Measurement of Cerebral Hemispheric Blood Flow by Intracarotid Injection of Hydrogen Gas

VALIDATION OF THE METHOD IN THE MONKEY

By Yukito Shinohara, M.D., John S. Meyer, M.D., Akira Kitamura, M.D., Masanaru Toyoda, M.D., and Tisuke Ryu, M.D.

ABSTRACT

To develop a reliable method for measuring hemispheric blood flow and metabolism in man, the clearance of hydrogen was measured in the cerebral lateral sinus blood of macaque monkeys after intracarotid injection. Hydrogen is an inert gas and its clearance from cerebral venous blood depends solely on arterial inflow, and since it is highly diffusible, rapid equilibrium is maintained between brain tissue and its capillary-venous blood. Cerebral venous clearance curves for hydrogen appeared to provide accurate and reproducible measures of cerebral blood flow.

A bolus of 0.2 to 0.3 ml of saline saturated with hydrogen was injected rapidly into the internal carotid artery. Electrodes placed on the cortex showed that the bolus was almost exclusively distributed to the ipsilateral cerebral hemisphere. Blood flow of each hemisphere was calculated by Meier and Zierler's formula based on the Stewart-Hamilton principle, as well as by compartmental analysis. The values obtained for hemispheric blood flow were in good agreement with average cerebral blood flow measured by inhalation of hydrogen using the Fick principle. Values for hemispheric blood flow were the same whether the intracarotid injection of hydrogen was rapid or slow.

ADDITIONAL KEY WORDS regional cerebral blood flow hyperventilation middle cerebral artery occlusion CO₂ inhalation

Although measurement of average cerebral blood flow by inhalation of nitrous oxide, utilizing the Fick principle, has been a standard method since its introduction in 1945 (1), it provides no information about regional cerebral blood flow.

Lassen, Ingvar, and associates were the first to derive regional cerebral blood flow from clearance curves of inert gases after intracarotid injection (2-4). The gases used were radioactive, and the curves were recorded by scintillation counters applied to the head. This method has contributed considerably to present knowledge of regional cerebral hemodynamics. There are some theoretical disadvantages to this method, which include the possibility of contamination of cerebral blood flow values by flows derived from extracranial sources, since the counter is applied to the head rather than to the exposed brain. Although it appears to be possible to record from circumscribed areas of the head using collimated detectors, the geometry of the zone measured is uncertain.

Several modifications of the above methods for measuring total, average, and localized cerebral blood flow have been reported; however, to the best of our knowledge, there is no widely accepted method for measuring average hemispheric cerebral blood flow with accuracy. If this were achieved, it might be possible to measure hemispheric blood flow and metabolism in man, since metabolism could be calculated from the arterio-lateral...
sinus differences for metabolites and the ratio of the distribution of hydrogen in each lateral sinus.

Bearing in mind the above considerations, plus the potential clinical usefulness of a method for accurately measuring hemispheric blood flow in man, we will describe a new method in which a bolus of hydrogen dissolved in saline was injected into the internal carotid artery of macaque monkeys and the clearance curves were recorded from the cerebral lateral sinus of the same side. It is generally accepted that the lateral cerebral sinus contains blood derived only from cerebral sources and the possibility of contamination by blood from extracerebral sources is virtually excluded.

Results obtained with this new method are described, together with a critical evaluation of their validity, by comparing them with results obtained under the same conditions using standard methods.

Methods

Successful measurements were made in 34 macaque monkeys weighing 3.5 to 10.5 kg. Prior to operation, 0.5 mg of atropine sulfate (Eli Lilly & Co.) was given intramuscularly. All procedures were carried out under ether (Mallinckrodt Chemical Works) anesthesia, supplemented with regional anesthesia by the use of 1% lidocaine hydrochloride (Xylocaine, Astra Pharmaceutical Products). Following tracheostomy, the animals were immobilized with gallamine triethiodide (Flaxedil, Davis & Geck). End-tidal carbon dioxide was recorded with a Beckman infrared gas analyzer (Spinco Model 3 LB-1) and maintained between 3.5% and 4% by an adjustable respirator (Harvard Model 607).

Catheters (polyethylene and Kel F) were inserted into both carotid arteries via the lingual arteries, into the lateral sinus via the facial or cephalic vein, and into the femoral artery and vein. Blood pressure was recorded with a Statham strain gauge (P 23AA) from a catheter placed in the femoral artery.

Sodium heparin (Liquaemin Sodium "10", Organon, Inc.) was injected intravenously in doses of 3,000 to 5,000 USP units. Cerebral venous blood was then pumped at approximately 5 ml/min through a cuvette containing a hydrogen electrode similar to that reported previously (5), except that there were four 200µ platinum wires sealed in the glass stem and the platinized platinum surfaces were covered with a polyethylene membrane 25µ thick. The response of this electrode was 95% complete within 10 seconds. The input signals from the hydrogen sensor, which are proportional to hydrogen partial pressure, were amplified by a direct-current microvolt ammeter (Millivac Instruments, Model 07C). After passing the blood through the cuvette, it was returned to the monkey via the femoral vein.

The following variables were recorded on a Grass polygraph (Model 7) or an Offner Type R Dynograph; partial pressure of hydrogen in the cerebral venous blood, blood pressure, and end-tidal CO₂. The EEG and ECG were also recorded by a Grass 8-channel electroencephalograph (Model 3).

METHOD FOR CALCULATION OF CEREBRAL BLOOD FLOW

Use of the Stewart-Hamilton Principle.—According to Meier and Zierler (6), the following relationships derived from the Stewart-Hamilton principle are mathematically valid:

\[ t = \frac{V}{F}, \]

where \( t \) denotes the mean transit time of the tracer particles, \( V \) the volume of distribution of the tracer in the tissue, and \( F \) the blood flow.

By dividing both the numerator and the denominator by the tissue weight, \( W \), one can obtain

\[ \frac{V}{W} \frac{1}{F \cdot W} = \lambda / f, \]

where \( \lambda \) equals the volume of distribution of the indicator in the organ per gram of tissue weight, i.e., the tissue: blood partition coefficient as defined by Kety (7), and \( f \), the blood flow per gram of tissue weight.

When the indicator is injected at an inflow orifice, and the measurement is done at an outflow orifice, one can obtain

\[ i = \frac{\int_{a}^{b} C(t) \, dt}{\int_{0}^{b} C(t) \, dt} = \frac{\int_{a}^{b} C(t) \, dt}{\int_{0}^{b} C(t) \, dt} \]

where \( t \) denotes the time after injection and \( C(t) \) is the observed concentration of the indicator at time \( t \) at exit.

When hydrogen is used as the diffusible indicator, the concentration of hydrogen in the blood may be quantitatively expressed as its gas tension, provided that molecular hydrogen does not combine with any of the blood constituents.

Hence: \( C(t) = [\alpha B \cdot P(t)]/760 \),

where \( \alpha B \) is the Bunsen solubility coefficient for
hydrogen gas in blood, and \( P(t) \) is the gas tension for hydrogen at the time \( t \).

\[
\int_0^\infty t \cdot P(t) \, dt
\]

Therefore:

\[
t = \frac{\int_0^\infty P(t) \, dt}{\int_0^\infty P(t) \, dt}
\]

The partition coefficient for hydrogen has been found to be unity both for the brain by Fieschi et al. (8) and for the kidney by Aukland et al. (9).

Thus, we may write:

\[
t = \frac{\int_0^\infty P(t) \, dt}{\int_0^\infty t \cdot P(t) \, dt}
\]

Use of Compartmental Analysis.—The desaturation phase for the clearance curve of hydrogen from cerebral venous blood may be considered as the sum of multiple monoeXponential functions, each of which represents the blood flow of a homogeneous tissue.

If \( f_i \) is the blood flow through the tissue \( i \), and \( \lambda_i \) is the tissue : blood partition coefficient for hydrogen in that tissue compartment \( i \), the following formula may be derived:

\[
\lambda_i = (\ln 2/T_{w,i}) \lambda_i = k_i \lambda_i,
\]

where \( T_{w,i} \) denotes the half life of the indicator in the tissue \( i \) calculated by conventional graphic analysis.

Analysis of the clearance curve has shown that in the great majority of cases, this curve can be described by only two monoeXponential functions. Therefore, if we can assume that \( \lambda_i \) is near unity (8), we can calculate the flow rate of these two compartments.

When we use the constant infusion method instead of a bolus injection, all compartments may approach closely to saturation at the beginning of desaturation.

Then, we may write:

\[
h(t) = \sum_{i=1}^n (F_i/F) k_i e^{-\lambda_i t}
\]

where \( h(t) \) is the frequency function of transit times, \( F \) is total blood flow, and \( F_i/F \) is the fraction of total blood flow perfusing the \( i \)th compartment.

During desaturation, the tension of hydrogen in effluent blood is:

\[
P(t) = (1/F) [1-H(t)],
\]

where \( I \) is the rate of constant injection, \( H(t) \) is the integral of \( h(t) \), and \( t \) is the time lapsed after injection ceased.

Equations 7 and 8 lead to:

\[
P(t) = P_{max} \sum_{i=1}^n (F_i/F) e^{-\lambda_i t}
\]

from which it follows that the \( i \)th intercept is \( P_{max} F_i/F \), where \( P_{max} \) equals \( I/F \).

With a bolus injection, however, zero time for each compartment is not the same, because the more rapidly perfused compartment would approach more closely to saturation than the slower compartment. Because of this potential error, the flow rates of the two compartments are calculated, but relative weights of the two compartments are not.

Results

AREA SUPPLIED BY ONE INTERNAL CAROTID ARTERY

Before the results of the present method can be interpreted, precise knowledge of the extent and distribution of the tissue perfused by hydrogen gas following intracarotid injection of the hydrogen is essential. The distribution recorded from the cortex of the ipsilateral

Non-Injected

\( \bullet \) Maximum Response

\( \circ \) Moderate

\( \square \) Minimum

\( \bigcirc \) Zero

Injected

\( \bigcirc \) Maximum Response

\( \circ \) Moderate

\( \square \) Minimum

\( \bigcirc \) Zero

FIGURE 1

Composite diagram of the data from six monkeys concerning the distribution of hydrogen gas in both cerebral hemispheres after injecting a bolus of saline saturated with hydrogen into one internal carotid artery. The distribution was mapped out on the exposed cortex by placing small hydrogen electrodes in different areas of the brain. The maximum response was almost exclusively distributed to the ipsilateral hemisphere. The minimum-to-moderate responses recorded from the medial aspect of the contralateral hemisphere are due to the common pericallosal artery in the monkey.
and contralateral hemispheres after the injection of the bolus was determined in six monkeys by using multiple placements of a hydrogen electrode. The diameter of the electrode was 5 mm, and its weight was 2.2 g. It was suspended from an adjustable rod by a spring.

Boluses of hydrogen-saturated saline measuring 0.2 to 0.3 ml were injected first into one internal carotid artery and then into the other. No changes in EEG and ECG were noted.

Figure 1 summarizes the distribution of hydrogen after internal carotid injection. The hydrogen was almost exclusively perfused throughout the entire ipsilateral hemisphere. A small amount was detected in the distribution of the anterior cerebral artery of the opposite side because there is a common pericallosal artery (formed by the junction of both anterior cerebral arteries) in the macaque monkey. The reason that less hydrogen was detected in the anterior cerebral artery territory of the opposite side was probably due to laminar flow. In two monkeys, hydrogen was detected at the ipsilateral occipital pole because, like man, some macaque monkeys have a posterior cerebral artery that receives an important contribution from the internal carotid artery (10).

It thus appeared from mapping the cortical distribution of hydrogen after injecting a bolus of it into the internal carotid artery that this method represented a fair measurement of hemispheric blood flow on the side injected.

**STEADY-STATE VALUES**

The clearance curves of hydrogen from the lateral sinus of the monkey were similar, but not identical, to those obtained from collimators applied to the head after intracarotid injection of a radioactive inert gas. After a rapid, almost vertical, saturation phase, there was a brief plateau with the fast and slow components of desaturation lasting about 10 minutes (Fig. 2). Therefore, the blood flow was calculated during the 10 minutes after injection of the bolus and expressed as ml/100 g brain/min. Values for the partial pressure of hydrogen were read off at intervals of 5 seconds from the actual records in arbitrary units. These values were also plotted against time on semilogarithmic paper for compartmental analysis.

In the steady state, the mean hemispheric

![Graph](Image)

**FIGURE 2**

Comparison of effects of inhalation of 5% CO₂ in air and hyperventilation with values for hemispheric blood flow (HBF) in the steady state. To show the slow component of flow to better advantage in the top and bottom records, the amplification was increased during recording.
MEASUREMENT OF HEMISPHERIC BLOOD FLOW

TABLE 1

<table>
<thead>
<tr>
<th>Analytic method</th>
<th>Steady state (n = 8)</th>
<th>5% CO₂ inhalation (n = 6)</th>
<th>Hyperventilation (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemispheric blood flow</td>
<td>43.3 ± 4.3</td>
<td>62.5 ± 6.7 (P &lt; 0.001)*</td>
<td>34.5 ± 5.0 (P &lt; 0.005)*</td>
</tr>
<tr>
<td>(ml/100 g brain/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compartmental analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ml/g brain/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f₁ (fast)</td>
<td>1.18 ± 0.19</td>
<td>1.61 ± 0.36 (P &lt; 0.02)*</td>
<td>0.87 ± 0.25 (P &lt; 0.005)*</td>
</tr>
<tr>
<td>f₂ (slow)</td>
<td>0.26 ± 0.05</td>
<td>0.39 ± 0.10 (P &lt; 0.05)*</td>
<td>0.23 ± 0.06 (0.2 &lt; P &lt; 0.3)</td>
</tr>
</tbody>
</table>

Values are means ± SD.
*Statistically significant difference from steady state.

blood flow was 43.3 ml/100 g brain/min with a standard deviation of 4.3 ml/100 g brain/min in eight monkeys (Table 1). Compartmental analysis showed the value for the slow component to be 1.18 ml/g brain/min and that for the fast component, 0.26 ml/g brain/min (Table 1).

EFFECTS OF INHALATION OF 5% CO₂ IN AIR

In six experiments, inhalation of 5% CO₂ in air was begun 5 minutes before the injection and was continued during the measurement. This procedure resulted in a statistically significant increase in hemispheric blood flow. The mean value rose to 62.5 ml/100 g brain/min or a mean increase of 44% (Table 1). Values for both the fast and slow components also increased significantly.

EFFECTS OF HYPERVENTILATION

The effects of hyperventilation on hemispheric blood flow were measured in six monkeys. Hyperventilation for 15 to 20 minutes produced a rapid reduction in end-tidal CO₂ from 3.5 to 1.4%. Hemispheric blood flow decreased significantly to 34.5 ml/100 g brain/min (Table 1). This is a reduction of 20%. Fast flow was also reduced significantly, but there was no significant change in slow flow values.

REPRODUCIBILITY OF THE METHOD

The reproducibility of the method was examined in eight monkeys according to the following formula:

Reproducibility = |Values of 1st measurement − 2d measurement| / Value of 1st measurement

During the first and second measurements, end-tidal CO₂ and blood pressure were maintained as constant as possible. As shown in Table 2, the reproducibility calculated by this method was 3.9 ± 3.1%. When the same formula was applied to test the radioisotope method, the reproducibility was 10.6 ± 6.4% (4) and 6.1 ± 4.1% (11), so that the hydrogen bolus method appears to compare favorably with other methods as far as reproducibility is concerned.

COMPARISON OF THE HYDROGEN BOLUS METHOD WITH THE HYDROGEN INHALATION METHOD

To validate the hydrogen bolus method, average cerebral blood flow was measured in nine normal macaque monkeys by using the hydrogen inhalation method (Table 3). Arterial blood and cerebral venous blood were pumped simultaneously from the femoral artery and the lateral sinus into separate cuvettes containing hydrogen electrodes. The arterial and cerebral venous desaturation curves following inhalation of 2.5% hydrogen for 13 to 15 minutes were used to calculate average cerebral blood flow by the Fick principle (5). The mean value for average cerebral blood flow was 45.1 ml/100 g brain/min (Table 3) and the reproducibility in six cases was 5.7 ± 5.0%.

Inhalation of a mixture of 5% CO₂ in air increased the average blood flow to a mean value of 66.6 ml/100 g brain/min, a mean increase of 48% (Table 3). In five cases, passive hyperventilation reduced the average cerebral blood flow to 37.4 ml/100 g brain/min, or a decrease of 17%.

It was apparent that values obtained by the
Reproducibility of the Bolus Method

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>First measurement</th>
<th>Second measurement</th>
<th>Reproducibility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>39.5</td>
<td>40.8</td>
<td>3.3</td>
</tr>
<tr>
<td>12</td>
<td>42.8</td>
<td>42.7</td>
<td>0.2</td>
</tr>
<tr>
<td>13</td>
<td>31.9</td>
<td>33.2</td>
<td>4.1</td>
</tr>
<tr>
<td>15</td>
<td>34.4</td>
<td>34.6</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>34.6</td>
<td>35.0</td>
<td>1.2</td>
</tr>
<tr>
<td>15</td>
<td>35.0</td>
<td>38.3</td>
<td>9.4</td>
</tr>
<tr>
<td>19</td>
<td>44.2</td>
<td>42.7</td>
<td>3.4</td>
</tr>
<tr>
<td>19</td>
<td>42.7</td>
<td>43.5</td>
<td>1.0</td>
</tr>
<tr>
<td>21</td>
<td>49.8</td>
<td>47.8</td>
<td>4.0</td>
</tr>
<tr>
<td>29</td>
<td>46.4</td>
<td>42.0</td>
<td>9.4</td>
</tr>
<tr>
<td>30</td>
<td>45.9</td>
<td>43.5</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Mean ± SD 40.7 ± 5.9 40.4 ± 4.5 3.9 ± 3.1%

Measurements are ml/100 g brain/min.

Two methods were in good agreement and the quantitative effects of CO₂ inhalation and passive hyperventilation were almost identical (Tables 1 and 3).

Comparison of Rapid Intracarotid Injection with Prolonged Infusion of Hydrogen

In five monkeys, saline saturated with hydrogen was slowly infused for 4 to 10 minutes into the internal carotid artery before abruptly discontinuing the infusion to measure hemispheric blood flow. A Harvard automatic infusion pump (Model 600-950) was used for infusion. In three monkeys, approximately 2.0 ml of hydrogen-saturated saline was infused rapidly for the first 30 seconds followed by an additional 3.5 to 5 ml over the next 3½ to 5 minutes. In another two monkeys, the infusion was continued at a speed of 1 ml/min for 7 to 10 minutes.

As shown in Figure 3, the hydrogen desaturation curves following prolonged infusion were almost identical to those following a rapid bolus injection. The hemispheric distribution of hydrogen was confirmed in one of these animals.

In Table 4, the results obtained with the rapid injection and more prolonged infusion of hydrogen in the same animals are compared. The flow values calculated after the use of either method were in good agreement. However, after the prolonged infusion, the mean value for the fast component was 0.98

Two methods were in good agreement and the quantitative effects of CO₂ inhalation and passive hyperventilation were almost identical (Tables 1 and 3).

Comparison of Rapid Intracarotid Injection with Prolonged Infusion of Hydrogen

In five monkeys, saline saturated with hydrogen was slowly infused for 4 to 10 minutes into the internal carotid artery before abruptly discontinuing the infusion to measure hemispheric blood flow. A Harvard automatic infusion pump (Model 600-950) was used for infusion. In three monkeys, approximately 2.0 ml of hydrogen-saturated saline was infused rapidly for the first 30 seconds followed by an additional 3.5 to 5 ml over the next 3½ to 5 minutes. In another two monkeys, the infusion was continued at a speed of 1 ml/min for 7 to 10 minutes.

As shown in Figure 3, the hydrogen desaturation curves following prolonged infusion were almost identical to those following a rapid bolus injection. The hemispheric distribution of hydrogen was confirmed in one of these animals.

In Table 4, the results obtained with the rapid injection and more prolonged infusion of hydrogen in the same animals are compared. The flow values calculated after the use of either method were in good agreement. However, after the prolonged infusion, the mean value for the fast component was 0.98
MEASUREMENT OF HEMISPHERIC BLOOD FLOW

TABLE 4
Comparison of Bolus Injection with Prolonged Infusion of Hydrogen

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>t</th>
<th>n</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>48.5</td>
<td>1.19</td>
<td>0.35</td>
</tr>
<tr>
<td>37</td>
<td>35.1</td>
<td>1.05</td>
<td>0.24</td>
</tr>
<tr>
<td>38</td>
<td>49.2</td>
<td>1.26</td>
<td>0.32</td>
</tr>
<tr>
<td>39</td>
<td>47.0</td>
<td>0.89</td>
<td>0.36</td>
</tr>
<tr>
<td>41</td>
<td>45.3</td>
<td>0.99</td>
<td>0.29</td>
</tr>
<tr>
<td>MEAN</td>
<td>45.0</td>
<td>1.08</td>
<td>0.31</td>
</tr>
<tr>
<td>SD</td>
<td>5.7</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.9</td>
<td>0.3 &gt; P &gt; 0.2</td>
<td>&gt;0.9</td>
</tr>
</tbody>
</table>

Values are ml/100 g brain/min.

TABLE 5
Effects of Craniotomy on Hemispheric Blood Flow

<table>
<thead>
<tr>
<th>Analytic method</th>
<th>Steady state (n = 16)</th>
<th>5% CO₂ inhalation (n = 6)</th>
<th>Hyperventilation (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemispheric blood flow (ml/100 g brain/min)</td>
<td>45.3 ± 7.2 (0.5 &gt; P &gt; 0.4)</td>
<td>60.4 ± 12.4 (P &lt; 0.005)*</td>
<td>39.1 ± 5.4 (P &lt; 0.02)*</td>
</tr>
<tr>
<td>Compartmental analysis (ml/g brain/min)</td>
<td>1.16 ± 0.24 (P &lt; 0.02)</td>
<td>1.68 ± 0.77 (P &lt; 0.05)*</td>
<td>0.99 ± 0.27 (P &lt; 0.05)*</td>
</tr>
<tr>
<td>f₁ (fast)</td>
<td>0.32 ± 0.06 (P &lt; 0.02)</td>
<td>0.37 ± 0.12 (P &lt; 0.05)</td>
<td>0.25 ± 0.05 (P &lt; 0.01)*</td>
</tr>
<tr>
<td>f₂ (slow)</td>
<td>(0.3 &gt; P &gt; 0.2)</td>
<td>(P &lt; 0.02)</td>
<td>(P &lt; 0.01)*</td>
</tr>
</tbody>
</table>

Values are means ± SD.
*Statistically significant difference from steady state values.
†Statistically significant difference from values before craniotomy.

ml/g brain/min, which was slightly lower than the mean value obtained by rapid injection, which was 1.08 ml/g brain/min. However, these differences were not statistically significant.

EFFECT OF CRANIOTOMY AND MIDDLE CEREBRAL ARTERY OCCLUSION ON HEMISPHERIC BLOOD FLOW

Table 5 shows the effect of craniotomy on hemispheric blood flow. Craniotomy was carried out with meticulous care in 16 animals. The mean value for hemispheric blood flow following craniotomy was 45.3 ml/100 g brain/min. The fast component of flow was 1.16 ml/100 g brain/min and the slow was 0.32 ml/g brain/min.

The mean value for the slow component was significantly greater than the value before craniotomy. In most cases, the dura mater was opened, so the difference might have been due to loss of hydrogen from the cortex to the air. Other factors to be considered in evaluating this difference are changes in intracranial pressure and dilatation of cortical vessels due to trauma or exposure.

After craniotomy, inhalation of 5% CO₂ increased hemispheric blood flow by 33% and
Table 6 shows the effect of occlusion of one middle cerebral artery at its origin on the blood flow of both cerebral hemispheres. In the hemisphere on the side of the occluded middle cerebral artery, blood flow was decreased from 44.7 to 40.3 ml/100 g brain/min, which was a statistically significant reduction. Values for the slow component of flow were decreased in most cases, but in four cases out of seven, the fast component was actually increased. In the opposite hemisphere, blood flow was not decreased.

Table 7 shows the effect of inhalation of a mixture of 5% CO₂ in air and hyperventilation on the blood flow of the ischemic hemisphere following occlusion of the middle cerebral artery. Inhalation of 5% CO₂ increased and hyperventilation decreased hemispheric blood flow and the fast and slow components. However, the percent of changes was less than when the brain was intact.

At the end of the experiments, each animal was killed by intravenous injection of a lethal dose of sodium pentobarbital (Pento, Detroit Veterinary Supply Co.), and 1 ml of India ink was injected into the internal carotid artery on the side of the occluded middle cerebral artery.
MEASUREMENT OF HEMISPHERIC BLOOD FLOW

artery to verify that the vessel was indeed occluded at its origin.

Discussion

Since hydrogen is an inert gas, its clearance from cerebral venous blood following the injection of a bolus of hydrogen-saturated saline into the carotid artery is influenced solely by the arterial inflow. The diffusion of hydrogen is sufficiently rapid to maintain equilibrium between cerebral tissues and venous blood leaving the same tissue. Hence, the clearance curve of hydrogen from the cerebral venous blood appeared to be a valid measure of cerebral blood flow.

The method employed was established as valid for measuring hemispheric blood flow by verifying the following assumptions:

1. When hydrogen dissolved in saline is injected into the internal carotid artery, it should exclusively perfuse the ipsilateral hemisphere.

2. The distribution of blood from one hemisphere into each lateral sinus as well as the hemispheric blood flow should remain constant during the interval of measurement.

3. Recirculation of hydrogen should not occur after passage through the pulmonary circulation.

It is generally accepted that after injection of an isotope or a dye into the internal carotid artery, the distribution is restricted to the ipsilateral hemisphere unless the opposite carotid artery is occluded (10,11).

The results of the present study with placement of hydrogen electrodes over multiple areas of the cortex confirmed that, in the monkey, the perfusion of hydrogen after injection into one internal carotid artery is limited almost exclusively to the ipsilateral hemisphere.

When the present method for measuring hemispheric blood flow by use of a bolus of hydrogen was applied to man (12), similar clearance curves were recorded from both lateral sinuses, and the calculated values for the blood flow of the hemisphere injected were the same from either the ipsilateral or contralateral sinus. In the steady state, repeated injections of hydrogen gave the same clearance curves in both lateral sinuses. This indicates that, as far as man is concerned, the distribution of venous blood from the injected hemisphere into each lateral sinus is constant in the steady state for the interval required for each measurement.

It should be borne in mind that the solubility of hydrogen in blood is extremely low (7) and the excretion of hydrogen via the lungs is extremely efficient, so that in the present experiments, as in man, we were unable to detect any recirculation at all following injection of the hydrogen bolus into the carotid artery by using a hydrogen electrode placed in the arterial blood.

It is possible, although we have seen no evidence of this, that a rapid injection might produce an artificial initial peak in the desaturation curve (11) due to an increase in the perfusion pressure. This is overcome by slower injection; however, prolonged infusion has the disadvantage that it is difficult to maintain the hydrogen level constant in the cerebral venous blood before stopping the infusion for desaturation.

Lassen et al. measured the clearance of radioactive krypton by using uncollimated probes applied to the head in such a manner that the area recorded was considered to be within the supply of the injected carotid artery, i.e., one hemisphere (4). While the isotope was no doubt distributed to the ipsilateral hemisphere after its carotid injection, there are certain disadvantages to this method, such as the effects of the inverse square law and self-absorption of the radioisotope as well as problems of extracerebral contamination and recirculation.

Marshall et al. (13) have attempted to measure hemispheric blood flow after the intravenous injection of technetium, but their method was not quantitative, and problems similar to those mentioned above were encountered.

With these considerations in mind, it appears that the technique described here is the most satisfactory method presently available for measuring hemispheric blood flow. As
might be expected, normal blood flow values for one hemisphere of the macaque monkey in the resting state were in good agreement with measurements of average cerebral blood flow using inhalation of hydrogen and with previously reported values using the bubble flowmeter (14). It has previously been shown, with the nitrous oxide method, that the macaque monkey has values for average cerebral blood flow per 100 g of brain that are similar to man (15). This similarity is further confirmed in the present study, since hemispheric blood flow values in the monkey were similar to reported values for cerebral blood flow in man, calculated to infinity, obtained with the radioisotope method (11).

The fast and slow components of flow calculated by means of the present method are in good agreement with values obtained for gray and white matter in the unanesthetized cat reported by Landau et al. (16). The fast flow is also in reasonable agreement with flow values determined from the parietal cortex of the cat by Lassen and Ingvar (2). However, in the present study, hydrogen electrodes applied to the exposed cortex recorded multiexponential curves. The type of electrode used can detect hydrogen to a measured depth of not more than 3 mm below the cortical surface, so that it must be concluded that in the cortex itself there exist at least two components of flow. Fast and slow components have also been recorded in measurement of blood flow in muscle (17) and kidney (9). Although the fast and slow components of cerebral blood flow may represent predominantly gray and white matter, respectively, the assumption that the fast component of the brain represents only gray matter should be reconsidered.

In the animals in which the middle cerebral artery was occluded, the blood flow of the ischemic hemisphere was decreased significantly, but nevertheless was not greatly reduced because of the well-known capacitance of the cerebral collateral circulation in the monkey. In four cases out of seven, the component of fast flow was increased, despite the general reduction of hemispheric blood flow. This may be interpreted to indicate zones of relative hyperemia around focal areas of ischemia (18), although the less likely possibility of hydrogen exchange between the occluded artery and surrounding veins exists. In these experiments, 5% CO₂ inhalation increased and hyperventilation decreased the blood flow of the hemisphere in which the middle cerebral artery was occluded. In the present series, there was no evidence of an "intracerebral steal" or the phenomenon of "reverse steal" (19). However, since blood flow of the entire hemisphere was measured, some focal shunting of circulation between ischemic zones and bordering areas of collateral flow may not have been detected.

Acknowledgment

Dr. Niels A. Lassen, Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen, Denmark and Dr. Martin Reivich, Department of Neurology, University of Pennsylvania, kindly provided consultation regarding theoretical considerations for the calculation of hemispheric blood flow. Dr. A. Kondo and Dr. F. Nomura, formerly Research Fellows of the Department of Neurology, Wayne State University, assisted with the surgical procedures and Dr. B. Guiraud performed the necropsy studies.

References

MEASUREMENT OF HEMISPHERIC BLOOD FLOW

Yukito Shinohara, John S. Meyer, Akira Kitamura, Masanaru Toyoda and Tisuke Ryu

Circ Res. 1969;25:735-745
doi: 10.1161/01.RES.25.6.735

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1969 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/25/6/735

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/