} varied from a minimum value of 5.3 mm Hg during hyperperventilation to a maximum of 418 mm Hg on breathing gas mixtures high in CO\textsubscript{2} content. The extremes in variation in arterial blood pH concomitant with the respiratory alkalosis and acidosis produced were 7.70 and 6.60, respectively.

Blood temperature varied from 33.90 to 37.65 C. An attempt was made to prevent a marked fall in blood temperature since this may affect cerebral blood flow. The mean drop in temperature during the experiments was 1.55 ± 0.35 C.

**DISCUSSION**

**Effect of Arterial PCO\textsubscript{2} on Cerebral Hemodynamics**

The full range of responsiveness of the cerebral vasculature to changes in arterial PCO\textsubscript{2} is represented by the curve in Fig. 3. The following equation, derived as stated in the APPENDIX, describes the relationship be-

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ARterial Pco2 and Cerebral Hemodynamics

TABLE 2. Experimental conditions

<table>
<thead>
<tr>
<th>Arterial O2 Sat., $%$</th>
<th>Temp., $^\circ$C</th>
<th>Arterial Pco2, mm Hg</th>
<th>Perfusion Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 94.1±1.2</td>
<td>34.61±0.68</td>
<td>116±90</td>
<td>64.8±3.5</td>
</tr>
<tr>
<td>2 97.1±3.1</td>
<td>37.16±0.41</td>
<td>207±109</td>
<td>73.88±2.98</td>
</tr>
<tr>
<td>3 89.7±5.4</td>
<td>36.19±0.73</td>
<td>99±68</td>
<td>99.38±2.17</td>
</tr>
<tr>
<td>4 88.3±11.0</td>
<td>35.02±0.26</td>
<td>136±88</td>
<td>77.6±2.94</td>
</tr>
<tr>
<td>5 93.8±3.6</td>
<td>35.39±0.71</td>
<td>108±43</td>
<td>90.13±3.01</td>
</tr>
<tr>
<td>6 98.7±1.0</td>
<td>34.57±0.66</td>
<td>91±63</td>
<td>87.81±1.36</td>
</tr>
<tr>
<td>7 98.9±1.4</td>
<td>35.59±0.40</td>
<td>192±49</td>
<td>93.05±1.24</td>
</tr>
<tr>
<td>8 96.4±3.2</td>
<td>36.33±0.45</td>
<td>174±50</td>
<td>89.00±1.80</td>
</tr>
</tbody>
</table>

49.3±6.2*  35.61±1.00*  148±83*  85.55±10.86*

The values (means and sxs) give an indication of the degree of variability present in parameters which were attempted to be controlled. These parameters were shown to have no significant effect on cerebral hemodynamics. *Over-all mean and sd.

The range of response of cerebral blood flow to change in cerebral perfusion pressure is maintained constant if arterial Pco2 is 85.6 mm Hg: 

$$CBF = 20.9 + \frac{92.8}{1 + 10570 e^{-2.61 \log Pco2}}$$

As arterial Pco2 is reduced, cerebral blood flow approaches a minimum value of 20.9 ml/min 100 g. This minimum is not reached until the arterial Pco2 is in the range of 15 mm Hg. Conversely, as arterial Pco2 increases, cerebral blood flow approaches a maximum value of 113.8 ml/min 100 g. This value is approximated when arterial Pco2 is raised to the level of 150 mm Hg. These predicted extreme values of cerebral blood flow compare favorably with the actual measured mean extreme values of 22.8 and 109.5 ml/min 100 g at Pco2 levels less than 15 mm Hg and greater than 150 mm Hg, respectively. The normocapnic cerebral blood flow obtained from the raw data in the range 38.5-42.5 mm Hg Pco2 (mean, 40.7 mm Hg) in these animals was 49.3 ml/min 100 g. The value predicted by the above equation is 48.8 ml/min 100 g at an arterial Pco2 of 40.0 mm Hg.

Since there is very little quantitative cerebral blood flow data for the monkey available in the literature, comparisons of the results of the present study will have to be made with human data, of which there is much more extant, as well as with monkey data. These two sets of data, human and monkey, though not strictly comparable because of species differences and the use of different methods for measuring cerebral blood flow, do, however, have similarities from which useful comparisons can be drawn. Thus, if we compare the normal cerebral blood flow predicted from the derived equation with values obtained by other workers (Table 3) who have measured cerebral blood flow in primates, we find fairly good agreement. It will be noted that these cerebral blood flow measurements were made at different mean levels of arterial Pco2. If these values are adjusted to a Pco2 of 40.0 mm Hg, using the factor 1.11 ml/min 100 g per mm Hg Pco2 (see below), the over-all mean is in even closer agreement with the value obtained in this study. If anything, the values obtained by the nitrous oxide method may be a little high, since this method tends to overestimate cerebral blood flow (1, 34, 31).

Another interesting comparison that can be made is the value of the sensitivity of cerebral blood flow to changes in arterial Pco2 obtained by various investigators. The maximum sensitivity occurs at the point of inflection of the logistic curve and equals the slope at that point. The slope of the curve at any point is given by the first derivative which is:

$$\frac{dy}{dx} = k_c r e^{-1 \log x}$$

The point of inflection can be determined from the second derivative which is:

$$\frac{d^2y}{dx^2} = \frac{k_c r e^{-1 \log x}}{x^2} \left[ \frac{1}{(1 + c e^{-1 \log x})^2} - \frac{x}{(1 + c e^{-1 \log x})^2} \right]$$

From these two equations it can be determined that the maximum sensitivity occurs at a Pco2 of 39.0 mm Hg and is 1.11 ml/min 100 g per mm Hg Pco2. This value is compared in Table 4 with values for the maximum sensitivity calculated from data in the literature. The calculated values were obtained by fitting the best straight line to that data in the range of Pco2 between 20-60 mm Hg, since it is in this range that the maximum sensitivity occurs and since the logistic curve is approximated by a straight line in this region. A straight line approximation was used because the available data does not cover a sufficient range of Pco2 to justify fitting a logistic curve to it.

The range of response of cerebral blood flow to change in Pco2 varied from a minimum flow of 45% of normal to a maximum flow of 240% of normal. In a study in dogs by Gurvich, Webster, and Stone (20) in which arterial Pco2 was varied from 10 to 90 mm Hg, cerebral blood flow, measured by changes in arteriovenous O2 differences, varied from a minimum of 70% to a maximum of 260% of normal flow. In primates, no other studies could be found in which arterial Pco2 was increased above 60 mm Hg. Therefore, a statement concerning the maximum cerebral blood flow response to be expected cannot be made. However, there is data available concerning the minimum flow in primates. By extrapolating the data of Wasserman and Patterson (39), it is suggested that in man a minimum cerebral blood flow of 60% of normal would be obtained. Their cerebral blood flow values are based on changes in $A-V_o2$ and the assumption that the rate of cerebral O2 consumption (CMR$O_2$) remains constant during active hyperventilation. They present data obtained by simultaneous measurements of $A-V_o2$ and cerebral blood flow by the nitrous oxide method to show that there is no significant change in CMR$O_2$ during active hyperventilation. Similar studies by Kety and Schmidt (26) demonstrated a significant increase in CMR$O_2$ during...
active hyperventilation of 5–35% (avg., 15%). However, as pointed out by Lassen (33), the 10-min nitrous oxide measurement of cerebral blood flow is about 10% too high at normal levels of cerebral blood flow and a somewhat greater error may be expected at low levels of cerebral blood flow. This might account for the 15% increase in CMRO_2 found by Kety and Schmidt.

Using data obtained in man by several investigators (26, 28, 30, 43, 44, 59) by means of the nitrous oxide technique, an estimate of the minimum cerebral blood flow to be expected in response to hypocapnia can be made. This was done by fitting an exponential curve to the data. A value of about 55% is obtained if this curve is extrapolated to the region of 0–10 mm Hg PCO_2. These estimates of the maximum and minimum cerebral blood flow produced by hypercapnia and hypocapnia, respectively, and of the sensitivity of cerebral blood flow to changes in arterial PCO_2 agree fairly well with the values obtained in the present study.

The equation which describes the relationship between arterial PCO_2 and cerebral vascular resistance is:

\[
CVR = \frac{85.55 + 904.40e^{-5.221 \log PCO_2}}{119.8 + 221.30e^{-5.86 \log PCO_2}}
\]

which was derived above.

Maximum cerebral vasodilation occurs as arterial PCO_2 approaches 450 mm Hg. The value of cerebral vascular resistance approached at these levels of PCO_2 is 0.76 mm Hg/ml min per 100 g. Maximum cerebral vasoconstriction occurs when arterial PCO_2 approaches zero. The cerebral vascular resistance approaches 4.10 mm Hg/ml min per 100 g at this level of PCO_2. These predicted extreme values of cerebral vascular resistance compare favorably with the actual measured mean extreme values of 0.81 and 3.92 mm Hg/ml min per 100 g at PCO_2 levels greater than 150 mm Hg and less than 15 mm Hg, respectively.

The cerebral vascular resistance predicted by this equation at a PCO_2 of 40.0 mm Hg is 1.78 mm Hg/ml min per 100 g and is compared in Table 3 with values in the literature. The effects on these values of a tendency to overestimate cerebral blood flow by the nitrous oxide method, and the PCO_2 levels slightly above 40.0 mm Hg at which these measurements were made, are in opposite directions and would tend to nullify each other. Thus the mathematical description appears to agree well with observed values of cerebral vascular resistance at this level of arterial PCO_2.

**Sources of Error**

1. Internal jugular measurement of cerebral blood flow. It was decided to measure cerebral blood flow via the venous outflow rather than the arterial inflow to the brain for several reasons. Methods requiring measurement of cerebral blood flow on the arterial side may interfere with the normal carotid innervation and thus grossly alter the physiological responsiveness of the preparation. Also, mechanical manipulation of cerebral arteries could lead to their artificial constriction. Pial vessels, at least, in such spasm have been reported to be unresponsive to CO_2 (10). Further, it would have been necessary to use flowmeters of smaller diameter on the arterial side and thus run the risk of increasing the effective cerebral vascular resistance which increases inversely with the fourth power of the radius (61, 62). Finally, the flowmeters were not placed on the arterial side since it has been shown by Folkow (16) that this may traumatize the blood with consequent release of vasodilating substances.

However, the use of venous outflow measurements of cerebral blood flow raises the question of the validity of
The proportion of cerebral venous outflow carried by the external jugular vein as a measure of total cerebral blood flow. In the rhesus monkey the cerebral arterial pattern, as well as the venous outflow, resembles that of man (3). It has been shown that blood from the internal jugular bulbs in man contains only about 3% of blood derived from extracerebral sources (56). However, a possible source of significant contamination is the common facial vein which drains into the internal jugular vein below its exit from the skull. Therefore, in these experiments the internal jugular vein was carefully dissected up to the base of the skull and the flowmeters inserted as close to the skull as possible. Any tributary veins from the external circulation joining the internal jugular above the flowmeter were ligated.

An estimate of the proportion of cerebral circulation draining via venous channels other than the internal jugular veins is difficult to make. About 22% of the blood in the external jugular veins in man is derived from the cerebral circulation (56). Also, there are veins on the caudal surface of the brain stem which drain into the veins around the spinal cord (23). Batson (2) showed that there is free communication between these vertebral veins about the cord and the intracranial venous channels both in man and in the monkey. Thus the cerebral venous outflow, exclusive of the internal jugular veins, returns by one of two main routes—the external jugular system and the internal vertebral system about the spinal cord.

The proportion of cerebral venous outflow carried by the external jugular system can be estimated by making use of the facts that 22% of the external jugular blood is derived from extracranial sources (56), and that approximately 80% of the common carotid flow is directed intracranially and 20% extracranially (21). Therefore, the blood present in the external jugular vein derived from intracranial sources represents only about 5% of the total cerebral blood flow. This estimate neglects any intracranial blood from the vertebral basilar system which may enter the external jugular veins since the figure of 22% was derived from studies in which dye was injected into the internal carotid artery only. However, the vertebral arteries, in man at least, contribute only a total of 10% to the total cerebral blood flow (92). Therefore, even if twice as much blood from the posterior circulation as from the carotid system drains via the external jugular veins, this would raise our estimate only to 5.5%. Thus the figure of 5% is probably a fair estimate of the proportion of total cerebral blood flow leaving the brain via the external jugular veins.

Since there is no data available on which to base an estimate of the proportion of cerebral venous outflow represented by the internal vertebral system, we will assume that it also represents 5%. Thus, a total of approximately 10% of the cerebral venous outflow leaves the brain via routes other than the internal jugular veins.

This is of the same order of magnitude as the accuracy (±7%) with which the flowmeters used were calibrated. Because of this and the uncertainty of the exact proportion of the total cerebral blood flow that is represented by the internal jugular veins, as well as not knowing if this proportion changes with changes in cerebral blood flow, it was decided not to make any corrections but to use the original flow data as obtained. No significant difference was found between the flows in each internal jugular vein.

2. Temperature effect on cerebral hemodynamics. An attempt was made to prevent lowering of the animal's temperature during the experiment since a reduction in body temperature can lower cerebral blood flow. The mean temperature at which the animals were kept was about 35.6 ± 1.6°C. The lowest value to which any animal's temperature dropped was 33.9°C. Bering et al. (4), working with monkeys, found no change in cerebral blood flow until their temperature fell below 30°C. Meyer and Hunter (40) made measurements of cortical arteries and veins with a micrometer microscope in cats and monkeys and noted no change in the caliber of these vessels until a temperature of 32°C was reached. A progressive reduction in the caliber of these vessels began at 32°C and became more marked at lower temperatures. However, they noted only slight, if any, change in cerebral blood flow until a temperature below 28°C was reached. Thus, at the temperatures at which these experiments were performed, there was probably no significant effect on cerebral blood flow.

3. Effect of anesthesia on cerebral hemodynamics. The effect of barbiturate anesthesia on cerebral blood flow must be considered. Wechsler et al. (60) found that thiopental anesthesia in man produced a significant reduction in the CMBF. However, they found no impairment of cerebral blood flow itself in these studies. Fazekas and Bessman (12) reported similar findings in barbiturate-induced coma. Other workers (47, 52),
changes in arterial pH, other than those produced by changes in arterial PCO₂, have a significant effect on cerebral hemodynamics is not entirely clear. Ketty et al. (24) found that in diabetic coma cerebral blood flow was increased even though arterial PCO₂ was markedly reduced. They attributed this increase in cerebral blood flow to vasodilation caused by the fall in pH due to the marked metabolic acidosis in these patients. However, the possible effect of other biochemical alterations in severe diabetic acidosis and coma cannot be eliminated.

Lambertsen and colleagues (31) experimentally separated in man blood pH and PCO₂ in both arterial and internal jugular blood and noted their effects on cerebral circulation. They concluded that cerebrovascular tone was almost quantitatively related to PCO₂ and unaffected by changes in pH that were not produced by changes in PCO₂. These studies were performed in the region of normal acid-base balance. The change in bicarbonate concentration was of the order of 4 mM/liter while, in the patients in diabetic coma, the change in bicarbonate concentration was about 20 mM/liter.

In the present study there was a tendency for metabolic acidosis to develop during the course of an experiment. The mean decrease in bicarbonate concentration at the end of these experiments due to metabolic acidosis was 5.0 ± 3.2 mM/liter. This figure is comparable to the change in bicarbonate concentration studied by Lambertsen et al. (31), although on the side of metabolic acidosis rather than alkalosis. It might be expected, therefore, that the degree of metabolic acidosis which developed in these experiments had little or no effect on cerebral hemodynamics.

6. Effect of cerebral perfusion pressure on cerebral hemodynamics. There is contradictory evidence in the literature concerning the effect of changes in cerebral perfusion pressure on cerebral blood flow. Schmidt (53) studied the effect of varying systemic blood pressure on cerebral blood flow in dogs and cats. He concluded that cerebral blood flow passively followed changes in systemic pressure. Sagawa and Guyton (50) reached the same conclusion in their study of pressure-flow relationships in the isolated cerebral circulation of the dog. Fog (15) observed the pial vessels of cats and dogs through cranial windows and noted the effects of changes in blood pressure. These vessels responded by active vasoconstriction to a rise in intravascular pressure until systemic blood pressure was extremely low when all active regulation of vasomotor tone seemed to be lost. His data support the view that autoregulation of the cerebral circulation is present. Lassen (33) published a graph relating cerebral blood flow to mean arterial pressure in man compiled from data in the literature from seven different sources. This shows a constant level of cerebral blood flow over a range of mean arterial pressure from 50 to 170 mm Hg. Not until mean arterial pressure falls below 50 mm Hg does the cerebral blood flow decline, and then it does so precipitously. These data tend to suggest the presence of autoregulation of cerebral circulation in man.

However, as Lassen points out, in the various hyper-

### Table 4. Maximum sensitivity of CBF to change in arterial PCO₂

<table>
<thead>
<tr>
<th>Frimate and Ref.</th>
<th>Maximum* Sensitivity, ml/min 100 g per mm Hg PCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man (26, 48)</td>
<td>1.75</td>
</tr>
<tr>
<td>Man (30, 1)</td>
<td>0.34</td>
</tr>
<tr>
<td>Man (44, 59)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

* Calculated from the slope of the best-fitting straight line through data in the range of PCO₂ between 20-60 mm Hg. | C. J. Lambertsen, personal communication.
data, however, no accurate statement concerning the cerebral blood flow at each level of arterial PCO₂. From these data was made. There was no significant effect on cerebral blood flow due to this degree of variation of cerebral perfusion pressure, an analysis similar to that performed with the arterial POT in these experiments. However, the mean level at which the cerebral perfusion pressure was maintained between animals varied from 64.9 to 99.4 mm Hg (overall mean perfusion pressure = 85.6 ± 10.8 mm Hg). This amount of variation in cerebral perfusion pressure could possibly have a significant effect on cerebral blood flow if so-called autoregulation does not exist in monkeys. To determine whether these data showed any significant effect on cerebral blood flow due to this degree of change in cerebral perfusion pressure, an analysis similar to that performed with the arterial PO₂ data was made. There was no significant effect on cerebral blood flow by this degree of variation of cerebral perfusion pressure at each level of arterial PCO₂. From these data, however, no accurate statement concerning the presence or absence of autoregulation in the monkey can be made since the range of perfusion pressure was purposely kept relatively narrow.

APPENDIX

Curve Analysis

Using the raw data (Table 1), a plot of PO₂ versus cerebral blood flow suggested that the data fit an asymmetric sigmoid distribution (Fig. 3). This type of curve would be reasonable to expect since both an upper limit to the maximum cerebral blood flow and a lower limit to the minimum flow would be anticipated. A plot of running averages of cerebral blood flow versus PO₂ (Fig. 5) made this relationship even clearer and tended to rule out the possibility of fitting an exponential curve to the data. Further, a semilogarithmic plot of running averages of cerebral blood flow values against PO₂ failed to approximate a straight line, thus arguing against a simple exponential curve as a good description of the data.

Several different types of curves can be used to fit a sigmoid distribution of data, e.g., a probit curve, an integrated skewed normal curve, a Gompertz curve, and a logistic curve. Of these various curves, we chose to fit a logistic curve to the data for several reasons. First, the logistic curve was developed (45) to describe the following characteristics of a set of data: (1) there is a finite limiting area in which the variable is operating; (2) there is an upper limiting asymptote; (3) there is a lower limiting asymptote, and (4) the general shape of the curve is sigmoid. These characteristics are all present in these cerebral blood flow data, i.e., there is a finite limiting area, the maximum dilation of the cerebral vascular bed, in which the cerebral blood flow can vary; a minimum and maximum cerebral blood flow would be expected corresponding to maximum vasoconstriction and maximum vasodilation, respectively, of the cerebral vasculature; and the general shape of the curve is sigmoid, as inspection of the data reveals.

Second, mathematical criteria can be used to differentiate a logistic and Gompertz curve (7). Namely, in a logistic curve the first differences of the reciprocals change by a constant per cent, while in a Gompertz curve it is the first differences of the logarithms which change by a constant per cent. Applying these criteria to the data indicated that the logistic curve would be a better description of the data.

Finally, a comparison of the root mean squares of the probit curve and integrated skewed normal curve with that of the logistic curve showed there was not a significantly different fit among the three curves (Fig. 5). Therefore, the logistic curve was chosen to describe the data.

Fitting the Logistic Curve (46)

The data can be converted into the form of a symmetrical logistic curve by plotting cerebral blood flow against log PO₂. The equation for a symmetrical logistic curve is:

\[ y = \frac{d + k}{1 + e^{r(x - c)}} \]

where \( y \) = cerebral blood flow, \( x = \log \text{PO}_2 \), \( d + k \) = maximum cerebral blood flow, and \( c \) and \( r \) are constants whose significance is shown below. This equation can be converted into the form of a straight line as follows:

\[ \ln \left( \frac{y - d}{y - k} \right) = \ln(c) + rx \]

Thus it can be seen that \( r \) represents the slope of this line and \( c \) the intercept of the ordinate axis. For the first approximation of the logistic curve, the best values for the maximum and minimum cerebral blood flows are chosen from the cerebral blood flow versus log PO₂ plot. Then values of \( (k - y + d)/(y - d) \) for each value of \( y \) are calculated and plotted against corresponding values of log PO₂. This produces a straight line from which can be calculated values for \( r \), the slope, and for \( c \), the intercept of the ordinate axis, by means of the least-squares method. These values of \( d \), \( k \), \( r \), and \( c \) give us the first approximation to the equation of the desired logistic curve.

The second approximation is obtained by expanding the equa-
Fig. 5. Comparison of three different types of asymmetric sigmoid curves fitted to the cerebral blood flow versus arterial PCO\textsubscript{2} data. o = Values of running averages of ten data points from all eight monkeys. There is not a significantly different fit among the three curves.

REFERENCES

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