PET Studies of Changes in Cerebral Blood Flow and Oxygen Metabolism After Unilateral Microembolization of the Brain in Anesthetized Dogs

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Cerebral blood flow and oxygen metabolism have been measured with the steady-state oxygen-15 technique and positron emission tomography in anesthetized dogs. Regional microembolization was induced by infusing Sephadex particles (diameter, 40 μm) into one of the common carotid arteries. In the first series of experiments, 2.5 mg Sephadex was infused, and the dogs were examined within 3–4 hours after embolization. In a second series 0.55 mg Sephadex was infused, and the dogs were examined either in the first 3–4 hours or 24–48 hours after embolization. Cerebral blood flow, oxygen extraction ratio, and cerebral oxygen utilization were measured at 3 Pco2 levels. In the acute experiments, cerebral oxygen utilization in the embolized hemisphere was 6 (0.55 mg Sephadex) and 25% (2.5 mg Sephadex) lower than on the contralateral side. While cerebral blood flow was symmetrically distributed in normocapnia and hypocapnia, it was 9 (0.55 mg Sephadex) and 35% (2.5 mg Sephadex) lower in the embolized hemisphere during hypercapnia. In normocapnia and hypocapnia the lower oxygen utilization in the embolized hemisphere was characterized by a lower oxygen extraction ratio, and in hypercapnia by an unchanged (0.55 mg Sephadex) or by a higher (2.5 mg Sephadex) extraction ratio. The different effect on oxygen extraction ratio in the control and embolized hemispheres resulted in images of uncoupling between perfusion and oxygen demand that varied according to the Pco2. The experiments also showed a fall in cerebral blood flow in the embolized hemisphere after 3–4 hours, indicating delayed hypoperfusion. After 24–48 hours, blood flow was about 10% higher in the embolized hemisphere, and this was observed at the 3 Pco2 levels, while the oxygen extraction ratio was systematically lower. Oxygen utilization in the embolized hemisphere was depressed to practically the same extent as in acute experiments. It can be concluded that between 4 and 24 hours after microembolization the cerebral microcirculation shows important changes, with installation of luxury perfusion in the face of an unchanging decreased oxygen metabolism. (Stroke 1987;18:128–137)

In acute stroke disease, measurements of changes in cerebral blood flow (CBF) alone have only a limited prognostic value; their clinical significance increases when they are analyzed in the context of metabolic alterations.1,2 The introduction of positron emission tomography (PET) represents a significant methodological advance because it allows accurate measurement of tissue radioisotope distribution in vivo, analogous to postmortem autoradiography in animals. Several radiopharmaceuticals are proposed to study CBF and cerebral energy metabolism with PET.3 Among those, the steady-state oxygen-15 inhalation technique elaborated by Frackowiak et al4 (following early work by Jones et al5) has the dual advantage of being relatively simple and allowing assessment of both CBF and oxygen extraction ratio (OER) with practically the same procedure.

Clinical studies show a high variability in changes of CBF and cerebral metabolism in ischemia. Most experimental models also suffer from a considerable variability in the severity of ischemia.6 In the present study we have measured CBF and cerebral oxygen metabolism with the steady-state oxygen-15 technique in experimental animals after cerebral microembolization, which induced very reproducible and dose-dependent effects. Our aim therefore was 1) to assess the possibilities of the steady-state oxygen-15 technique in animals with standardized experimental cerebral ischemia; 2) to investigate the early changes in CBF and cerebral metabolic rate of oxygen (CMRO2) in this particular type of ischemia; 3) to study the influence of changes in Pco2 on these parameters; and 4) to compare the acute effects with the situation 24–48 hours later.

Materials and Methods

The experiments were performed on anesthetized and artificially ventilated mongrel dogs of both sexes with body weights between 16 and 29 kg. There were 2 series of experiments, the experimental designs of which are depicted in Figure 1.

Series I: Acute Experiments with Severe Embolization

Anesthesia was induced with i.m. injection of xylazine (Rompun, 1.5 mg/kg) followed by i.v. injection of pentobarbital (10 mg/kg) 15 minutes later. After
muscular relaxation (gallamine 10 mg/kg i.v. followed by additional doses when necessary) the animals were intubated with a cuffed endotracheal tube and artificially ventilated with a N\textsubscript{2}O:O\textsubscript{2} mixture (2:1 v/v) by means of a constant-volume Starling-type respirator (Palmer, London, England). Respiratory rate was set at 14 breaths/min, and tidal volume was adjusted to maintain Paco\textsubscript{2} at 30–35 mm Hg. End-tidal CO\textsubscript{2} concentration was continuously measured with an infrared analyzer (Capnograph, Godart, Bilthoven, The Netherlands) and kept constant by electronic feedback adjustment of tidal volume as described previously.\textsuperscript{7} Polyethylene tubing (Clay Adams, Parsippany, N.J.) was inserted into femoral arteries and veins for arterial blood sampling, monitoring of arterial blood pressure, and i.v. injections. Another tube was inserted into the left thyroid artery and directed towards the common carotid artery (CCA) for subsequent regional embolization of the brain. After completion of surgical preparation, the head of the animal was fixed in a stereotactic frame made of aluminum and perspex (to minimize photon attenuation during PET) and placed in the gantry of the PET scanner. Experimental regional cerebral ischemia was induced by infusing 2.5 mg Sephadex G 25 particles (Pharmacia, Uppsala, Sweden; mean diameter, 40 \textmu m) into the left CCA. Sephadex particles were suspended in 50 ml physiological saline and infused at a rate of 7.64 ml/min. During the infusion the suspension was continuously agitated by a magnetic stirrer. To increase the number of particles flowing to the brain, the dogs were made hypercapnic (Paco\textsubscript{2} ca. 55 mm Hg) by adding 6% CO\textsubscript{2} to the inhalation gas mixture 10 minutes before the start of the Sephadex infusion. At the end of the infusion, the animals were immediately returned to normocapnia. As depicted in Figure 1, 4 groups of experiments were performed, each consisting of 6 dogs — 2 groups with sham embolization and 2 other groups with microsphere embolization. The first CBF measurement (N\textsubscript{1}) was made 30 minutes after Pco\textsubscript{2} had returned to normal following embolization, and the final CBF measurement (N\textsubscript{2}) also was performed in normocapnia about 3 hours later. In the time between those 2 normocapnic CBF measurements, Paco\textsubscript{2} was either increased to about 55 mm Hg (by substitution of 6% CO\textsubscript{2} for O\textsubscript{2} in the gas mixture and adjusting tidal volume) or decreased to about 25 mm Hg (by adjusting tidal volume). CBF was measured at the beginning (H\textsubscript{1}) and at the end (H\textsubscript{2}) of the hypercapnic or hypocapnic period. The H\textsubscript{1} measurement was followed by a \textsuperscript{15}O\textsubscript{2} scan to assess oxidative metabolism in hyper- or hypocapnia. At the end of the experiment, the animals were sacrificed by i.v. injection of saturated KCl solution.

**Series II: Mild Embolization**

**GROUP 1: acute experiments.** Eight dogs were instrumentally prepared as described above except that regional cerebral infarction was produced by infusing 0.55 mg Sephadex particles. After embolization, repetitive \textsuperscript{13}O\textsubscript{2} and \textsuperscript{15}O\textsubscript{2} scans were obtained at 3 differ-
ent Pco₂ levels, each level being maintained for 60–70 minutes as illustrated in the lower part of Figure 1.

**GROUP 2: 24–48-HOUR EXPERIMENTS.** The experiments were performed on 8 dogs that had been embolized 24 or 48 hours previously. After anesthesia and installing artificial ventilation similar to that in the other experiments, polyethylene tubing was inserted into the left thyroid artery and 0.55 mg Sephadex particles was infused. Surgical wounds were closed and antibiotics given. The procedure lasted 45–60 minutes. After recovery from anesthesia, all dogs were conscious but had neurological deficits. Most frequently we observed tonic deviation of the head and circling movements. Three of the 8 dogs showed paresis of the lower extremities. After 24 hours (4 dogs) or 48 hours (4 dogs), anesthesia was again induced with xylazine and pentobarbital (xylazine was reduced to 1.0 mg/kg). Further procedures were as described for the acute experiments.

**Measurement of CBF, OER, and CMRO₂**

The procedures were essentially similar to those described by Frackowiak et al., with some modifications. All measurements were made using a Neuro-Ecat PET scanner (EG&G Ortec, Oak Ridge, Tenn.) equipped with 2 rings of detectors and with lateral and axial resolution of 8.1 mm and 14.0 mm respectively. Distance between the centers of the 2 detector rings is 32 mm. The scanner was previously calibrated to accurately measure in vivo concentrations of positron-emitting isotopes. Phantom studies on a dog skull with the cranial cavity filled with Na₂C O₃ solutions with a density of 1.05 mg/ml blood. Radioactivity was measured pixel-by-pixel according to the formula

\[
\text{CBF (ml/min)} = \frac{100 \lambda}{(C_p/C_i) - 1}
\]

where \(C_i\) = arterial radioactivity concentration (mean of 2 samples), \(C_p\) = tissue radioactivity concentration in a particular pixel (pixel size was 2.77 mm), \(\lambda\) = radioactive decay constant for oxygen-15 (0.338/min). Measurement of CBF with H₂¹⁵O requires knowledge of the extraction of H₂¹⁵O and its partition coefficient between brain tissue and blood. In this formula a partition coefficient of 1 ml/ml is assumed as well as complete extraction of water (see “Discussion”).

From these “pixel blood flows,” CBF was calculated in 4 elliptical regions of interest, 2 in each plane, that were essentially hemispheric (surface 3.93 and 2.39 cm² in posterior and anterior plane respectively). Since they were not systematically different from each other, CBF values in the 2 planes were combined.

**O₂ SCAN.** To measure OER, H₂¹⁵O was inhaled at a rate of 45 μCi/min, and similar procedures were used as described above except that scan time was extended to 400 seconds and plasma was obtained by centrifugation at 9,000g for 2 minutes. To measure radioactivity, about 0.5 ml plasma was transferred into tared tubes with paraffin, and the volume was calculated by assuming a density of 1.03 mg/ml plasma. Radioactivity concentrations in blood and plasma were about 4.0 and 0.8 μCi/ml respectively, and usually ca. 1.5 million true coincidence counts were collected per slice. OER was computed pixel-by-pixel according to the formula

\[
\text{OER} = \frac{(C_i/C_p) \times (C_i/C_p) - A}{(C_i/C_p) - A}
\]

where \(C_i\) = activity concentration in blood during \(\text{C}^{15}\text{O}_2\), \(C_p\) = activity concentration in plasma during \(\text{C}^{15}\text{O}_2\), \(C_p\) = activity concentration in brain during \(\text{C}^{15}\text{O}_2\), \(C_p\) = activity concentration in blood during \(\text{H}^{15}\text{O}_2\), \(C_p\) = activity concentration in plasma during \(\text{H}^{15}\text{O}_2\), \(C_p\) = activity concentration in brain during \(\text{H}^{15}\text{O}_2\), \(A\) = ratio of activity concentration in brain to that in plasma during \(\text{C}^{15}\text{O}_2\) inhalation. The value for A for human blood can be calculated from the hematocrit (Hct) according to the formula A = 1 − 0.245 Hct. In dogs we found excellent agreement between directly measured and calculated values for A. In 16 experiments where A was measured and calculated the greatest difference was 2.66%, and in 12 of these the difference was <1%.

Measurement of OER requires knowledge of intravascular radioactivity within each pixel. In this formula, however, the contribution of intravascular radioactivity is neglected (see “Discussion”). From
these "pixel OER's," mean hemispheric OER was calculated.

CMRO2. Hemispheric CMRO2 (ml/100 ml/min) was calculated according to the equation CMRO2 = CBF x OER x CaO2, where CaO2 = arterial oxygen content. Because in our experiments PaO2 varied between 120 and 170 mm Hg, oxygen saturation should be almost 100%, and CaO2 is approximated by the equation CaO2 = 1.34 x Hb, where Hb is the hemoglobin concentration.

Chemical Analysis

pH, Po2, and PCO2 were measured in arterial blood samples with specific electrodes (Radiometer, Copenhagen, Denmark). Hct was measured by centrifugation of blood for 5 minutes at 11,000g in capillary tubes. Hb was measured with the cyanohemoglobin method.

Statistical Analysis

Significance was determined by t test for paired (within each group) or unpaired (between different groups) values. Probability (p) values <0.05 were considered significant.

Results

Series I — Severe Embolization

Results in sham-embolized animals (Groups 1 and 2) are represented in Figure 2. In these animals hemispheric blood flow never showed a left-right (L-R) difference. In Group 1 (Figure 2 A) hemispheric blood flow was 23.2 ml/100 ml/min in normocapnia (mean of L and R values) and increased (p<0.001) to 45.9 (H1) and 39.5 (H2) in hypercapnia. The difference between H1 and H2 is significant (p<0.01). The hypercapnic response between N1 and H1 was 0.98 ml/100 ml/min/mm Hg. On return to normocapnia, CBF decreased to 23.7, which is statistically not different from the initial value. OER and CMRO2 were also symmetrical, with values in hypercapnia of 33.0% and 2.98 ml/100 ml/min respectively (Figure 2 C and D).

In Group 2, normocapnic CBF was 22.7 ml/100 ml/min, decreased (p<0.001) to 19.1 (H1) and 17.0 (H2) in hypocapnia, and again increased to 19.9 on return to normocapnia. Although the H2 and N2 values are both about 2 ml/100 ml/min lower than their corresponding preceding value, the differences are not significant (Figure 2 B). In hypocapnia OER and CMRO2...
were 72.6% and 2.93 ml/100 ml/min respectively (Figure 2 C and D).

The results in embolized animals (Groups 3 and 4) are represented in Figure 3.

In spite of unilateral embolization there was no L–R difference in hemispheric blood flow at $N$, during normocapnia. In Group 3 CBF was 24.5 ml/100 ml/min. The effect of hypercapnia was very different in the 2 hemispheres (Figure 3 A). In the control hemisphere* CBF increased ($p < 0.001$) to 44.7 ($H_1$) and 43.6 ($H_2$) ml/100 ml/min (difference not significant). The hypercapnic response between $N$ and $H_1$ was 0.88 ml/100 ml/min/mm Hg. These values were practically identical to the corresponding values in sham-embolized animals. In the embolized hemisphere CBF increased ($p < 0.01$) only to 29.1 ($H_1$) and 26.6 ($H_2$) ml/100 ml/min (difference not significant). The hypercapnic response between $N$ and $H_1$ was only 0.19 ml/100 ml/min/mm Hg. The difference in CBF between the 2 hemispheres during hypercapnia is significant ($p < 0.001$), with ratios of 0.65 ($H_1$) and 0.62 ($H_2$). On return to normocapnia, CBF in the control hemisphere decreased ($p < 0.001$) to 23.2 ml/100 ml/min, which was similar to the $N$ value. In the embolized hemisphere, CBF decreased ($p < 0.001$) to 19.9 ml/100 ml/min. The L–R difference (ratio 0.86) is significant ($p < 0.001$). This asymmetrical blood flow at $N$ and the decrease in ratio between $H_1$ and $H_2$ ($p < 0.05$) indicate delayed hypoperfusion in the embolized hemisphere.

Marked L–R differences were also observed in CMRO$_2$ and OER (Figure 3 C and D). In hypercapnia OER was 16% higher in the embolized than in the control hemisphere ($p < 0.001$). The higher OER, however, only partially compensated for the lower CBF, and CMRO$_2$ was 26% lower in the embolized than in the control hemisphere.

In Group 4 CBF in normocapnia ($N_r$) was 31.6 ml/100 ml/min (Figure 3 B). We have no explanation for the higher CBF's in this group, where subsequent values in hypocapnia were also somewhat higher than in Group 2. Hypocapnia, in contrast to hypercapnia, had practically the same effect in the 2 hemispheres. CBF decreased ($p < 0.001$) to about 21 ($H_1$) and 19 ($H_2$) ml/100 ml/min (difference not significant). At both times there was no significant L–R difference, but the slight decrease in ratio (from 1.03 to 0.97) was
significant (p < 0.05). On return to normocapnia, CBF in the control hemisphere increased (p < 0.001) to 22.5 ml/100 ml/min. In the embolized hemisphere it merely increased (not significantly) to 20.0 ml/100 ml/min. The L-R difference was significant (p < 0.01). The fall in ratio between H1 and H2, the asymmetrical blood flow at N2, and the failure of CBF to increase on transition from hypo- to normocapnia again indicate delayed hypoperfusion in the embolized hemisphere.

Cerebral OER and CMRO2 also showed marked L-R differences (Figure 3C and D). In hypocapnia, when CBF was practically identical in both hemispheres, CMRO2 and OER were respectively 21 and 22% lower in the embolized than in the control hemisphere.

Series II — Mild Embolization

The results obtained in acute experiments are indicated in Figure 4. In general, CBF shows the classical \( Pco_2 \) response, and CMRO2 is practically independent of \( Pco_2 \). As a result, OER decreases in hypocapnia and increases in hypocapnia. In normocapnia and in hypocapnia there were no significant L-R differences in hemispheric blood flow, with levels at about 19 and 16 ml/100 ml/min respectively. In hypercapnia CBF was 9% lower in the embolized than in the control hemisphere (p < 0.01). The CBF responses to hypercapnia in the control and in the infarcted hemisphere were 1.08 ± 0.245 and 0.90 ± 0.252 ml/100 ml/min/mm Hg respectively (mean ± SD, p < 0.01) (Figure 4 A). In normocapnia as well as in hypocapnia, OER and CMRO2 were between 6 and 8% lower in the embolized than in the control hemisphere (p < 0.001). In hypocapnia OER was slightly but not significantly higher in the embolized hemisphere, and CMRO2 was 6% lower (p < 0.01) (Figure 4 B and C).

The results obtained after 24–48 hours are indicated in Figure 5. The values for CBF (and OER) again show the classical \( Pco_2 \) responses. The CBF responses to hypercapnia in the control and in the infarcted hemisphere were 1.41 ± 0.245 and 1.37 ± 0.153 ml/100 ml/min/mm Hg respectively (mean ± SD, p < 0.01) (Figure 5 A). In general, CBF and CMRO2 values were somewhat higher than in the acute experiments, but the differences in CMRO2 were not significant. At each of the 3 \( Pco_2 \) levels, CBF was between 7 and 12% higher in the embolized hemisphere than in the control hemisphere (p at least < 0.01). On the other hand, OER (p < 0.001) and CMRO2 (p at least < 0.05) were lower in the embolized hemisphere, the differences being between 11 and 19 and between 5 and 9%, respectively (Figure 5 B and C).

Discussion

In the above-described experiments we measured CBF, OER, and CMRO2 in dogs with acute regional microembolization of the brain. Two doses of microembolization were used; with mild microembolization the mortality rate was 0, and the animals were also studied 1 or 2 days after embolization.

The experiments indicate that microembolization 1) immediately induces relative luxury perfusion, which in the course of 3 hours is followed by a delayed hypoperfusion; 2) decreases hemodynamic reserve in acute hypercapnia; 3) does not affect the hypocapnic CBF response; 4) causes a dose-dependent decrease in the CMRO2; and 5) produces luxury perfusion after 24–48 hours with restoration of the hemodynamic reserve. However, before discussing the pathophysiological aspects of the experiments, the method and procedures used need comment.

Comments on Methods and Experimental Model

The theoretical principles of the steady-state oxygen-15 technique as well as its potential inaccura-
FIGURE 5. Results of Series II, 24-48 hour experiments (Group 2). See legend to Figure 4, except the respective Pacos' were 34 ± 1.8, 60 ± 3.1, and 21 ± 1.1 mm Hg.

cies are well documented. Using this technique we found a CBF value in nonembolized animals of 23 ml/100 ml/min (Paco2 = 33 mm Hg) with an increase to 46 ml/100 ml/min in hypercapnia (Paco2 = 56 mm Hg) and a decrease to 19 ml/100 ml/min in hypocapnia (Paco2 = 27 mm Hg). CMRO2 was independent of Paco2 and amounted to 2.95 ml/100 ml/min. As a result, OER was inversely related to Paco2 with a value of 73% in hypocapnia and 33% in hypercapnia. We have no normocapnic OER measurement in nonembolized animals, but with mild embolization OER is about 70% in the control hemisphere.

The absolute values thus obtained suffer to a certain degree from a number of instrument- and model-related limitations.

1. The CBF measurement requires knowledge of the extraction of H215O and its partition coefficient between brain and blood. By assuming unlimited diffusion of H215O, as we did, true CBF is underestimated, although for practical use the effect is usually ignored. The C15O2 technique also is sensitive to error in the partition coefficient, especially at higher flow rates. The correct value of the partition coefficient is a matter of debate, and although individual variations occur in the function of Hct, a standard value is usually accepted. We accepted a value of 1 ml blood/ml brain.

2. The C15O2 model itself predicts a systematic CBF underestimation in areas with mixed gray and white matter because blood flow varies as a nonlinear, in fact a concave, function of the radioactivity concentration in the brain. In view of the size of the dog's brain, e.g., the thickness of its cortex (approx 2.5 mm) and the resolution of the Neuro-Ecat PET scanner, most of the pixel values will actually represent a weighted average of radioactivities in purely white and purely gray matter, which does not correspond to a weighted average of flow. It has been argued that the ensuing underestimation of CBF is at maximum 20% for the affected pixels.

3. We did not correct the 15O2 scan for cerebral blood volume, which would require an additional CO scan for each Paco2 level and would strongly interfere with our experimental setup. Omitting such correction leads to a systematic overestimation of OER. In normal humans corrected OER is about 10% less than uncorrected OER. That difference increases with increasing cerebral blood volume and with arterial hyperoxia, and therefore in our experiments may exceed 10%.

It can be concluded that we probably underestimated CBF and overestimated OER. It should be noted, however, that the main aim of our study was to investigate differential changes. The degree of CBF underestimation was assessed in a series of 7 dogs by simultaneously measuring CBF with the C15O2 inhalation technique and with the labelled microspheres technique. Using microspheres with a mean diameter of 15 μm (New England Nuclear, Boston, Mass.), CBF was 34.0 ± 15.1 ml/100 g/min compared with 25.6 ± 3.91 ml/100 ml/min with the C15O2 method (mean ± SD). In baboons, however, comparable values were reported with both methods. Our divergent results can perhaps be attributed to species differences or to the difference in technique, since in the baboon experiments the microspheres in the brain were not measured according to the standard technique but with a PET technique.

In a recent study in which CBF and oxygen metabolism in dogs were measured with the oxygen-15 technique, normocapnic values for CBF and OER were 40 ml/100 ml/min and 50% respectively. The fact that our experiments showed a higher CBF and a lower OER is probably related to the use of a different anesthetic. Indeed, since the completion of the present experiments, we induce anesthesia with thiopental instead of xylazine-pentobarbital, which gives normocapnic values for CBF and OER of 40.4 ± 5.31 ml/100 ml/min and 41.8 ± 6.45% respectively (mean ± SD).

In spite of these limitations, we found a high reproducibility in the measurements of CBF and OER,
which illustrates the reliability of the oxygen-15 method for studying the effect of ischemia in experimental animals. In our comparative study mentioned above, the oxygen-15 technique for CBF measurement appeared to have an even greater precision than the microsphere technique (coefficients of variation of 15 and 44% respectively).

In our experiments ischemia was induced by means of regional microembolization, the pathophysiology of which differs fundamentally from that of other forms of ischemia, and therefore is perhaps less relevant to the clinical condition. The number of particles entering the brain was increased by raising $P_{CO_2}$ during the embolization. Orientation experiments in which radioactive particles (carbonized plastic, mean diameter 15 $\mu$m, New England Nuclear, Boston, Mass.) were infused into the CCA have indeed indicated that the ratio of microsphere distribution between the ipsilateral hemisphere and the ipsilateral masseter muscle was 20–30 times higher in hypercapnia than in normocapnia. Using this procedure the effects of microembolization on CBF and OER were very reproducible; indeed, the scatter of the results is comparable in the embolized and in the control hemisphere. Such reproducibility is in contrast to most other experimental models of ischemia and is an advantage when different groups are compared.

**Effects on CBF**

The 2 series of experiments clearly indicate that in the acute phase after microembolization, CBF in the infarcted hemisphere remains practically unchanged in comparison with the control hemisphere, unless hypercapnia is induced. This finding suggests that this form of microembolization immediately induces dilation of nonoccluded vessels. This reactive dilation was also observed in cats that were embolized with plastic microspheres (diameter, 15 $\mu$m) — even in amounts that caused brain death within a few hours. Although dilation of nonoccluded vessels allows for a normal overall blood flow in normocapnia and in hypocapnia, it no longer allows a complete adaptation in hypercapnia, which indicates decreased hemodynamic reserve after embolization. The decrease is dose-dependent and amounts to 35 (ratio 0.65) and 9% (ratio 0.91) with severe and mild embolization respectively. Unilateral occlusion of the CCA in rats also does not affect hemispheric CBF in normocapnia but has a profound effect in hypercapnia.

In the different groups of animals of Series I, CBF decreased somewhat with time, and the $N_2$ and $H_2$ values were usually lower than their corresponding previous values. In the embolized animals, however, the decrease with time is more marked in the embolized than in the control hemisphere. In both groups with microembolization, CBF at the end of the experiment and in normocapnia ($N_2$) was 12–14% lower in the embolized hemisphere than in the control hemisphere. This asymmetrical blood flow was at variance with the situation at the onset of the experiments and does not occur in the sham-embolized animals. In the embolized animals there is a slight decrease in hemispheric ratio between $H_2$ and $H_2$ that is not observed in the nonembolized animals and that also indicates decrease of CBF in the embolized hemisphere with time. This delayed hypoperfusion can result from ischemic brain edema developing around the occluded vessels or from further metabolic depression as a result of ischemic neuronal damage.

The experiments of Series II indicate that 1 and 2 days after embolization, the hemispheric CBF was significantly higher in the embolized than in the control hemisphere, indicating hyperperfusion in the embolized hemisphere. The fact that the hypercapnic response of CBF, which was depressed in the acute phase, now attains the same value in both hemispheres is also remarkable. Concerning the mechanism of the hyperperfusion and restoration of hemodynamic reserve we can merely speculate. Obviously there must be a compensation for the intravascular obstruction leading to a decrease of the vascular resistance and to an increase of the local perfusion pressure, e.g., by dilation of collateral channels.

**Effects on CMRO$_2$**

As expected and also observed by Rhodes et al CMRO$_2$ in nonembolized dogs is practically independent of acute changes in $P_{CO_2}$, and a rise in CBF is characterized by a fall in OER. The present work extends this observation to infarcted brain tissue.

In our experiments unilateral embolization induced a dose-related interhemispheric difference in CMRO$_2$. In the acute experiments with mild embolization, CMRO$_2$ is 6% lower in the infarcted than in the control hemisphere, and with severe embolization this difference increases to 15%. The experiments falsely suggest that a 6% decrease in CMRO$_2$ produces neurological deficits, which were indeed observed when the animals recovered from anesthesia. In clinical studies with stroke patients, CMRO$_2$ in the infarcted region is usually > 30% lower than on the contralateral side.

The smaller figure in the present experiments, which might suggest a lower CMRO$_2$ threshold to induce necrosis, is probably due to the special nature of embolization (which in contrast to clinical stroke induces multifocal small infarcts) and/or to the effect of anesthesia (which decreases the difference in CMRO$_2$ between normal and infarcted brain tissue). A decrease of CMRO$_2$ in the other hemisphere due to contralateral embolization is another possibility, although less probable, since CMRO$_2$ in the contralateral hemisphere attains practically the same value as in nonembolized animals. On the other hand, the true difference in CMRO$_2$ could be underestimated due to methodological limitations. Because of the small size of the dog's brain relative to the resolution of the scanner, the region examined was essentially hemispheric and therefore hardly limited to the infarct. Moreover, we accepted a similar value in normal and infarcted brain for the extraction of water, its partition coefficient, and for the regional blood volume (which in both conditions was accepted to be 0). In this regard it has been demon-
strated that the overestimation of OER increases with decreasing OER; therefore in our experiments the true difference in OER between the 2 hemispheres was certainly greater than the measured difference. Although the importance of such factors is difficult to quantify, it can be concluded that the decrease of CMRO$_2$ in the infarcted region is probably more important than indicated by the measured hemispheric values, and that the CMRO$_2$ threshold is thus greater than 6%.

In the second series of experiments, the mean values for CMRO$_2$ are somewhat higher in Group 2 (24-48 hours) than in Group 1 with acute embolization. The difference is not significant, and we concluded that CMRO$_2$ remained unchanged.

**Effects on OER and Coupling Between CBF and Metabolism**

The experiments indicate that OER decreases in hypercapnia and increases in hypocapnia in the infarcted as well as in the contralateral hemisphere although with a L–R difference. This difference is not constant and varies according to the experimental conditions, especially Pco$_2$ and time, indicating changes in the coupling between CBF and metabolism.

In the early phase after embolization and in normocapnia, OER is lower in the infarcted than in the control hemisphere — with mild embolization the measured difference amounts to 8%. The lower OER goes hand-in-hand with the lower CMRO$_2$ because CBF is the same in the 2 hemispheres. Although we have not measured OER in normocapnia after severe embolization, there is indirect evidence that the interhemispheric difference was between 20 and 25%. Indeed, CBF was the same in both hemispheres, and the difference in CMRO$_2$ as it was measured in hypocapnia and in hypercapnia was between 20 and 25%. The lower OER in the infarcted hemisphere is in agreement with the experiments of Vise et al.$^{25}$ who described cerebrovenous hyperoxia upon microembolization in normocapnic cats. Both our study and that of Vise et al. indicate relative luxury perfusion in the embolized hemisphere, which is in contrast to usual clinical findings. Results of PET studies with oxygen-15 in cerebral ischemia in man were recently reviewed by Frackowiak.$^{24}$ From these clinical studies, it appears that "misery perfusion"$^{22}$ with low CBF and high OER is the usual finding in the first hours after clinical stroke. Thereafter, relative luxury perfusion with low OER and CBF becomes the usual finding, and on rare occasions a focal increase of OER persists beyond the first hours after stroke.$^{23,25,26}$ In our experimental conditions we did not observe a lower CBF in the infarcted hemisphere. The differential effects of clinical stroke and microembolization have been previously stressed by Hossmann.$^{19}$

On transition from normocapnia to hypocapnia, CBF decreased to the same extent in both hemispheres with severe as well as with mild embolization. As a result, the condition of relative luxury perfusion with lower OER in the infarcted hemisphere was main-

**KEY WORDS** • experimental ischemia • positron emission tomography • microembolization • cerebral blood flow and metabolism
PET studies of changes in cerebral blood flow and oxygen metabolism after unilateral microembolization of the brain in anesthetized dogs.

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