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Chapter 10

SPECT measurements of regional cerebral blood flow, blood volume and hematocrit in stroke

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The clinical importance of measurement of the regional cerebral hemodynamics, using positron emission tomography (PET) or single-photon emission computed tomography (SPECT), is to ascertain the viability of the ischemic tissue or to predict the functional outcome after ischemic cerebral vascular diseases. Specifically, the following aspects may be considered important: **1**) to determine the state of the hemodynamics in regions of the brain identified from clinical signs and symptoms as ischemic or infarcted, **2**) to determine whether the local flow is sufficient or at risk, **3**) to estimate the prognosis with or without intervention and **4**) to assess whether the risk of a second post-acute infarction has been reduced after treatment.

In addition to investigations of the regional cerebral blood flow (CBF), there is now a growing interest in the role of the cerebral blood volume (CBV) and blood viscosity in the pathophysiology of cerebral ischemia. Recent studies have focused on the effectiveness of hemorheological approaches, including hemodilution therapy, in the treatment of cerebral vascular diseases [1]. Employing PET, Gibbs et al. [2] and Powers et al. [3] suggested that the cerebral mean transit time derived from the ratio between CBF and CBV might serve as a sensitive parameter for estimating the circulatory reserve in the ischemic tissue.

In the present study, SPECT was used to measure the regional CBF, CBV and cerebral hematocrit in normals and patients with occlusive cerebral vascular diseases. Based on these three cerebral hemodynamic parameters, the regional pathophysiology during the acute stages of cerebral infarction and of transient ischemic attack (TIA) was evaluated.

Materials and Methods

Twenty-one neurologically normal subjects aged 32–43 years, 34 patients with cerebral infarction and five patients with TIA due to severe stenosis or occlusion of the internal carotid or middle cerebral arteries were studied.

The SPECT system employed in the present study was a GE Maxi 400T camera connected to an Informatec Simis 3 computer or a GE Starcam 400 AC/T camera system. The radius for 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 of horizontal sections of the brain parallel to the OM line for every 1.2 cm from the vertex. A filtered back projection method was employed for reconstruction of the images. The spatial resolution measured in a skull phantom, expressed by the full width at half maximum (FWHM) was 1.4 cm for the GE Starcam 400AC/T system, and the cold lesion detectability was a cylinder measuring 1.8 cm in diameter.

The regional CBF was measured using *N*-isopropyl-*p*-^{123}I-iodoamphetamine (IMP). SPECT scans of the head were performed three times following intravenous injection of IMP at 15 min, 2 h and 4 h. Arterial blood and jugular venous blood were sampled serially and each sample was subjected to octanol extraction to measure the proportion of IMP to its metabolites. Arterial IMP input curves were employed for calculating the regional CBF values [4].

CBV was measured using both a red blood cell (RBC) tracer and a plasma tracer [5]. For the RBC volume study, a sample of the subject's RBC was labelled with 20 mCi of ^{99m}Tc using stannous pyrophosphate as a reducing agent. For the plasma volume study, 20 mCi of ^{99m}Tc-labelled human serum albumin (HSA) was used as a plasma tracer. The label ratio for RBC remained constant during the first hour at 97.2±1.2% (n=10). The radioactivity of the labelled albumin reached a plateau within 7 min following the intravenous injection, and then remained constant thereafter for an interval of 45 min. A study by gel partition chromatography of plasma samples, obtained at 45 min after the injection of ^{99m}Tc-labelled HSA, revealed that the mean label ratio for albumin in the circulating blood was 96.1±2.4% (n=5).

The RBC volume study and plasma volume study were performed either separately at an interval of 48 h or serially on the same day. CBV was calculated according to Eqn. 1, which gives the ratio of the radioactivity per weight of brain to the estimated radioactivity per ml of cerebral whole blood [5,6].

$$CBV = \frac{C_{brain}}{@\cdot Hct\cdot C_{rbc}+(1-@\cdot Hct)\cdot C_{plasma}}\cdot 100 \quad (1)$$

where C_{brain} is the activity per g of brain determined by scanning and the denominator is the activity of the cerebral whole blood estimated from arterial blood counts. C_{rbc} and C_{plasma} are the activities per ml of RBC and plasma in the arterial blood. Hct is the large vessel hematocrit measured in the arterial samples. The constant @ represents the ratio of the cerebral small vessel hematocrit to the large vessel

hematocrit, and the factor of 100 converts the CBV values to ml/100 g brain.

If Eqn. 1 is applied to both the RBC and HSA studies for the calculation of CBV, the results should give the same CBV values if a correct @ is employed in the equation. Instead of inserting the standard value of 0.85 [7], we calculated the constant @ by using the two sets of data for the RBC and HSA studies [5].

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

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

Results

CBF measurements using IMP

Following intravenous injection of IMP in normals, the arterial activity reached an initial peak within 5 min. The jugular venous activity also showed a smaller but similar initial peak. After the initial peak, arterial activity was maintained but gradually approached an equilibrium with the jugular venous activity at around 45 min, indicating a balance between wash-in and wash-out of the cerebral activities. After 2 h, the jugular venous activity exceeded the arterial activity, indicating wash-out of the tracer from the brain. In the artery, the ratio of octanol-extracted radioactivity, which represents non-metabolized IMP, was 74±11% during the initial peak of 5 min, but gradually declined to 45% at 2 h. In the jugular vein, the percentage of IMP to metabolites was initially lower, but gradually rose. The mean value for the cerebral extraction fraction of IMP during the initial 5 min in normals (n=4) was 84.5±5%. The CBF calculated without correcting for extraction and binding underestimated the value by 10–12%. The mean CBF in normals corrected for the extraction ratio was 44.8±6.4 ml/100 g brain per min.

Relative changes for cerebral accumulation of IMP were calculated from the arterial-jugular venous differences. In normals, the cerebral activity of IMP formed a plateau during the first hour and thereafter showed a normal clearance curve. In patients with cerebral infarction, however, the increase in cerebral accumulation of IMP was slower, the plateau was lower and the clearance was delayed. Accumulation of metabolites was detected and became increased after 2 h, suggesting that the brain images after 3–4 h may be contaminated by metabolites of IMP.

In normals, the early brain images presented regional differences between the gray and white matter showing a normal flow distribution. In later scans, the distribution pattern disappeared and the IMP images became homogeneous.

During the acute stages of cerebral infarction, CBF reduction in the ischemic hemisphere measured from the early scan was seen in larger areas than the low density on the CT scan. The area of reduced IMP accumulation in the early scan was filled-in with IMP in later scans. Lack of late filling indicated a failure of the IMP binding capacity and a poor functional prognosis. In patients with good clinical recovery, the area of low flow in the early image showed late accumulation of IMP.

Hemispheric asymmetry became minimal in the images at 2 and 4 h. Late filling reached equilibrium within 2–3 h. In three patients, a region of hyperactivity was observed in the 4-h image corresponding to the ischemic region. Delayed accumulation of IMP metabolites was suggested by studies measuring the arterial-jugular venous differences in tracer activities. The prognosis was poor in these patients leaving a large area of low density on the CT scan.

CBV and cerebral hematocrit

The mean hemispheric CBV value in normals was 4.81±0.37 ml/100 g brain. The mean RBC volume in the resting state was 1.50±0.09 ml/100 g brain. This was significantly smaller than the mean of the plasma volume, which was 34±1.8 ml/100 g brain. The mean cerebral hematocrit calculated from these values was 31.3±1.8%, and the cerebral-to-large vessel hematocrit ratio was 75.9±2.1%.

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

CBV was increased in the ischemic hemisphere corresponding to the zone of reduced flow compared to the non-ischemic hemisphere. The cerebral hematocrit did not show any significant hemispheric asymmetry in patients with good clinical recovery. In patients with a poor clinical prognosis, the cerebral hematocrit was higher in the ischemic hemisphere during the acute stage.

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

Discussion

IMP-CBF studies

IMP has a very high brain extraction ratio. Early researchers estimated that within a few minutes of injection, 90% or more is taken up by an effective first-pass extraction [8]. However, by the time the SPECT imaging procedure is completed 30–45 min has elapsed, which is well beyond the 'first pass' period. Since the true first pass of the tracer through the brain should occur within 20–30 s, it is more appropriate to refer to what images immediately post-injection as an 'initial peak' or 'initial extraction' rather than 'first-pass extraction'. This initial extraction is a product of flow, diffusion and tissue binding. The extraction ratio calculated from our tracer activity studies was 84%, as opposed to 90% or more estimated by previous investigators [9]. The extraction ratio was consistent across the wide range of normal individuals

studied. Among patients with stroke, however, the values were lower ranging between 60 and 80%.

Even after the IMP dose peaks in the artery, it is possible to see a continuing background level of IMP delivered to the brain from some organs, mainly the lung. Following injection of IMP, only 5–7% of the dose goes to the brain. Most is trapped within the lung, which in turn acts like a continuous pump delivering IMP to the brain. Our studies have also indicated that, given sufficient time, even areas of very low perfusion have the ability to take up IMP [9]. Therefore, after a certain period, we can neglect the flow effect and observe only the binding capacity of IMP. We found a difference in IMP activity between the artery and internal jugular vein with time. Following the initial peak, the IMP levels in the two vessels gradually became closer, and reached equilibrium between 45 min and 2 h. We hypothesize that an IMP brain image obtained during that time would provide optimum information about the tissue binding capacity. Among patients with cerebral ischemic diseases, brain images made at 2 h post-injection exhibited the highest uniformity of uptake into areas of low perfusion.

Examination of the arterial activity and brain scans at 4–5 h after injection revealed continuing activity and uptake. However, between 50 and 70% of the radioactivity was shown to be IMP metabolites. Metabolites may accumulate in the non-viable tissue, since some of them are known to accumulate in acidic brain tissue via such mechanisms as pH shift.

CBV and cerebral hematocrit studies

Our study demonstrates that the use of SPECT enables us to measure the cerebral hematocrit in humans. It also appeared that the method can reveal variations of cerebral hematocrit during different physiological and pathological conditions. The cerebral-to-large vessel hematocrit ratio in the present study was 75.9%, which is lower than the previously reported standard value of 85% [7,10,11]. It seems likely that the cerebral hematocrit measured by three-dimensional resolution [12] presents more regional values closer to the true tissue hematocrit which is known to be lower than in large diameter vessels [13,14].

Reduction of the large vessel hematocrit by isovolemic hemodilution increased the cerebral-to-large vessel hematocrit ratio. The results indicate that changes in cerebral hematocrit are not linearly dependent on changes in large vessel hematocrit. The cerebral hematocrit in the non-ischemic state appears to remain unchanged despite changes in the large vessel hematocrit. This is in agreement with the report of Rosenblum [15] that, when the blood viscosity is increased, the normal difference between the RBC velocity and plasma velocity becomes increased and the cerebral hematocrit ratio becomes 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 the present study, a low CBF was associated with an increased CBV during the acute stage of cerebral infarction and during symptom-free intervals of TIA. It also appeared that the cerebral hematocrit increased in the ischemic region of poor prognosis. In the region of cerebral ischemia, if CBV is maximally increased, then

the blood viscosity assumes a greater importance in the determination of the cerebral perfusion. The question of whether increases of the cerebral hematocrit in the ischemic tissue could be a predictor for a further reduction in CBF or are simply reflecting the result of completed stroke with blood stasis should be answered by a larger series of studies.

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Discussion

Bollinger: You have shown two examples of patients with acute arterial occlusion, one concerning the middle cerebral and the other the internal carotid artery. In the first situation, there was practically no recovery of hypoperfusion during 2 h; but in the second, there was rapid recovery. Was this observation a constant one? In other words, is collateral development always better in occlusion of the internal carotid than in the middle cerebral artery as would be expected from anatomical differences?

Sakai: Measurement of the perfusion pressure will provide a final answer. In the case of internal carotid occlusion with good collaterals, the tissue perfusion pressure should be preserved at a relatively higher level than in occlusion of the middle cerebral artery without collaterals. What we have found so far is that for a case with good prognosis or more collaterals, the tissue hematocrit may not change and the increase in blood volume is sufficient, while the tissue-binding capacity for the tracer substance, iodoamphetamine (IMP), is preserved.

Chien: I would like to ask you about the arterial and venous concentrations of IMP. The two peak values are very close. Can the lack of complete extraction be explained by a lack of complete extraction in all pathways or the presence of 'shunt' pathways where there is no extraction while the other pathways are extracting nearly completely?

Sakai: With this particular tracer, a lack of extraction is due mainly to a lack of tissue binding capacity for the tracer amine: that is the whole basis for the measurement technique. The entire series of studies was to see if you can measure the blood flow; in other words, if the tissue binds the tracer. In that sense, I don't think I can answer your questions: we need better tracers.

Chien: If you use an intravascular tracer to obtain arterial and venous concentration curves, then you can deconvolute the data and obtain a distribution of intravascular transit time profiles. A comparison of the A-V data on IMP with the results for such an intravascular tracer may shed some light on the pathway taken by the non-extracted IMP.

Scremin: I noticed that you do not show quantitative values for blood flow in your slides. Can you tell us what additional information is necessary to obtain such values and what confidence can be placed on their accuracy?

Sakai: The whole point in doing this kind of study is to answer your question, and we don't have a final answer yet. For pathological tissues, it still seems difficult to get the extraction fraction and binding capacity of the tracer. The values obtained so far are normally 40–50 ml/100 g brain. Also, for the pathological tissue, we have to establish the baseline for the tissue binding and then recalculate the accumulation of the tracer in the early image to obtain the flow value.