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Authors

Sakai, Fumihiko

Igarashi, Hisaka

Suzuki, Syuichi

et al.

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Cerebral blood flow and cerebral hematocrit in patients with cerebral ischemia measured by single-photon emission computed tomography

Fumihiko Sakai, Hisaka Igarashi, Syuichi Suzuki & Yoshiaki Tazaki

Department of Medicine, School of Medicine, Kitasato University, Kanagawa-ken, Japan

ABSTRACT - Single-photon emission computed tomography (SPECT) was used for the measurement of regional cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral hematocrit (Hct). CBF was measured using N-isopropyl-p-I-123-Iodoamphetamine. CBV was measured by both RBC tracer (Tc-99m RBC) and plasma tracer (Tc-99m human serum albumin) and cerebral hematocrit (Hct) was calculated. In normals, the cerebral-to-large vessel Hct ratio was 75.9%. Isovolemic hemodilution in patients with high Hct tended to increase the cerebral-to-large vessel Hct ratio. Low CBF, high CBV and slow cerebral blood mean transit time (MTT by dynamic CT scanning) was seen during the acute stage of completed infarction and during the symptom-free interval of TIA. Cerebral Hct was increased in the ischemic region of poor prognosis.

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There is now a growing interest in the role of blood viscosity in the pathophysiology of cerebral ischemia. Recent studies have been focused on the effectiveness of the hemorheological approach, including hemodilution therapy, in the treatment of cerebrovascular diseases (1). Many studies have measured changes in cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolism after stroke. Little attention has been paid to the role of cerebral hematocrit (Hct) in the pathophysiological mechanism of acute cerebral ischemia.

We used single-photon emission computed tomography (SPECT) for the measurement of CBF, CBV and cerebral Hct in normals and in patients with occlusive cerebrovascular diseases.

Subjects and methods

Twenty-one neurologically normal subjects aged 32–43 years, 32 patients with cerebral infarction and 9 patients with TIA or RIND due to severe stenosis or occlusion of internal carotid or middle cerebral arteries were studied.

The SPECT system used for the present study was a GE Maxi 400T camera connected to an Informatek Simis 3 computer or a GE Starcam 400AC/T camera system. The radius for the rotation of the camera was set at 14–16 cm depending on the size of the head, and the data were collected through 64 equal angular samplings. A low-energy, high resolution collimator was used. The brain images were reconstructed in a series

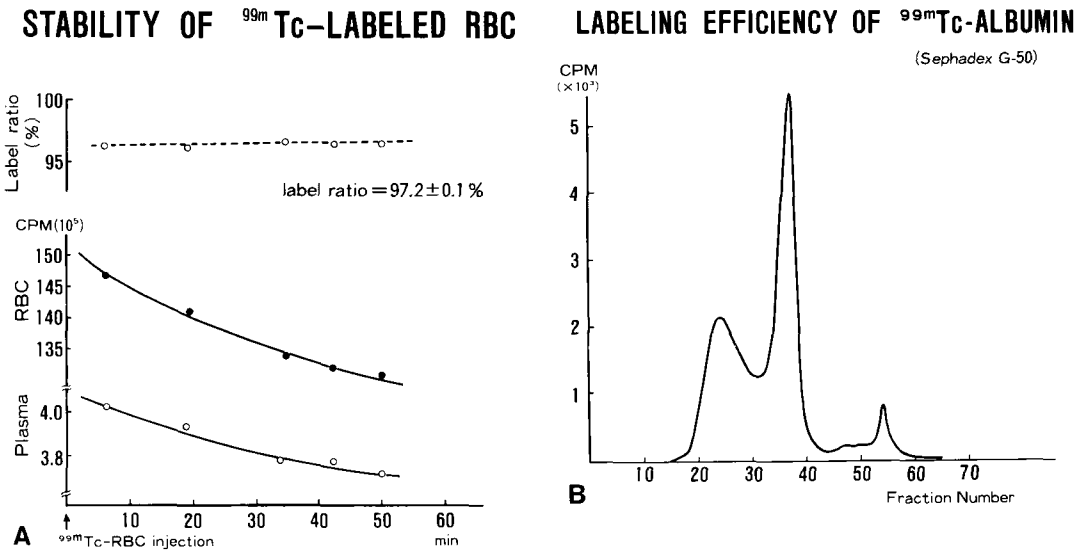


Fig. 1. The label ratio for Tc-99m red blood cell remained constant during the 1st hour at 97.2±1.2% (Fig. 1A). A study by gel partition chromatography for plasma samples obtained at 45 min after the injection of Tc-99m-labeled human serum albumin (Fig. 1B) revealed that the mean label ratio for albumin in the circulating blood was 96.1±2.4% (The third peak from the left is the unlabeled fraction).

of horizontal sections of the brain parallel to the anatomical line (Reid's line) for every 1.2 cm from the vertex. A filtered back projection method was used. The spacial resolution, measured in a skull phantom, expressed by the full width half maximum was 1.4 cm for the GE Starcam 400AC/T system and the cold lesion detectability was a cylinder measuring 2 cm in diameter.

Regional CBF was measured using N-isopropyl-p-I-123-iodoamphetamine (IMP). SPECT scan of the head was performed 3 times following the intravenous injection of IMP at 15 min, 2 h and 4 h. Arterial and jugular venous bood was sampled serially and each sample was subjected to octanol extraction to measure the proportion of IMP to its metabolites.

Arterial IMP input curve was used for calculating regional CBF values.

For the RBC volume study, a sample of subject's RBC was labeled with 20 mCi of Tc-99m using stannous pyrophosphate as a reducing agent. For plasma volume measurement, 20 mCi of Tc-99m-labeled human serum albumin (HSA) was used as the plasma tracer. The label ratio for RBC remained constant during the 1st h at 97.2±1.2% (Fig. 1A) in 10 subjects. The radioactivity of labeled albumin reached a plateau within 7 min following the intravenous injection, then stayed constant thereafter for an interval of 45 min. A study by gel partition chromatography for plasma samples, obtained 45 min after the injection of Tc-99m labeled HSA, revealed that the mean label ratio for albumin in the circulating blood was 96.1±2.4% (N = 5) as shown in Fig. 1B.

CBV was measured using both RBC tracer and plasma tracer. These two CBV studies were performed either separately after an interval of 24 h or serially on the same day.

CBV was calculated by Eq. 1, which gives the ratio of the radioactivity per weight of brain to the estimated radioactivity per milliliter of cerebral whole blood.

$$CBV = \frac{C_{brain}}{\alpha \cdot Hct \cdot + (1-\alpha \cdot Hct) \cdot C_{plasma}} \cdot 100 \quad \text{(Eq·1}$$

where C_{brain} is the activity per gram of brain determined by scanning and the denominator is the activity of cerebral whole blood estimated from arterial blood counts. C_{rbc} and C_{plasma} are

activities per milliliter of RBC and plasma in the sampled arterial blood, respectively. Hct is the large vessel arterial Hct measured in arterial samples. The constant α represent the ratio of the cerebral small-vessel Hct to the large-vessel Hct, and the product of 100 converts CBV values to milliliters per 100 g brain.

If Eq. 1 is applied to both RBC and HSA studies for the calculation of CBV, the results should give the same CBV values if the correct α is used in the equation. Instead of using the standard value of 0.85 (2), we calculated the constant α by using the two sets of data for RBC and HSA studies (3).

The brain scans were calibrated by matching to the scan of a skull phantom filled with known radioactivity.

MTT was calculated using the time-concentration curve following the intravenous injection of iodine-contrast material (Iopamidol 40 ml) and serial CT scanning using GE CT/T 8800. Total of 18 scan images were obtained with a scan time of 3.4 s for each image. Gamma-variate curve fitting was performed on the original data. MTT was obtained from the interval between the first moments of the input function and the output function, which were derived by differentiating the original curve and correcting for the overlap effect according to the method reported by Tomita et al (4). The calculation of MTT was performed for each pixel of 110 × 120 image matrix, and MTT values were displayed as a slice image corresponding to the image of CT scan.

For all the cerebral hemodynamic images hemispheric mean values were calculated and were compared between the ischemic and non-ischemic hemisphere.

Results

Tracer kinetics of IMP and CBF values

After the intravenous injection of IMP in normals, arterial radioactivity reached an initial peak within 5 min. Jugular vein also showed a small but similar initial peak. In the artery the ratio of octanol-extracted radioactivity, which is non-metabolized IMP, was 74±11% (N = 4) during the initial peak. In the jugular vein the percentage of IMP to metabolites was lower initially, but was gradually increased. Mean value for cerebral extraction fraction of IMP during the initial 5 min in normals (N = 4) was 84±5%. CBF values calculated without correcting for the extraction and binding were underestimated by 8–12%. Mean CBF in normals corrected for octanol-extraction ratio and cerebral extraction ratio was 44.8±6.4 ml/100 g brain/min.

CBV and cerebral Hct in normals

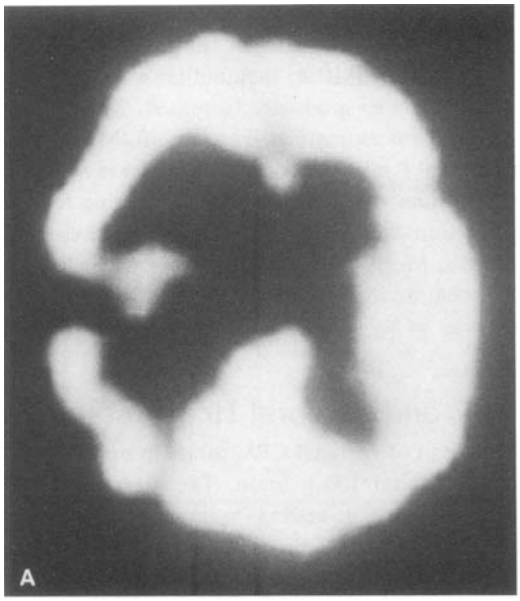
The mean of regional CBV values in normals was 4.81±0.37 ml/100 g brain. The mean for RBC volumes in the resting state was 1.50±0.09 ml/100 g brain. This was significantly smaller than mean of the plasma volume, which was 3.34±1.8 ml/100 g brain. The mean cerebral Hct calculated from these values was 31.3±1.8%, and the mean ratio of the cerebral-to-large vessel Hct was 75.9±2.1%.

Within the normal range of large vessel Hct there was no correlation between cerebral-to-large vessel Hct ratio and large-vessel Hct. When high systemic Hct was redued by isovolemic hemodilution, cerebral-to-large vessel Hct ratio tended to be increased. As a result, in spite of the significant reduction in large-vessel Hct, the reduction in cerebral Hct was minimal.

Cerebral hemodynamics in patients with cerebral ischemia

Patients with TIA (N = 5), hemodynamic TIA due to the occlusion or severe stenosis of internal carotid artery, were studied during the symptom-free interval. CBF was reduced in 3 patients in the region responsible for TIA and was normal in 2 patients. CBV was increased in all the patients in the ischemic hemisphere. There was no significant hemispheric asymmetry in cerebral Hct.

During the acute stages of cerebral infarction, the reduction of CBF in the ischemic hemisphere was seen in larger areas than the low density on CT scan. CBV was increased in the ischemic hemisphere corresponding to the zone of the



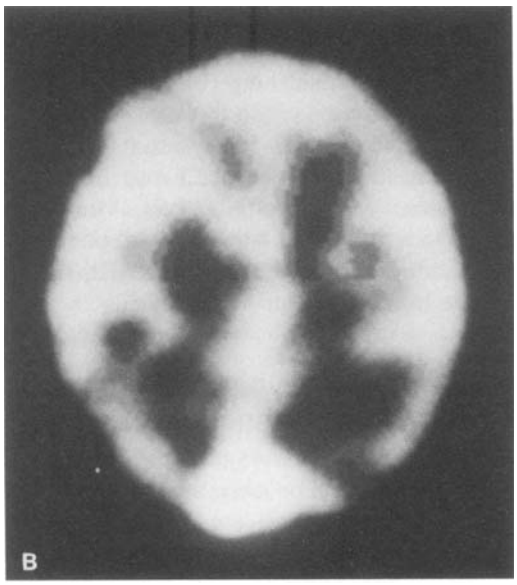


Fig. 2. A 59-year-old patient with right middle cerebral artery occlusion was studied during the acute stage. Functional prognosis was poor. The reduction of CBF in the right hemisphere (Fig. 2A) was associated with relatively mild increase in CBV (Fig. 2B) and with marked increase of cerebral Hct (Fig. 2C). Cerebral Hct in the right ischemic hemisphere was 60–85%, which was higher than the systemic Hct.

reduced flow compared to the non-ischemic hemisphere. Cerebral Hct did not show significant hemispheric asymmetry in patients with good clinical recovery. In patients with poor clinical prognosis, cerebral Hct was higher in the ischemic hemisphere when measured during the acute stage.

Fig. 2 illustrates cerebral hemodynamic images measured in a patient with right middle cerebral artery occlusion during the acute stage, who eventually showed poor functional prognosis. Regional reduction of CBF in the right hemisphere (Fig. 2A) was associated with relatively mild increase in CBV (Fig. 2B), and with marked increase of cerebral Hct in the right ischemic hemisphere (Fig. 2C). Cerebral Hct in the right ischemic hemisphere was calculated to be in the range 60–85% which was higher than systemic Hct.

Discussion

Our study demonstrated that the use of SPECT enables us to measure multiple hemodynamic parameters such as CBF, CBV and cerebral Hct

in humans. It was also suggested that the method can reveal variations of cerebral Hct during different physiological and pathological conditions. The cerebral-to-large vessel Hct ratio in the present study was 75.9%, which is lower than the previously reported standard value of 85% (2). It is likely that cerebral Hct measured by the three-dimensional method (5) presents more regional values closer to the true tissue Hct which is known to be lower than in large diameter vessels (6).

The reduction of large-vessel Hct by isovolemic hemodilution increased the cerebral-to-large vessel Hct ratio. The result indicates that changes in cerebral Hct are not linearly dependent on the changes in large-vessel Hct. Cerebral Hct in a non-ischemic state seems to remain unchanged despite the changes in large-vessel Hct. This is in agreement with the report by Rosenblum (7) who found that, when the blood viscosity was increased, normal difference between RBC velocity and plasma velocity became increased and cerebral Hct ratio became reduced. The reason for the increased plasma transit time in the brain tissue with increased blood viscosity may well be explained by an increase in plasma skimming.

In our preliminary study, two-dimensional measurements of MTT by RBC tracer and plasma tracer were also performed in patients with high systemic Hct before and after isovolemic hemodilution. Hct was reduced from an average of 52% to 40%. MTT was reduced by hemodilution, but the reduction was more in the plasma transit time than in the RBC transit time, indicating that the velocity ratio between RBC and plasma in the brain tissue became smaller after hemodilution. This result agrees well with the increase in cerebral-to-large vessel Hct ratio when large vessel Hct was reduced.

In the present study low CBF was associated with increased CBV during the acute stage of cerebral infarction and during symptom-free interval of TIA. It was also suggested that cerebral Hct was increased in the ischemic region of poor prognosis. In the region of cerebral ischemia, if cerebral blood volume is maximally increased, then the blood viscosity assumes greater importance in the determination of cerebral perfusion. The question of whether the increase of cerebral Hct in the ischemic tissue could be a predictor for further reduction in CBF, or is simply showing the result of completed stroke with blood stasis, should be answered in larger series of studies.

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Address:
Fumihiko Sakai, M.D.
Department of Medicine
School of Medicine
Kitasato University
1-15-1 Kitasato
Sagamihara, Kanagawa-ken
Japan (228)
Phone: 0427-78-8111