Interrelationships Among Regional Cerebral Blood Flow, Mean Transit Time, Vascular Volume and Cerebral Vascular Resistance

BY YOSHIHIRO KURIYAMA, M.D., PH.D., TAKASHI AOYAMA, M.D., KUNIHICO TADA, M.D., SHOTARO YONEDA, M.D., TADAATSU NUKADA, M.D., PH.D., AND HIROSHI ABE, M.D., PH.D.

Abstract:

The simultaneous measurement of regional cerebral blood flow (rCBF), mean transit time (MTT), vascular volume (CVV) and cerebral vascular resistance (CVR) was performed in patients with cerebrovascular diseases. The measurement was made by a gamma-ray scintillation camera assisted by a minicomputer. A diffusible indicator of 133Xe for CBF determination and a nondiffusible indicator of 99m Tc for MTT determination were used.

The relation between rCBF and MTT showed a negative correlation in the nonfocal areas. The rCBF value in patients with normal brain was constant at high and low blood pressures. In patients with cerebral infarction there was a positive correlation between rCBF and mean arterial blood pressure. MTT had a negative correlation with mean arterial blood pressure in both patients with normal brain and those with cerebral infarction. In patients with normal brain a good negative correlation between CVV and CVR was found. In the nonfocal areas of cerebral infarction a high level of CVR was maintained regardless of the level of CVV.

Additional Key Words

nondiffusible indicator
gamma-ray scintillation camera
diffusible indicator
nonfocal area

Introduction

The parameters representing cerebral circulation are regional cerebral blood flow (rCBF), mean transit time (MTT), cerebral vascular volume (CVV) and cerebral vascular resistance (CVR). It has been reported that there was a correlation between CBF and MTT and between CBF and CVV, and that one of these parameters could represent cerebral hemodynamics. It can be surmised, however, that each of these parameters may change synchronously to maintain the physiological state of cerebral circulation, and that in the pathological state this synchronism may be broken. In this regard few investigations have been made.

In this study, rCBF, MTT, CVV and CVR were measured simultaneously and analyzed in normal brains and in nonfocal areas of cerebral infarction.

Methods

INSTRUMENT

The gamma-ray scintillation camera (RC-IC-1205, Hitachi Medical Co. Ltd., Tokyo, Japan) and on-line RI data processing system were used. This system has been described in detail elsewhere. The outline of this system is as follows. The scintillator of 10 inches NaI crystal was equipped with 5,600 hole collimator. The on-line RI data processing system had a built-in small computer (HITAC-10, 8k) and a high-speed magnetic tape as an auxiliary memory device. The 4,096 channels, consisting of 64 x 64 grids, recorded the activities from 4 mm square of the camera surface.

MEASURING PROCEDURES

The gamma-ray scintillation camera, of which photopeak was at 81 kev for 133Xe and at 140 kev for 99m Tc using a 10% window, was placed with the center of the crystal 10 cm above the external auditory meatus in parallel with the sagittal plane of the head. Approximately 4 mCi of 133Xe in 2 ml of saline was injected into the internal carotid artery through a Teflon catheter. The position of the tip of the catheter was ascertained by saline injections resulting in eyelid blanching. Sampling time was settled one second during the initial two minutes and then every ten seconds for the following ten minutes. After the external counting of 133Xe activities, 4 mCi of 99m Tc in 2 ml of saline was injected through the same catheter. Activity was collected over one-second intervals and ended 40 seconds afterward. Arterial Po2 and Pco2 were measured by IL meter Model 113 (Instrumentation Laboratories Inc., Lexington, Kentucky).

CALCULATION

If a certain amount of RI indicator is injected into an internal carotid artery, mean transit time (MTT) can be expressed as follows.

MTT = (area under the RI clearance curve) / (maximum height of the RI clearance curve)

(1)

MTT of 133Xe, which leaks freely out of blood vessels and distributes into the tissue, represents the passing time through the tissue.

From the First Department of Internal Medicine, Osaka University Medical School, 3 Dojimahamadori, Fukushima, Osaka 553, Japan.
rCBF_{10\text{ min}} was obtained by the method of stochastic analysis.\(^5\)

\[
rCBF_{10\text{ min}} (\text{ml/100 gm brain per minute}) = 100 \lambda \frac{H(10)}{A(10)}
\]

Here, \(H(10)\) is the difference between the zero time height and the height after ten minutes of clearance, \(A(10)\) is the area under the clearance curve between zero and ten minutes, and \(\lambda\) is a distribution coefficient between blood and tissue. The calculation was made by using a minicomputer attached to the processing system.

When nondiffusible indicator which distributes only in the vessels is used, MTT represents the passing time through the vessels. In order to clarify whether 99m Tc was a nondiffusible indicator or not, 99m Tc and 99m Tc labeled albumin were injected individually into an internal carotid artery. The clearance curves of 99m Tc and 99m Tc albumin, obtained from cerebral parenchyma, showed a good agreement as seen in figure 1. This fact indicated that 99m Tc could be treated as a nondiffusible indicator as far as the first circulation. The time course of RI activity at the respective regions is shown in figure 2. The data in Results were values obtained from the areas of brain parenchyma excluding sinus and jugular vein. After the 99m Tc injection as an impulse manner, the time course of RI activity from brain parenchyma by the external counting satisfied the equation to calculate MTT. The calculation was made by equation (1). Cerebral vascular volume (CVV) was obtained from the following equation (2) which was a fundamental relation of organ circulation.\(^6\)

\[
\text{CVV (ml/100 gm brain)} = rCBF \times \text{MTT}
\]

Cerebral vascular resistance (CVR) was calculated from the following equation.\(^7\)

\[
\text{CVR (mm Hg/ml/100 gm brain/min)} = \frac{\text{MABP/rCBF}}{}
\]

(MABP: mean arterial blood pressure.)

**Subjects**

The 16 cases included nine patients with cerebral infarction in 20 days to three months after the onset, two patients with arteriovenous malformation and five patients who had no organic brain lesion. The occluded area of cerebral infarction and the shunted area of arteriovenous malformation were excluded. The area of interest was settled at brain parenchyma of nonfocal area.

**Results**

**PARAMETERS OF CEREBRAL CIRCULATION**

The parameters of cerebral circulation in 16 cases are listed in table 1. A comparison was made between nine cases of cerebral infarction and five cases of normal brain, the cases with cerebral infarction showed significant low values of rCBF and arterial PO\(_{2}\) and high value of CVR. No significant difference was found in MTT, CVV, MABP and arterial Pco\(_{2}\).

**RELATION BETWEEN MTT AND rCBF**

The relation between MTT and rCBF revealed a negative correlation in patients with normal brain and those with cerebral infarction (\(r = -0.703, P < 0.001\)) (fig. 3).

**RELATION BETWEEN MABP AND EACH PARAMETER OF CEREBRAL CIRCULATION**

**rCBF**

Figure 4 shows the relationship between MABP and rCBF. In the normal brain, represented by open circles, the rCBF remained constant, irrespective of the level of MABP. In cases with cerebral infarction a positive correlation was observed (\(r = 0.903, P < 0.01\)) as shown by the closed circles. The rCBF of patients with higher blood pressure showed the value closing with the normal value.

**MTT**

Figure 5 shows the relation between MABP and MTT. A trend for shorter MTT was recognized at higher blood pressure in comparison with the normal blood pressure cases. The relation between MTT and MABP indicated the separate and negative correlation in normal brain cases and in cases with cerebral infarction.

**CVV and CVR**

The relation between CVV and CVR is presented in figure 6. In the normal brain as shown with open circles, CVV and CVR showed a negative correlation (\(r = -0.964, P < 0.001\)). Meanwhile, different from...
REGIONAL CBF, MEAN TRANSIT TIME, VASCULAR VOLUME AND CVR

T.I.C.A.

**Mean Transit Time (X)**
- **X**(brain) 3.60 seconds
- **X**(sinus) 5.42 seconds
- **X**(I.J.V.) 19.25 seconds

**FIGURE 2**

RI activities from respective regions — internal carotid artery, brain parenchyma, sinus and internal jugular vein. Right picture indicated how to settle the area of interest.

**TABLE 1**

Parameters of Cerebral Circulation of the Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>MABP (mm Hg)</th>
<th>CBF (ml/100 gm brain per minute)</th>
<th>MTT (second)</th>
<th>CVV (ml/100 gm brain)</th>
<th>CVR (mm Hg per milliliter per minute)</th>
<th>Paco2 (mm Hg)</th>
<th>Pao2 (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of normal brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>107.3</td>
<td>49.5</td>
<td>3.0</td>
<td>2.5</td>
<td>2.2</td>
<td>45</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>128.7</td>
<td>53.6</td>
<td>2.4</td>
<td>2.2</td>
<td>2.4</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>83.3</td>
<td>52.5</td>
<td>3.6</td>
<td>3.1</td>
<td>1.6</td>
<td>40</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>106.6</td>
<td>43.3</td>
<td>2.9</td>
<td>2.1</td>
<td>2.5</td>
<td>41</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>75.0</td>
<td>46.0</td>
<td>4.0</td>
<td>3.0</td>
<td>1.6</td>
<td>39</td>
<td>96</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>100.2 ± 19.1</td>
<td>49.0 ± 3.9*</td>
<td>3.2 ± 0.6</td>
<td>2.6 ± 0.4</td>
<td>2.1 ± 0.4*</td>
<td>41.4 ± 2.1</td>
<td>99.8 ± 5.4*</td>
</tr>
<tr>
<td>Cases with cerebral infarction of recent stage (nonfocal area)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>107.0</td>
<td>35.8</td>
<td>5.7</td>
<td>3.4</td>
<td>3.0</td>
<td>40</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>119.0</td>
<td>44.1</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
<td>40</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>138.0</td>
<td>47.8</td>
<td>3.3</td>
<td>2.6</td>
<td>2.9</td>
<td>39</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>96.0</td>
<td>39.9</td>
<td>5.7</td>
<td>3.8</td>
<td>2.4</td>
<td>39</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>120.0</td>
<td>43.2</td>
<td>5.3</td>
<td>3.8</td>
<td>2.8</td>
<td>41</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>118.0</td>
<td>41.6</td>
<td>4.7</td>
<td>3.2</td>
<td>2.8</td>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>134.7</td>
<td>45.1</td>
<td>3.3</td>
<td>2.5</td>
<td>3.0</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>107.0</td>
<td>35.8</td>
<td>5.7</td>
<td>3.4</td>
<td>3.0</td>
<td>41</td>
<td>90</td>
</tr>
<tr>
<td>14</td>
<td>101.7</td>
<td>37.5</td>
<td>5.6</td>
<td>3.5</td>
<td>2.7</td>
<td>42</td>
<td>105</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>115.7 ± 13.5</td>
<td>41.2 ± 4.0*</td>
<td>4.8 ± 0.9</td>
<td>3.2 ± 0.4</td>
<td>2.8 ± 0.2*</td>
<td>40.2 ± 0.9</td>
<td>90.0 ± 6.5*</td>
</tr>
<tr>
<td>Cases with arteriovenous malformation (nonfocal area)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>80.7</td>
<td>43.1</td>
<td>4.2</td>
<td>3.0</td>
<td>1.9</td>
<td>38</td>
<td>90</td>
</tr>
<tr>
<td>16</td>
<td>86.0</td>
<td>52.0</td>
<td>3.9</td>
<td>3.4</td>
<td>1.7</td>
<td>40</td>
<td>108</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>83.4 ± 2.7</td>
<td>47.6 ± 4.5</td>
<td>4.1 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>39.0 ± 1.0</td>
<td>99.0 ± 9.0</td>
</tr>
</tbody>
</table>

*Paired t test (P < 0.01), MABP (mm Hg), CBF (ml/100 gm brain per minute), MTT (second), CVV (ml/100 gm brain), CVR (mm Hg per milliliter per minute), Paco2 and Pao2 (mm Hg).
normal brain cases, the nonfocal areas in cases with cerebral infarction showed elevated CVR, even though CVV was not decreased.

Discussion

CBF
The mean values of CBF reported by various methods in normal men are 54 ± 12 with the nitrous oxide technique,8 54 ± 9 using Krypton-85,9 and 49.8 ± 5.4 ml/100 gm brain per minute using 133Xe and multidetector system.10 In this study in which the gamma-ray scintillation camera was used, the normal value was 49.0 ± 3.9 ml/100 gm brain per minute, being well approximated to the results of the previous reports.

The cerebral blood flow of the cases with normal brain was maintained constantly in spite of the changes of blood pressure. This phenomenon was called autoregulation of CBF.11 It had been reported that after cerebrovascular accidents the autoregulation of CBF was impaired and it took several months for its restoration after the onset.12 In this study, the fact that the value of rCBF in normal brain cases was constant independent of MABP indicated that autoregulation existed. Dysautoregulation was suggested in cases with cerebral infarction, by observing a positive correlation between rCBF and MABP.

MTT
According to Nylin et al.,13 the normal value of MTT was ten seconds by the outflow detection method. Oldendorf and Kitano14 reported that the normal value was eight seconds by the intravenous injection method. MTT value in this work was 3.2 ± 0.6 second in five cases with normal brain, which was remarkably shorter than those of previous reports. It may be the result from the method that the observed area in this study was set only at brain parenchyma, excluding the large vessels such as venous sinus and internal jugular veins. It had been reported that MTT was shortened in hypertensive cases and extended in the cases with cerebral infarction.14 This was recognized by the fact that MTT stood in a negative correlation with MABP in both patients with normal brain and those with cerebral infarction.
Regional CBF, Mean Transit Time, Vascular Volume and CVR

The CVV value reported by animal experiments were 2.0 to 2.3 ml/100 gm brain in vitro and 4.8 ± 0.3 ml/100 gm brain in vivo. The calculated CVV value in this study was 2.6 ± 0.4 ml/100 gm brain in five cases with normal brain. In in vivo animal experiments CVV was calculated by the result of separate measurement of CBF and MTT which was the blood passage time from the artery to the venous sinus. This was the reason why the MTT was prolonged and the calculated CVV was expanded compared with our result of CVV. Fog observed, by the skull window technique, that the pial vessels were expanded in diameter when the blood pressure was decreased and the vessels were contracted when the blood pressure was elevated. It was imagined that the peripheral resistance was controlled by the change of the vessel diameter. In this study CVR of normal brain cases had a negative correlation with CVV, while in cases with cerebral infarction there was no correlation between CVR and CVV. When the fluid flows in the rigid tube, the following Poiseuille's law can be applied:

\[ F = \frac{\pi pr^4}{8\eta l} \]

\( F \) = flow in the tube, \( p \) = pressure difference between inlet and outlet of the tube, \( r \) = radius of tube, \( \eta \) = viscosity coefficient, \( l \) = length of tube. The volume \( V \) in tube is \( \pi r^2 l \). Therefore, Poiseuille's law can be expressed as follows:

\[ R = \frac{8\pi \eta l^3}{V^2} \]

In other words, the vascular resistance \( R \) is changed in inverse relation to the square of the vascular volume. In this study, however, CVR of normal brain cases showed a linear correlation with CVV (Fig. 6). This result coincided well with the theoretical value, if it was taken into consideration that construction of the vessels was not simple as a rigid tube, the flow in the vessels was not laminar, and the CVV measured represented not only the resistance vessels but the total sum of the vascular volume of arteriole, capillary and venule.

One of the reasons why CVR was so high in cases with cerebral infarction in spite of moderately increased CVV might be due to the increased local viscosity. It has been reported on the microcirculation of an organ that the plasma passes through a long route with low hematocrit value, while erythrocytes select the shorter route with high hematocrit value. This phenomenon was called plasma skimming and might be concerned with local viscosity of organ circulation. The significance of the plasma skimming under physiological and pathological states is not yet clear. It is conceivable that the local viscosity relating to plasma skimming might play a considerable role as a factor to advent the disturbance of cerebral circulation in cases with cerebral infarction.

Conclusion
A study on the cerebral circulation by the combined use of a diffusible indicator (133Xe) and a nondiffusible indicator (99m Tc) was performed in patients with normal brain and those with cerebral infarction.

1. A negative correlation was noted between MTT and rCBF.
2. The rCBF in cases with normal brain was constant irrespective of MABP. In cases with cerebral infarction, the normotensive patients showed low rCBF values in comparison with hypertensive patients.
3. A negative correlation between MTT and MABP was found in both cases with normal brain and those with cerebral infarction.
4. The relation between CVV and CVR showed a negative correlation in cases with normal brain. On the other hand, no correlation was found between them in nonfocal areas of cerebral infarction. The increased CVR of cases with cerebral infarction might be related to local change of blood viscosity.

Acknowledgments
The authors wish to express their grateful appreciation to Kazufumi Kimura, M.D., Department of Nuclear Medicine, Osaka University Hospital, Osaka, Japan, for his suggestions and support. The technical assistance of Mr. Keizo Kusumi and the assistance of Miss Hisae Onoda in preparing the illustrations are gratefully acknowledged.

References
Interrelationships Among Regional Cerebral Blood Flow, Mean Transit Time, Vascular Volume and Cerebral Vascular Resistance
YOSHIHIRO KURIYAMA, TAKASHI AOYAMA, KUNIHIKO TADA, SHOTARO YONEDA, TADAATSU NUKADA and HIROSHI ABE

Stroke. 1974;5:719-724
doi: 10.1161/01.STR.5.6.719
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/5/6/719

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at:
http://stroke.ahajournals.org//subscriptions/