Blood Flow in the Central and Peripheral Nervous System of Dogs Using a Particle Distribution Method

BY THOMAS H. TSCHETTER, M.D., ARTHUR C. KLASSEN, M.D., JOSEPH A. RESCH, M.D., AND MAURICE W. MEYER, PH.D., D.D.S.

Abstract:
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In this study known activities of $^{85}$Sr and $^{109}$Yb-labeled microspheres were injected sequentially into the left ventricle of anesthetized dogs. Cardiac output was determined before and after each microsphere injection. Blood flow to brain, brain stem, spinal cord, and sciatic nerve was measured from fractional distribution of the microspheres in the tissue samples. Both blood flow and fractional uptake value tended to be higher for brain and brain stem than for spinal cord or sciatic nerve. Increases in arterial $P_{CO_2}$ were positively correlated with increases in blood flow to both central and peripheral nervous tissue. Initial trapping of the labeled microspheres seems to have little effect on subsequent flow to the tissue capillary bed. It appears that the particle distribution technique may provide a reasonable estimate of blood flow in central and peripheral nervous tissue of dogs.

ADDITIONAL KEY WORDS: isotope-labeled microspheres, spinal cord, brain stem, peripheral nerves

Introduction

Total, hemispheral, and regional cerebral blood flow has been intensively investigated in both man and animals in recent years. In contrast, relatively few observations have been made on blood flow in other nervous system tissues. Some values for quantitative blood flow in brain stem and spinal cord of cats have been previously reported.\(^1,2\) Sciatic nerve blood flow in cats has been estimated using diffusible indicators.\(^3\) The qualitative effects of $CO_2$ and drugs on spinal cord flow have also been studied by a variety of methods\(^1,4-7\) in both animals and man.

This article presents results of quantitative measurement of blood flow in mixed brain, brain stem, spinal cord and sciatic nerve of dogs using the particle distribution technique.

This technique is a modification of the isotope fractionation technique\(^8\) and utilizes the fractional distribution of cardiac output. Its validity has been previously evaluated,\(^9-11\) and the method has been used to measure regional cerebral blood flow in dogs.\(^12\)

Method

Six small (7 to 15 kg) dogs, anesthetized intravenously with sodium pentothal, were used. Tracheostomy was performed to provide positive pressure artificial respiration with an animal respirator using room air. The rate and/or depth of respiration was adjusted to vary the $P_{CO_2}$ as desired. Cannulation of the brachial artery, femoral artery, and femoral vein were performed, and patency was maintained with intermittent heparin-saline flush. The brachial artery cannula was passed into the left ventricle and its position confirmed at the end of each experiment. Intraarterial blood pressure and cardiac rate were monitored constantly.

Known quantities (10 to 15 mg) and total radioactivities ($A_o$) of $^{85}$Sr and $^{109}$Yb-labeled microspheres were injected sequentially into the left ventricle of anesthetized dogs. Cardiac output was determined before and after each microsphere injection. Blood flow to brain, brain stem, spinal cord, and sciatic nerve was measured from fractional distribution of the microspheres in the tissue samples. Both blood flow and fractional uptake value tended to be higher for brain and brain stem than for spinal cord or sciatic nerve. Increases in arterial $P_{CO_2}$ were positively correlated with increases in blood flow to both central and peripheral nervous tissue. Initial trapping of the labeled microspheres seems to have little effect on subsequent flow to the tissue capillary bed. It appears that the particle distribution technique may provide a reasonable estimate of blood flow in central and peripheral nervous tissue of dogs.

ADDITIONAL KEY WORDS: isotope-labeled microspheres, spinal cord, brain stem, peripheral nerves

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microspheres (25 ± 5 microns in diameter)∗ were injected sequentially into the left ventricle. The initial injection of either 85Sr or 169Yb microspheres was followed by the injection of the other labeled microspheres approximately five minutes later. The order of injection was alternated in each experiment. Cardiac output was determined before and after each microsphere injection using the cardio-green indicator dilution technique. Arterial blood samples for determination of pH, P_{O_2}, and P_{CO_2}, were taken in each animal shortly before and after injection of the microspheres. The animals were then sacrificed using intravenously administered saturated potassium chloride.

Immediately after stopping the heart in systole, tissue samples of mixed brain tissue; brain stem; cervical, thoracic, and lumbosacral cord; and sciatic nerve were obtained. The activity of each isotope per gram of tissue (A) was then determined. Separation of the emitted gamma activity of the two isotopes using a pulse height analyzer was possible because of their different energy levels. The fractional uptake of labeled microspheres per gram of tissue (Q) is defined as A/A_{0}. The blood flow (F) to the tissue is thus equal to the product of the fractional uptake per gram of tissue and the cardiac output (F = Q \times CO).

### Results

The values obtained for blood flow (F) and fractional uptake of the isotope-labeled microspheres (Q) in mixed brain and brain stem are shown in table 1. The mean values for both flow and fractional uptake were greater in mixed brain than corresponding values in the brain stem. Table 2 presents blood flow and fractional uptake values in the cervical, thoracic, and lumbosacral cord and the sciatic nerve. Blood flow and fractional uptake values were higher in the brain stem (table 1) than in the spinal cord or sciatic nerve (table 2). The blood flow and fractional uptake values tended to be higher in the lumbosacral cord than in the cervical or thoracic cord. The lowest values were obtained in the sciatic nerve. Blood flow values for brain stem and spinal cord obtained with 85Sr microspheres were compared with values obtained using 169Yb microspheres (fig. 1). An almost perfect correlation is seen.

For each type of tissue sampled, correlation coefficients and the slopes of the “least squares” regression lines relating blood flow and fractional uptake to arterial P_{CO_2} were calculated (table 3). The arterial P_{CO_2} values reported in table 1 and used in subsequent calculations were obtained at the time of the

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*Purchased from 3M Nuclear Products Division, St. Paul, Minnesota.
TABLE 2

Blood Flow (F) in ml/min/100 gm in the Cervical, Thoracic, and Lumbosacral Cord and Sciatic Nerve as Determined from Fractional Uptake (Q) of 169Yb and 90Sr-Labeled Microspheres

<table>
<thead>
<tr>
<th>Dog #</th>
<th>Label</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Lumbosacral</th>
<th>Sciatic nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F (x10^-3)</td>
<td>F (x10^-3)</td>
<td>F (x10^-3)</td>
<td>F (x10^-3)</td>
</tr>
<tr>
<td>1</td>
<td>Yb</td>
<td>11</td>
<td>4.5</td>
<td>17</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>Sr</td>
<td>7</td>
<td>2.9</td>
<td>12</td>
<td>4.9</td>
</tr>
<tr>
<td>2</td>
<td>Yb</td>
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<td>6.0</td>
<td>17</td>
<td>7.3</td>
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<tr>
<td></td>
<td>Sr</td>
<td>8</td>
<td>3.4</td>
<td>18</td>
<td>7.7</td>
</tr>
<tr>
<td>3</td>
<td>Yb</td>
<td>9</td>
<td>4.7</td>
<td>22</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>Sr</td>
<td>11</td>
<td>5.7</td>
<td>22</td>
<td>11.5</td>
</tr>
<tr>
<td>4</td>
<td>Yb</td>
<td>8</td>
<td>5.4</td>
<td>12</td>
<td>8.2</td>
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<td>6.1</td>
<td>11</td>
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</tr>
<tr>
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<td>Yb</td>
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<td>24.0</td>
<td>37</td>
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<td>26.9</td>
<td>43</td>
<td>30.4</td>
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<tr>
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<td>Yb</td>
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<td>Sr</td>
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<td>43.8</td>
<td>34</td>
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<td>23</td>
<td>13.5</td>
</tr>
<tr>
<td>± SE</td>
<td></td>
<td>±7</td>
<td>±4.8</td>
<td>±3</td>
<td>±2.5</td>
</tr>
</tbody>
</table>

TABLE 3

Correlation Coefficients (r) and Slopes (b) of the “Least Squares” Regression Lines Relating Blood Flow (ml/min/100 gm) and Fractional Uptake of Labeled Microspheres per Gram to Arterial P<sub>CO2</sub>

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Blood flow versus arterial P&lt;sub&gt;CO2&lt;/sub&gt;</th>
<th>Fractional uptake versus arterial P&lt;sub&gt;CO2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>b</td>
</tr>
<tr>
<td>Brain†</td>
<td>0.74</td>
<td>4.9</td>
</tr>
<tr>
<td>Brain stem</td>
<td>0.83</td>
<td>3.3</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>0.72</td>
<td>2.9</td>
</tr>
<tr>
<td>Thoracic</td>
<td>0.84</td>
<td>1.4</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>0.66</td>
<td>2.6</td>
</tr>
<tr>
<td>Sciatic nerve</td>
<td>0.67</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Indicates significance of correlation.
†Obtained from mixed brain samples.

Discussion

Techniques usually used in the measurement of cerebral blood flow such as the Kety-Schmidt method<sup>18</sup> or the isotope clearance methods of Ingvar and Lassen<sup>14</sup> cannot be readily applied in the study of noncerebral nervous system tissue blood flow. The technique used in this study may provide a method estimating both cerebral and noncerebral blood flow in animals.

Using the particle distribution technique, blood flow is defined as the product of the fractional uptake and the cardiac output. We have noticed in both this and other studies that cardiac output in dogs seems to be at least
A PARTICLE DISTRIBUTION METHOD

A plot relating blood flow determined with $^{153}$Yb to blood flow determined with $^{85}$Sr for brain stem and spinal cord tissue samples. The perfect correlation (1:1) line is shown.

FIGURE 1

A plot relating blood flow (ml/min/100 gm) to arterial $P_{CO_2}$ (mm Hg) for brain stem and thoracic cord tissue samples. The perfect correlation (1:1) line is shown.

FIGURE 2

A plot relating fractional uptake per gram $\times 10^{-5}$ to arterial $P_{CO_2}$ (mm Hg) for brain stem and thoracic cord tissue samples. The correlation coefficient ($r$) for brain stem is 0.83 and for thoracic cord is 0.84.

FIGURE 3

A plot relating fractional uptake per gram $\times 10^{-5}$ to arterial $P_{CO_2}$ (mm Hg) for brain stem and thoracic cord tissue samples. The correlation coefficient ($r$) for brain stem is 0.80 and for thoracic cord is 0.78.

on controlled respiratory assistance. Cardiac output tends to be lower under conditions of artificial respiration as applied in our laboratory than under spontaneous unassisted respiration. Changes in arterial $P_{CO_2}$ appear to have little effect upon cardiac output. In analyzing the effect of arterial $P_{CO_2}$ on blood flow, it may therefore be better to use the fractional uptake (which is a normalized value) rather than blood flow per se.

The flow values for mixed cerebral tissue reported here are generally in the same range as those previously reported. Brain stem and spinal cord flow values in this study also agree with previously published values. Comparison of sciatic nerve flow values was difficult, since little work has been done on peripheral nerve flow. We have found blood flow in dog vagus nerve, using both $^{86}$Rb (a diffusible indicator) and $^{169}$Yb-labeled microspheres in the same experimental animal, to be about 14 ml/min/100 gm. Other investigators, using $^{86}$Rb and iodoantipyrine, estimated peripheral nerve flow in rats to be about 11 ml/min/100 gm. This group reported the fractional uptake of $^{86}$Rb in brain and spinal
cord to be about 10% to 20% of the iodoantipyrine fractional uptake. In our earlier study\textsuperscript{12} $^{86}$Rb was used to estimate the cardiac output by the indicator dilution method, and its fractional uptake by the brain tissues averaged about 4% of the microsphere uptake in the same brain samples. It appears that diffusible indicators such as $^{86}$Rb or $^{42}$K may be useful in estimating peripheral nerve blood flow, but would tend to underestimate central nervous system blood flow.

The effect of arterial $P_{CO_2}$ on cerebral blood flow has been extensively investigated by other workers. In this study, both blood flow and fractional uptake for mixed brain, brain stem, spinal cord and sciatic nerve were positively correlated with arterial $P_{CO_2}$ as shown in table 3. Of interest is the effect of $P_{CO_2}$ on peripheral nerve tissue, which to our knowledge has not been reported previously.

This study was also designed to examine the possible effect of initial trapping of microspheres on subsequent blood flow in tissue capillary beds. This was investigated using two differently labeled particle indicators injected sequentially. In figure 1 the almost perfect correlation between values obtained for $^{85}$Sr and $^{168}$Yb microspheres implies that the initial trapping of particles has little, if any, effect on subsequent blood flow.

The tendency for average spinal cord blood flow to be higher in the lumbosacral cord than in other cord regions agrees with an earlier observation.\textsuperscript{2} Although this effect may be due to relatively larger amounts of spinal cord gray matter in the lumbosacral cord than in other regions, no attempt was made to separate white from gray matter in these tissue samples.

### Conclusions

The particle distribution method appears to be useful in estimating quantitative blood flow at various levels of the neuraxis in experimental animals. Blood flow is correlated with arterial $P_{CO_2}$ in peripheral nerve as well as in the central nervous system. Initial embolization by 25 micron microspheres does not appear to affect subsequent blood flow in the tissues studied.

### References

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