Regional Cerebral Blood Flow Measured by the Gamma Camera After Direct Injection of $^{133}$Xe into the Distal Stump of the Occluded Middle Cerebral Artery

BY ERWIN O. OTT, M.D., JACOB ABRAHAM, M.D., JOHN STIRLING MEYER, M.D., CORNELIUS A. F. TULLEKEN, M.D., NINAN T. MATHEW, M.D., F.R.C.P.(C), AMRIT N. ACHARI, M.D., MINORU AOYAGI, M.D., AND RONALD F. DODSON, PH.D.

Abstract:
Regional cerebral blood flow (rCBF) was measured after intracarotid injection of $^{133}$Xe concurrently with measurements of local cerebral blood flow (LCBF) after injection of $^{133}$Xe directly into the distal stump of the occluded middle cerebral artery (MCA) by the use of the gamma camera after producing experimental ischemia in baboons by occluding the MCA. Regional MCA stump pressure (rMCAP) was also measured. Regions of ischemia assessed by intracarotid injection of $^{133}$Xe correlated well with the territory of infarct defined by injection of $^{133}$Xe into the distal MCA stump. Flow values in ischemic regions obtained by direct injection of $^{133}$Xe into the MCA were 15% to 20% lower than those obtained by intracarotid injection of $^{133}$Xe. Possible explanations for these differences are discussed. During induced hypertension autoregulation in ischemic areas was abolished and paradoxical responses of LCBF and rMCAP to changes in arterial carbon dioxide tension (Paco$_2$) were confirmed.

Additional Key Words
paradoxical response
dysautoregulation
MCA occlusion
local cerebral blood flow

D Blood flow within the territory supplied by an occluded middle cerebral artery (MCA) has been assessed by a number of different techniques for measuring regional cerebral blood flow (rCBF) in both man and experimental animals. In earlier animal experiments where rCBF was measured with implanted electrodes, the territory of the infarct was determined with great accuracy. When measurements were made by means of extracranial monitoring of radioactivity after injecting gamma-emitting radioisotopes into the carotid artery, assessment of ischemic regions was based on patterns of reduced flow using generally accepted methods of calculations such as stochastic or bicompartmental analysis. However, it has been suggested that the flow measured by external counting after intracarotid injection may overestimate flow values in the ischemic region, since bordering zones supplied by collateral flow may scatter radioisotope activity so that real and actual flows in the ischemic zone may be lower than the measured values.

The present experiments were designed, therefore, to compare regional flow values measured by the gamma camera in the territory of the occluded MCA in the baboon after: (1) injection of $^{133}$Xe into the internal carotid artery, and (2) injection of a small bolus of $^{133}$Xe into the distal stump of the MCA. Likewise, changes of rCBF in the ischemic territory induced by changing arterial carbon dioxide tension (chemical regulation) or induced hypertension (autoregulation) measured by the two methods of injecting the bolus of $^{133}$Xe were also compared.
Methods

Ten baboons (Papio anubis) of either sex, weighing 8 to 10 kg, were anesthetized with pentobarbital (30 mg per kilogram I.V.) and supplemental intravenous doses were given periodically to maintain continuous light anesthesia. Tracheostomy was performed and the animals respirated by means of a variable speed respirator to keep arterial carbon dioxide tension (Paco2) constant after immobilization with gallamine triethiodide (Flaxedil®), 10 mg per kilogram I.V. End-tidal CO2 was recorded on a polygraph with an infrared gas analyzer and the body temperature of the animals was maintained at circa 36.8°C by means of heating pads.

A polyethylene catheter was introduced into the descending aorta via one femoral artery in order to record mean arterial blood pressure (MABP) with a pressure transducer. Throughout the experiment intermittent samples of arterial blood were drawn to measure Paco2, hematocrit and hemoglobin. A second polyethylene catheter was introduced into one femoral vein to permit administration of intravenous fluids and supplemental pentobarbital. Intracranial venous pressure (ICVP) was measured by means of a third polyethylene catheter introduced into the proximal stump of one internal jugular vein up to the lateral sinus and connected to a pressure transducer after all tributaries were ligated.

The right linguofacial artery was cannulated with a fourth polyethylene catheter so that its tip was located circa 0.5 cm below the bifurcation of the common carotid artery and was used for intracarotid injection of 133Xe. All other branches of the right external carotid artery were ligated. The right MCA was approached by enlarging the optic canal. The right MCA was identified and ligated by the use of a dissecting microscope and a thin catheter was introduced into the proximal stump for injection of a small bolus of 133Xe and for measuring regional middle cerebral artery pressure (rMCAP) by means of a pressure transducer. For injection of 133Xe into the isolated middle cerebral artery, a tuberculin syringe containing about 0.2 to 0.3 me of the isotope dissolved in 0.4 to 0.5 ml of normal saline was used. Care was taken to see that this solution was injected at the lowest possible pressure. Skin and temporalis muscle including the peristeum over the right calvarium were removed to expose the entire lateral surface of the skull and to exclude the possibility of contamination of the results by muscle flow.

Regional CBF was measured first in the conventional methods by intracarotid injection of 1.5 to 2 me (1 ml) 133Xe and the gamma camera. Using a discriminator setting at 81 kev with a window of ± 17.5%, the calculated photopeak efficiency of the gamma camera system used is 86% for 133Xe. The resolution of the pho-gamma/III is in the range of 10 to 15 mm. A 10,000 high-sensitivity parallel hole collimator used with the system increases the depth resolution. Moreover, within the range of resolution, the overlapped of the areas observed is slight. After this clearance curve was complete 0.2 to 0.3 me 133Xe was injected into the MCA stump and the two clearance curves from the territory supplied by the MCA were determined by the computer in an identical manner for purposes of comparison.

All clearance curves were recorded on magnetic tape for ten minutes and a specially programmed computer provided automatic calculation and printout of rCBF in 14 contiguous square areas, or so-called regions of interest (ROI), throughout the infarcted hemisphere (fig. 1). The same manner in all animals. Flow values were calculated by stochastic analysis (rCBFt, LCBFt).

The experimental protocol was as follows: Four hours after MCA occlusion the lateral aspect of the baboon’s head was positioned over the collimator of the gamma camera and fixed over a grid in a standard manner by the use of adhesive tape. In six animals measurements of rCBF were followed by those of LCBF. In two animals the effect of changes in Paco2 on LCBF was tested by manipulating the CO2 clearance from the lungs by altering the speed of the respirator. In two additional animals metaraminol (Aramine®) was infused intravenously to test the effect of induced hypertension on LCBF. After all measurements were completed, the animals were killed by whole body perfusion with a glutaraldehyde-phosphate fixative. The brain was then removed and sectioned coronally so that the anatomical distribution and pathological characteristics of the infarction could be determined by gios inspection light microscopy and by means of representative sampling for electron microscopy. The extent of infarction and cerebral edema was anatomically confirmed. These pathological observations will be the subject of a companion publication.

In each experiment, cerebral infarction in the distribution of the MCA and zones of reduced rCBF were confirmed by macroscopic, microscopic and ultrastructural observations.

Results

While it is possible that manipulation and cannulation of the artery can result in spasm of the artery, under the dissecting microscope, no such spasm was observed in the cases reported in this article.

Mean values for rCBF in the ischemic hemisphere measured by intracarotid injection of 133Xe four hours after MCA occlusion are displayed in table 1. Regions with rCBF values at least 20% below the mean rCBF were arbitrarily designated as ischemic. The ischemic zones were found to consist of

Typical scintiphotol obtained from the oscilloscope of the gamma camera after intracarotid injection of 133Xe four hours after MCA occlusion. The grid for determining 14 standard regions of interest (ROI) overlies the cerebral hemisphere, which is outlined by the isotope, marked (O) at the occipital pole and (F) at the frontal pole.

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TABLE 1
Mean rCBF_{10} and rCBF_{10} in Ischemic Regions After MCA Occlusion

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Paco$_2$ (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>ICVP (mm Hg)</th>
<th>Mean rCBF$_{10}$ (ml/100 gm/min)</th>
<th>Mean rCBF$_{10}$ (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>83</td>
<td>8</td>
<td>25.1</td>
<td>20.9 (4)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>85</td>
<td>6</td>
<td>24.4</td>
<td>20.2 (3)</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>90</td>
<td>6</td>
<td>26.5</td>
<td>21.4 (6)</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>100</td>
<td>8</td>
<td>33.6*</td>
<td>26.7 (3)</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>93</td>
<td>9</td>
<td>30.4*</td>
<td>22.6 (3)</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>75</td>
<td>6</td>
<td>31.3*</td>
<td>27.9 (3)</td>
</tr>
</tbody>
</table>

Mean ± SD 39.6 ± 1.9 87.2 ± 9.6 7.2 ± 13 28.6 ± 3.7 23.2 ± 3.2

*In these experiments, regions with rCBF 20% above the mean rCBF and usually designated hyperemic 1 were also observed. These regions were confined to the periphery of the ischemic zone.

( ) = Number of ischemic regions.

three to six adjacent regions (4, 5, 9, 12, and 13 in fig. 1) as can be seen in table 1. Hyperemic zones with rCBF values 20% above the mean were noted in three animals (Nos. 4, 5 and 6 in table 1). The hyperemic zones were always found to border the ischemic zone (regions 1, 2, 6 and 10 in fig. 1).

Local CBF measurements of the ischemic area obtained by direct injection of $^{133}$Xe into the distal stump of the MCA were found on the average to be 17% less than rCBF measurements of the same area measured by intracarotid injection of $^{133}$Xe (table 2). Four to eight regions were regularly displayed on the gamma camera oscilloscope (fig. 2). There was good regional correlation, however, between zones of ischemia assessed by rCBF measured by intracarotid injection or LCBF by injection of $^{133}$Xe into the distal stump of the MCA ($r = 0.8756, P < 0.01$). Likewise, mean rCBF in the ischemic zone correlated closely with LCBF ($r = 0.825, P < 0.05$).

When Paco$_2$ was lowered by increasing the speed of the respirator, LCBF increased in the ischemic zone accompanied by an increase in the stump pressure of the MCA (table 3, fig. 3). The increase in LCBF during hyperventilation was less in peripheral regions of the ischemic zone as determined by injection of $^{133}$Xe into the MCA (fig. 3). The ICVP decreased slightly as Paco$_2$ was lowered by hyperventilation (fig. 3).

When hypertension was induced by intravenous infusion of metaraminol, LCBF increased uniformly in all regions of ischemia accompanied by an increase in rMCAP (table 4).

**Discussion**

In the present investigation the clearance curves obtained by the two routes of injection of $^{133}$Xe were calculated by stochastic analysis for purposes of comparison since calculation of the curves by bicompartimental analysis after direct injection of $^{133}$Xe into the distal stump of the MCA revealed that 70% showed monoeXponential clearance, excluding valid separation of the so-called "fast" and "slow" components. These findings confirm those of Fieschi et al., who reported monoeXponential clearance curves when rCBF approached values below 20 ml/100 gm per minute, and recently Symon et al. reported that following establishment of an ischemic zone, previously biexponential clearance curves tended to show monoeXponential clearance. Flow values measured in the ischemic zones and calculated by stochastic analysis correlated closely when calculated by stochastic analysis whether obtained by either intracarotid injection or direct injection of $^{133}$Xe into the MCA stump.

It was also evident from the clearance curves obtained from the zone rendered ischemic by occlusion of the MCA that some flow was still preserved, presumably derived from the collateral flow of blood into the ischemic area through the collateral circulation.

TABLE 2
Mean LCBF$_{M}$ After MCA Occlusion

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Paco$_2$ (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>rMCAP (mm Hg)</th>
<th>LCBF$_{M}$ (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>83</td>
<td>30</td>
<td>16.3 (7)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>83</td>
<td>30</td>
<td>15.4 (7)</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>81</td>
<td>30</td>
<td>18.9 (8)</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>97</td>
<td>39</td>
<td>32.5 (4)</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>93</td>
<td>33</td>
<td>18.7 (6)</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>72</td>
<td>30</td>
<td>13.6 (6)</td>
</tr>
</tbody>
</table>

Mean ± SD 38.5 ± 3.8 84.8 ± 8.9 32.0 ± 3.6 19.2 ± 6.8

( ) = Number of regions.
rCBF MEASURED BY THE GAMMA CAMERA

Outline of maximal zone of MCA territory defined by injection of \( ^{133}Xe \) into the distal stump of the MCA four hours after its occlusion. The size of the territory ranged from four (ROI Nos. 4, 5, 8, 9) to eight regions. Note that the parasagittal and occipital regions are not perfused with the isotope.

It will also be noted that some intra-arterial pressure (perfusion pressure) in the MCA stump distal to the occlusion was still maintained (fig. 3), which is in agreement with multiple direct pressure measurements of the small cortical arterioles reported previously. Paulson suggested that real flow values in ischemic zones obtained by intracarotid injection of \( ^{133}Xe \) in human patients with MCA occlusion were probably much lower than the values he obtained by the method. Since the area of ischemia produced by MCA occlusion in the monkey is quite comparable to that produced by acute MCA occlusion in man due to thrombosis or embolism, it appears reasonable to infer from the present results that rCBF in ischemic regions obtained by intracarotid injection of \( ^{133}Xe \) may be overestimated by 15% to 20% if collateral flow is present.

Loss of autoregulation and impaired chemical regulation (tables 3 and 4) with paradoxical responses of LCBF in the ischemic zone to changes in cerebral perfusion pressure and Paco2 have been accounted for by many as due to maximal vasodilatation (vasoparalysis) in these zones as a result of accumulated acid metabolites with tissue acidosis. Dysautoregulation in the ischemic zone has indeed been demonstrated by passive pressure-flow relationships (table 4), as has been repeatedly described in man and experimental animals.

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The phenomenon of paradoxical decrease in LCBF in ischemic zones when the Paco2 was increased has been termed "intracerebral steal" by Lassen and also has been observed in humans and animals in areas of acute and massive cerebral infarction. The theoretical explanation for this paradoxical response was that blood vessels in the ischemic zone were no longer able to respond to changes in Paco2 by further dilatation, hence vasodilatation of bordering vessels during hypercapnia surrounding the non-ischemic zones shunted blood from infarcted to normal zones of the brain. The opposite phenomenon during hypocapnic hyperventilation was termed the "inverse steal." However, intracranial and cerebral venous pressures increased during hypercapnia with passive displacement of blood from the infarcted zone, a phenomenon described by this laboratory as the "intracerebral squeeze." It has been termed "intracerebral steal."
Hyperventilation

\[ \text{PaCO}_2 = 53 \text{ mmHg} \]
\[ \text{ICVP} = 8 \text{ mmHg} \]

Local \( rCBF \) values (ml/100 gm/min) obtained by injection of \( ^{133} \text{Xe} \) into the distal stump of the MCA corresponding to regions numbered 4, 5, 6, 8, 9, 10 and 13 in figure 2. After \( \text{Paco}_2 \) was lowered by hyperventilation the stump pressure in the MCA (rMCAP) increased and so did \( LCBF \). The increase in \( LCBF \) was more in regions located in the center of the ischemic zone. The local cerebral venous pressure (LCVP) decreased as \( \text{Paco}_2 \) was lowered.

It is concluded that measurements of \( LCBF \) in zones of the brain rendered ischemic by MCA occlusion by injection of \( ^{133} \text{Xe} \) into the distal stump of the MCA gave flow values which measured 15% to 20% lower than those obtained by intracarotid injection. Nevertheless, regions shown to be ischemic by these measurements of \( LCBF \) after intracarotid injection of \( ^{133} \text{Xe} \) correlated well with (a) regions shown to be ischemic by injection of \( ^{133} \text{Xe} \) into the distal MCA stump, and (b) infarction of the brain shown at autopsy. During induced hypertension, dysautoregulation was present in the ischemic zone so that \( LCBF \) passively showed changes in cerebral perfusion pressure and decreases of \( \text{Paco}_2 \) induced by hyperventilation were followed by an increase of \( LCBF \) and rMCAP. The latter phenomenon, variously called the reverse intracerebral steal or inverse intracerebral squeeze, appears to result from changes in regional pressure gradients in ischemic brain.

**Acknowledgment**

The authors wish to acknowledge the technical assistance of Mr. Peter Miller.

**References**


**TABLE 4**

<table>
<thead>
<tr>
<th>Animal no.</th>
<th>Exp. proc.</th>
<th>( \text{Paco}_2 ) (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>rMCAP (mm Hg)</th>
<th>( LCBF_o ) (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>After MCA occlusion</td>
<td>40</td>
<td>72</td>
<td>32</td>
<td>16.4 (5)</td>
</tr>
<tr>
<td>9</td>
<td>Induced hypertension after MCA occlusion</td>
<td>41</td>
<td>122</td>
<td>48</td>
<td>27.1* (5)</td>
</tr>
<tr>
<td>10</td>
<td>After MCA occlusion</td>
<td>41</td>
<td>73</td>
<td>25</td>
<td>17.7 (5)</td>
</tr>
<tr>
<td>10</td>
<td>Induced hypertension after MCA occlusion</td>
<td>43</td>
<td>113</td>
<td>33</td>
<td>24.7* (5)</td>
</tr>
</tbody>
</table>

* = Significant compared with steady state.
( ) = Number of regions.

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