External Measurement of Regional Cerebral Blood Flow in Man by Common Carotid Arterial Injection of Radioactive Krypton-85 Saline Solution

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Summary

1) External recording of cerebral clearance was performed after Kr\(^{85}\) saline solution injection into the common carotid artery. Clearance curve thus obtained was divided into 3 exponentials. The 3rd phase represents mainly clearance of the area perfused with external carotid artery and the rest of the curve after subtraction of the 3rd phase can be treated in the similar way to that of reported by Lassen et al.

2) The method was applied on the 43 cases. Cerebral blood flow was decreased in cases with cerebrovascular diseases. This is proved to be the result of decrease of both blood flow and relative weight of grey matter. Blood flow of slow phase (representing white matter) is insignificantly decreased. Whereas blood flow of grey and white matter shows increase during 4% carbon dioxide inhalation.

3) Advantage of this simplified method was discussed.

Additional Indexing Words:

Clearance curve  Hypertension  Cerebrovascular diseases
Carbon dioxide  100% Oxygen

In our previous report\(^1\) cerebral hemodynamics was studied with non-diffusible radiopharmaceuticals (\(I^{131}\) human serum albumin). This method does not give us cerebral blood flow rate but only certain parameter of it. Rapidly diffusible radioisotopes (Kr\(^{85}\)) has been known to be used for the measurement of regional cerebral blood flow (CBF). The method was first reported by Lassen and Ingvar in 1961.\(^2\) They injected Kr\(^{85}\) saline solution into the common carotid artery of the cat and counted radioactivity of \(\beta\)-ray with G-M tube attached to the surface of the brain. Regional CBF was calculated by analyzing the clearance curve. The method was applied to the human during craniotomy by the same authors.\(^3\) Thereafter external \(\gamma\)-
Two methods for analysis of the clearance curve have been reported. These are the 2 compartments model analysis\(^4\) and the method using mean circulation time.\(^7\),\(^8\) In the former method, the clearance curve was analyzed as 2 compartments system. However, exact slope of the clearance curve of the 2nd compartment is sometimes difficult to be determined. Injection into the internal carotid artery is also often difficult procedure. In this report the method of common carotid arterial injection was studied in order to avoid the above difficulties.

**MATERIALS AND METHOD**

Seventy studies of cerebral blood flow were performed on 43 cases, 47.7 years old on the average, ranging from 23 years to 73 years old. They consisted of 18 normal cases (aged 23 to 66 years, mean 38.5 years), 13 cases with hypertension (aged 24 to 72 years, mean 48.9 years), and 12 cases with cerebrovascular diseases (aged 47 to 73 years, mean 60.1 years).

About 10 ml. of Kr\(^{85}\) saline solution (10 mC.) was injected into the internal, external or common carotid artery according to the purposes. A polyethylene tubing (PX-018) was introduced and advanced so as to reach the internal or external carotid artery selectively through lumina of a needle inserted in the common carotid artery. Then needle was removed while the position of the tubing was maintained. Position of the tip of the tubing was judged by the appearance of cold sensation at the face, tongue or pharynx during rapid flushing of several ml. of cold saline through the tubing. When tube lies in the internal carotid artery, subject did not feel cold sensation anywhere. Direct puncture was adopted in case of the common carotid arterial injection.

Scintillation detector with thallium activated sodium iodinated type (1\(\frac{1}{2}\)ø×1") and the tapered collimator with isosensitivity characteristics illustrated in Fig. 1 were used.

![Fig. 1.](image-url)
The detector was placed at the midpoint of the temporoparietal region of the injected side. Other detector with the wider collimator was placed at the opposite side in some cases in order to study local difference of CBF.

Change of counting rate was recorded on the semilogarithmic paper and clearance curve was obtained. Recording was continued for one hour in cases of common carotid arterial injection.

In some cases, 2 measurements were successively performed by the same method and the steadiness of this method was studied.

**PRINCIPLE OF CALCULATION**

Clearance curve $F(t)$ is a function of regional blood flow ($f_i$) and regional tissue/blood partition coefficient ($\lambda_i$). When there are more than one component, sum of each compartment multiplied with each relative weight determines $F(t)$.

$$F(t) = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + \cdots$$

Clearance curve of Kr$^{85}$ is composed of 2 compartments when injected into the internal carotid artery. However, it is composed of more than 2 when injected into the common carotid artery. In the latter case, the third phase of slower clearance is observed. By the subtraction of the last exponential curve the similar 2 exponential curves in the former case were obtained.

According to the procedure reported by Lassen et al.,\textsuperscript{4} slopes ($K_1$ and $K_2$) and partition of each component ($I_1$ and $I_2$) were calculated. The latter was obtained by extrapolating the exponential of clearance line to time 0.

The first rapid clearance was regarded as that of grey matter and $\lambda_1$ was assumed as 0.95,\textsuperscript{4} and the second slow clearance was considered to represent that of white matter and $\lambda_2$ was assumed as 1.30.\textsuperscript{4}

Cerebral blood flow was calculated as follows, assuming specific gravity as a unity.

Blood flow corresponding to the first phase $f_1 = \lambda_1 K_1 = 0.95 K_1$

Blood flow corresponding to the second phase $f_2 = \lambda_2 K_2 = 1.30 K_2$

Mean cerebral blood flow $f$ is,

$$f = \frac{W_1 \lambda_1 K_1 + W_2 \lambda_2 K_2}{W_1 + W_2}$$

where $W_1$ and $W_2$ are relative weight of 2 tissue compartments.

While

$$I_1/I_2 = W_1 \lambda_1 K_1/W_2 \lambda_2 K_2$$

therefore

$$f = \frac{I_1 + I_2}{I_1/\lambda_1 K_1 + I_2/\lambda_2 K_2}$$

while

$$W_1 + W_2 = 1$$

therefore

$$W_1 = \frac{I_1 f_2/I_1 + f_1}{I_1 f_2/I_1 + f_1}, \quad W_2 = 1 - W_1$$
RESULTS

1. Influence of the sites of injections on the clearance curves

1) Internal carotid arterial injection and common carotid arterial injection

![Graphs showing clearance curves for different sites of injection.]

**Fig. 2.**

![Graph showing relationship between common carotid arterial injection and internal carotid arterial injection.]

**Fig. 3.**
Both procedures were successively applied to 5 subjects. Clearance curve has 3 compartments when injected into common carotid artery. The curve obtained by subtracting the last phase from the original one was similar to that obtained by internal carotid arterial injection (Fig. 2). Cerebral blood flows calculated from each procedure were represented in Fig. 3 and Table I. Very good correlation ($r=0.87$) was observed ($p<0.01$).

2) External carotid arterial injection and common carotid arterial injection

Both procedures were successively applied to 3 subjects. Terminal slope of both clearance curve was quite similar to each other as listed in Table II.

2. Location of scintillation detector and CBF (Fig. 4)

Two detectors were placed on ipsilateral and contralateral side of $\text{Kr}^{85}$ injection at the same time in 33 cases and measured CBFs of the different parts of the brain. CBFs measured from both sides were well correlated ($r=0.56$, $p<0.01$).

3. Reproducibility of the measurement (Fig. 5)

### Table I. Influence of the Sites of Injection (I)

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Mean CBF</th>
<th>Rapid Phase</th>
<th>Slow Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>S. O.</td>
<td>49</td>
<td>F</td>
<td>51.7</td>
<td>35.3</td>
<td>84.4</td>
</tr>
<tr>
<td>T. K.</td>
<td>28</td>
<td>M</td>
<td>46.3</td>
<td>48.0</td>
<td>92.7</td>
</tr>
<tr>
<td>Z. N.</td>
<td>56</td>
<td>M</td>
<td>43.7</td>
<td>45.1</td>
<td>94.1</td>
</tr>
<tr>
<td>A. K.</td>
<td>71</td>
<td>M</td>
<td>36.2</td>
<td>35.6</td>
<td>57.2</td>
</tr>
<tr>
<td>S. O.</td>
<td>72</td>
<td>M</td>
<td>48.8</td>
<td>45.2</td>
<td>84.4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>45.3</td>
<td>41.8</td>
<td>82.6</td>
</tr>
</tbody>
</table>

I: Internal carotid injection  
C: Common carotid injection

### Table II. Influence of the Sites of Injection (II)

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>$K_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>T. S.</td>
<td>53</td>
<td>M</td>
<td>0.028</td>
</tr>
<tr>
<td>C. N.</td>
<td>63</td>
<td>M</td>
<td>0.025</td>
</tr>
<tr>
<td>M. K.</td>
<td>37</td>
<td>M</td>
<td>0.034</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
</tbody>
</table>

C: Common carotid injection  
E: External carotid injection
Two measurements were repeated in 6 subjects. Mean value of percentage of the difference of 2 measurements against the first one was $-1.3\% \pm 12.6$ (S.D.). Correlation coefficient of 2 CBF values was 0.91 ($p<0.01$).

4. CBF measured by this method (Fig. 6, 7)

Cerebral blood flow measured by this method in 18 normal subjects ranged
39.9 to 73.1 ml./100 Gm. brain/min. (unit is omitted in the following description) (mean 51.9±8.8 (S.D.)). Blood flow of rapid phase ranged 66.8 to 134.5 (mean 93.5±18.1) and that of slow phase ranged 17.6 to 36.0 (mean 24.4±4.3). Relative weight of rapid phase was 39.8±10.9%.

Cerebral blood flow in 13 cases with hypertension ranged 38.3 to 63.6 (mean 47.9±6.5). Blood flow of rapid phase ranged 53.3 to 113.5 (mean 81.7±18.0) and that of slow phase ranged 21.2 to 27.2 (mean 23.9±1.9). These values were insignificantly less than those in normals. Relative weight of rapid phase was 38.9±11.2%.

Cerebral blood flow in 12 cases with cerebrovascular diseases ranged 26.7 to
46.3 (mean 36.9 ± 5.9). Blood flow of rapid phase ranged 50.6 to 98.3 (mean 72.9 ± 13.3) and that of slow phase ranged 17.1 to 26.6 (mean 22.3 ± 3.0). Cerebral blood flow was significantly lower than that in normals ($p < 0.05$). But blood flow of slow phase was insignificantly decreased. Relative weight of rapid phase was 31.8 ± 11.2% and this was significantly lower than that in normals ($p < 0.05$).

5. Influence of 4% CO$_2$ and 100% oxygen inhalation (Fig. 8, 9)

Cerebral blood flow of 10 patients was measured during breathing air or other 2 gases—the mixed gas that was composed of 4% carbon dioxide, 21% oxygen and 74% nitrogen or pure oxygen.

Cerebral blood flow increased during 4% carbon dioxide inhalation from

![Graphs showing blood flow changes](image1)

*Fig. 8.*

![Graphs showing blood flow changes](image2)

*Fig. 9.*
Blood flow of rapid phase increased from 84.8±25.8 to 105.8±27.3 by the factor of 32.9% (p<0.01). Blood flow of slow phase increased from 21.8±4.8 to 27.2±3.4 by the factor of 30.7% (p<0.01).

Cerebral blood flow decreased during pure oxygen inhalation from 52.2±6.9 to 44.4±5.2 by the factor of 14.4% (p<0.01), that of rapid phase decreased from 103.9±20.7 to 98.2±17.5 by the factor of -3.3%, whereas that of slow phase increased from 25.1±4.4 to 25.4±3.0 by the factor of +2.5%.

**DISCUSSION**

Clearance curve which represents washout rate of the gas from the tissue is a function of blood flow rate to the tissue and of blood/tissue partition coefficient of the gas. Since blood/tissue partition coefficient is different among various parts in the brain, clearance curve could be composed of many exponentials. Cerebral clearance curve, however, can be mainly divided into 2 parts, which are perfusing grey matter and white matter respectively, according to the results obtained from autoradiography of I131-CF3 by Kety et al. and the results of us using I131-MAA. When Kr saline solution is injected into the common carotid artery, clearance of areas perfused by external carotid artery is added to them. Therefore cerebral clearance curve in this case is expected to be sum of the three and it is really proved. This concept is supported by agreement of the slope acquired by external and common carotid arterial injection, and by agreement of the slopes which are obtained by internal carotid arterial injection and by subtracting clearance curve of external carotid arterial areas from that of common carotid arterial areas. Clearance curve obtained from common carotid arterial injection is thus divided into 3 exponential curves; the first rapid phase represents mainly blood flow of the grey matter, the second phase represents mainly blood flow of the white matter and the third phase represents mainly blood flow of areas perfused by external carotid artery. Contribution of area perfused by external carotid artery is as low as 1/47 and 1/37 in our condition of the measurement.

There is a little part of rapid clearance (but always slower than the rapid phase of internal carotid arterial perfusion), when Kr is selectively injected into the external carotid artery. This phase is always neglected in subtraction of the 3rd phase on the recording paper. Cerebral blood flow is underestimated in our series—51.9±8.8, comparing with that of Kety et al.—54±12. Relative weight of grey matter is underestimated by about 10% in our series, comparing with the other author’s report. These may result from under-
subtraction of external carotid arterial areas.

This method can detect changes in cerebral blood flow in disease and during inhalation of carbon dioxide or oxygen. These results are consistent with those reported by others.\textsuperscript{13–15}

This method is useful not merely for the regional measurement of cerebral blood flow but for the separate measurement of blood flow of grey matter (rapid phase) and blood flow of white matter (slow phase) and for the estimation of relative weight of these 2 compartments. Decreased CBF in cerebrovascular diseases is caused mainly by decrease of rapid phase. Relative weights of rapid phase decreased to 80\% of normals. Blood flow of rapid phase decreased to 78\% of normals. Decrease in both blood flow rate and relative weight of rapid phase is thought to be the major pathophysiological change in cases with cerebrovascular disease.

During the inhalation of 4\% carbon dioxide mean cerebral blood flow and blood flow of rapid and slow phase showed increase. Relative weight cannot be shown to change in this acute experimental condition. Therefore vasodilatation and increased blood flow occurs both in grey and white matter. This explanation was supported by animal experiment of us using I\textsuperscript{131}-MAA and I\textsuperscript{125}-MAA.\textsuperscript{10} This different response of 2 phases is worth studying in various disease state.

The method requires as long as 45 to 60 min. But direct puncture of the common carotid artery is much easier than selective injection of indicator into the internal carotid artery giving less trouble to the subject with reasonable results.

\textbf{REFERENCES}