Computed Tomographic Measurement of Local Cerebral Blood Flow by Xenon Enhancement

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SUMMARY The present technique was developed to overcome some of the disadvantages of measuring cerebral blood flow by radionuclide methods, such as poor localization of flow values and errors that result if the brain is pathological and local partition coefficients are altered.

Serial CT scanning in humans was carried out during and after inhalation of 50 to 70% non-radioactive xenon. This diffusible gas with high atomic number enhanced gray matter first by 19 ± 4 Hounsfield Units (HU) and later white matter by 24 ± 4 HU. The regionality of flow values were cursoried on CT pictures with a high spatial resolution of 4 × 4 mm (64 pixels) or 0.16 cm² × 0.5 cm. In seven normal subjects, blood flow in gray matter was 82 ± 11 ml/100 gm/min and that in white matter 24 ± 5 ml/100 gm/min. The partition coefficient (λ), which is not obtainable in vivo by radionuclide scanning, was 0.9 ± 0.1 for normal gray matter, 1.4 ± 0.2 for normal white matter. Reduced flow, 13% in gray matter and 46% in white matter, was found in a large infarct secondary to complete occlusion of middle cerebral artery. In edematous tissue, blood flow was not significantly impaired in gray matter but was reduced to 29 to 54% in white matter. Local λ values were reduced to 0.6-0.9 in edematous tissue, and 0.3-0.7 in infarction.

This method appears to have several advantages over conventional isotope methods of measuring cerebral blood flow and provides useful clinical and research information.

RADIONUCLIDE TECHNIQUES have been used to measure regional cerebral blood flow (rCBF) in clinical practice and research. Inhalation techniques have distinct advantages over methods that require carotid injection, the former being non-invasive and time-saving. However, isotope studies have inherent limitations, such as extracerebral contamination that creates measurement error, poor regionality of flow values, and an undetermined partition coefficient.

In order to overcome some of these limitations, serial computed tomographic scanning was carried out to estimate local CBF (LCBF) during inhalation of non-radioactive xenon gas in humans. Xenon is an anesthetic gas in high concentration but otherwise is chemically inert, freely diffusible in brain tissue and also radiopaque by virtue of high atomic number (54). The present method allowed not only quantitative determination of flow rate in relation to CT images, but also estimation of local partition coefficients λL, which have been demonstrated to vary considerably in pathological tissues.

This report presents the results obtained by this method, and discusses its potential usefulness as well as certain technical limitations encountered.

Material and Method

Normal values for LCBF were derived from 7 patients: two with pituitary adenoma, two with small AVM, one with an aneurysm, one with a jugular fora-
developed respiratory disturbance such as laryngospasm or bronchospasm, which was detected by a change in CO₂ in the expired air, 250 mg of amnoptyline was administered.

CT scans were performed using a Multi-purpose AS&E scanner with a 512X 512 matrix and 5 mm collimation. Exposure factors included a 10 sec scan time, 100 KVP, and 20mA. From the statistical point of view, region of interest larger than 4 × 4 mm (64 pixels) or 0.16 cm² × 0.5 cm (8 voxels) was cursored to derive the average CT numbers. To verify the stability of the derived CT numbers, a water phantom was scanned using the same time intervals as were used in human head. The deviation of average CT number was less than 1 Hounsfield Unit (HU: 1,000 scale). For the enhanced scans, a minimum increase of CT above base line CT were required to exceed the signal to noise ratio (p < 0.05). However, with sequential scanning, HU increase necessary for analysis of the saturation curve could be reduced to approximately 0.5 – 1 HU. To facilitate comparison of flow values among subjects, a standard scan slice was taken at the level of pineal body, including the basal ganglia. An additional slice at a higher level was taken during the saturation phase to verify the consistency and the reliability of flow values.

The saturation and desaturation curves were analyzed by a program developed by Obrist et al.¹ for the 133-xenon inhalation study of CBF that is based on the principle of inert gas exchange between blood and tissue set forth originally by Kety.² This program was modified for present applications. The LCBF can be derived from the time-dependent xenon concentrations in arterial blood and the tissue of interest. In the iso- tope method, each head curve must be analyzed in two or three compartments, i.e., gray matter, white matter and extracerebral tissue because each head probe counts the sum of activity from these compartments.¹, ² In the present method, one compartment can be assumed for each curve as long as sampling of the region on CT is restricted to a certain anatomical locale without contamination of other adjacent structures. For a monocompartmental perfusion:

\[ C(t) = f \int_0^t C_0(t-u)e^{-K(t-u)}du \]  

where \( C \) and \( C_0 \) are xenon concentrations of the tissue and blood respectively.¹ In order to reduce the statistical variation that is a consequence of having a limited number of data points, the curve was extrapolated linearly between scan intervals. It can be safely assumed that changes in attenuation coefficient parallel the xenon concentration in the tissue.¹⁴ The arterial xenon curve was replaced by the end-tidal xenon concentration, as was done in Obrist’s study.¹, ² The limitations of this procedure in the present study using high concentration of xenon are discussed below. \( K \) is the flow rate constant and \( f \) is blood flow in the particular region.

\[ f = \lambda K \]  

where \( \lambda \) is the tissue: blood partition coefficient, which is determined separately in the same region. The advantage of using the formula (1) in our study is that the head curve can be used even starting in the saturation phase or the beginning of desaturation phase, a time when the curve is distorted significantly by scattered radiation in isotope studies.¹, ² The spatial resolution of CT permits estimation of brain: blood partition coefficient in small regions of the brain. If equilibrium between the arterial blood and the selected brain region is established, then

\[ \lambda = \frac{\Delta HU \text{ brain}}{\Delta HU \text{ blood}} \]

Such an equilibrium is confirmed by obtaining consistent CT enhancement in blood and brain on serial CT scans performed during inhalation. In gray matter locales, equilibrium was obtained about 10 min after the air curve reached a plateau. On the other hand, equilibrium was not reached in white matter by the end of the period of xenon inhalation. Therefore, the CT number at equilibrium was estimated by extrapolating the saturation curve to infinity. This formula is expressed as:

\[ C_w(\infty) = \frac{C_w(t)}{1 - e^{-\frac{t}{a}}} \]

where \( C_w(t) \) and \( C_w(\infty) \) are the concentration of xenon at time \( t \) and infinity and \( a \) is a constant.

**Results**

During the period of inhalation, the concentration of xenon in the expired air was gradually raised to 37 ± 5% at 5 min and 56 ± 11% at peak. Arterial blood at equilibrium was found to be enhanced by 13 to 27 HU. Gray matter enhancement at equilibrium ranged from 13 to 23, averaged 19 ± 4 HU, and white matte: enhancement at the end of inhalation from 17 to 27, average being 24 ± 4 HU (fig. 2). The differential enhancement of gray and white matter could be visualized on the sequential CT scans (fig. 1). In the early stages of inhalation, gray matter was prominently enhanced with xenon, especially around 5 min, because of the faster blood flow. With continued inhalation for more than 20 min, white matter was gradually enhanced and to a higher degree due to the higher partition coefficient, i.e., solubility, which resulted in progressive loss of contrast between gray and white matter. After inhalation of xenon was stopped, the contrast was reversed due to the faster washout in gray matter, especially in cases with high flow. Gray matter approached saturation within 10 min while white matter took as long as 40 min to reach complete equilibrium (fig. 2).

Initially we employed the original Obrist’s program of two-compartment deconvolution model for analyzing the faster gray matter clearance and the slower white matter curve, although each curve was consid-
were in good agreement with those obtained by two-compartment analysis. It was possible to calculate a flow rate constant from build-up portion of the curve alone, or clearance portion, or the entire curve. The best computer fits were obtained from build-up curve rather than from the clearance curve.

Table 1 presents K, λ and blood flow values for 7 neurologically normal subjects obtained from build-up curve analysis by monocompartment program. Yielded blood flow values were in good agreement with those reported by Ingvar et al. and Obrist et al. Gray matter flow ranged from 66 to 95 with an average of 82 ± 11 ml/100 gm/min, while white matter flow from 17 to 32, averaged 24 ± 5 ml/100 gm/min.

As opposed to results obtained by the isotope 133-Xenon inhalation method, head curves were unaffected by extracerebral contamination. Therefore figures obtained by this method are comparable to those obtained by three-compartment analysis, which separate extracerebral flow from gray or white matter flow. In order to compute a flow rate constant from the clearance curve, data points 5 to 10 min before the start of desaturation were utilized for computation. Otherwise

<table>
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<tr>
<th>Patient</th>
<th>age</th>
<th>PaCO₂</th>
<th>Kg</th>
<th>Kw</th>
<th>λg</th>
<th>λw</th>
<th>Fg</th>
<th>Fw</th>
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<td>41</td>
<td>1.12</td>
<td>0.17</td>
<td>0.8</td>
<td>1.6</td>
<td>90</td>
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<td>1.12</td>
<td>0.14</td>
<td>0.8</td>
<td>1.2</td>
<td>90</td>
<td>17</td>
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<tr>
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<td>46</td>
<td>1.06</td>
<td>0.18</td>
<td>0.9</td>
<td>1.4</td>
<td>95</td>
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<td>K. S.</td>
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<td>0.66</td>
<td>0.20</td>
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<td>1.6</td>
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<td>44</td>
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<td>1.3</td>
<td>88</td>
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<tr>
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<td>75</td>
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<td>0.18</td>
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<td>0.04</td>
<td>0.1</td>
<td>0.2</td>
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Figure 1. Serial CT scan during and after xenon inhalation in a neurologically normal case. 5 min following inhalation, gray matter was enhanced first as indicated with white arrow in the right thalamus while white matter (double-headed arrow in the left internal capsule) was not enhanced yet. By 20 min, white matter was enhanced gradually and to a higher degree than gray matter. 2 min after inhalation was discontinued, fast clearance from gray matter was visualized, resulting in reversed contrast with 5 min scan.

Figure 2. Changes in Hounsfield unit (HU) and expired air (%) during 25 min inhalation of xenon and after discontinued. Gray matter curve reached plateau by 15 min, whereas white matter curve was still rising at 25 min. Typical curves from case Y. N.
the early part of the clearance curve was a poor fit because of the scarcity of data points, and the result was that consistently lower K values were computed. Since each scan was performed at intervals of minutes rather than seconds, time displacement of the air curve recommended by Obrist for 133-xenon inhalation studies was not employed. The partition coefficient for gray matter was 0.9 ± 0.1 (range 0.8–1.1), and white matter 1.4 ± 0.2 (range 1.2–1.6). The error involved in calculating λ is larger for white matter because of the extrapolation maneuver. It was difficult to obtain a consistent CT number from the blood samples due to sedimentation in the syringe during the 10 sec interval of scanning, but this was partially corrected by vigorous shaking before scanning. A significant escape of xenon was observed during the long delay between sampling and scanning unless the blood-filled syringes were kept in cold water.

When the inspired xenon concentration was raised above 20 to 30%, subjects displayed reduced responses and sometimes fell asleep. At concentrations between 30 to 40%, which took 5 to 10 min, subjects occasionally exhibited periods of excitability and restlessness. At higher xenon concentrations, they showed impaired responsiveness compatible with a light anesthetic level (first plane third stage anesthesia). Five to 10 min following cessation of inhalation, full consciousness was regained and by the end of study they were fully oriented. Ten to 15 min after xenon inhalation was started, bronchospasm was sometimes encountered, especially in young subjects. It was relieved in a few minutes by the intravenous administration of aminophylline in a dose of 250 to 500 mg. The PaCO2 occasionally rose by 10 mm Hg from the control period to the end of 25 to 30 min inhalation. However, blood flow values for both gray and white matter were most dependent on the data points obtained around 5 min, since these points are located near the turning point of exponential curve. Therefore, L, and LCBF values from two subjects that showed increases of PaCO2 of 5 mm Hg and 10 mm Hg after 20 min as a consequence of bronchospasm were discarded. One of them had a history of asthma that had not been symptomatic for years. Blood pressure and pulse rate remained stable throughout the study except in the two cases in which marked respiratory trouble occurred. PaO2 ranged from 256 to 417 mm Hg during 100% O2 inhalation and 170 to 240 mm Hg while 50 to 70% xenon mixed with O2 was inhaled.

The following two cases will be summarized, one with infarction and the other with edema after removal of a meningioma. They are presented to demonstrate K (flow rate constant), λ (partition coefficient) and flow values in normal and pathological tissues.

Case 1

This 54-year-old man with a cardiac arrhythmia sustained a sudden left hemiplegia without losing consciousness three months prior to admission. EKG revealed atrial fibrillation. A routine CT scan demonstrated large low density area in the right frontotemporal region that failed to enhance with iodine contrast (fig. 3). An angiogram showed obstruction of the right internal carotid artery at bifurcation of the middle and anterior cerebral arteries (ACA). The right ACA was found to be filled via left internal carotid artery through anterior communicating artery. The Xe-CT study revealed remarkably low flow rate constant (K) of 0.18 in the infarcted region, compared to a K value of 0.50 in the right caudate nucleus. K values for the posterior limb of the right internal capsule, which appeared infarcted on plain CT, was 0.27 min⁻¹, which is normal. The K values for white matter of frontal lobe, caudate nucleus and thalamic nucleus of the right hemisphere were not significantly different from those of the homologous sites for the left hemisphere. L estimates of both hemispheres were normal or slightly high except in the infarcted tissue and the right internal capsule. L in the infarction varied from 0.3 to 0.7, and it was 0.6 when the whole area of the infarction was censed. While blood flow, a product of LK and LA, was highly variable in each locale, it was consistently lower in the right hemisphere (occluded side) except for the right thalamus. In the infarction, blood flow estimate was remarkably reduced to 11 ml/100 gm/min, which was 13% of normal gray matter flow and 46% of normal white matter flow.

Case 2

A 33-year-old man underwent craniotomy and removal of meningioma in the right precentral parasagittal region in 1977. Follow-up CT three years later revealed recurrence of the tumor with additional growth in the opposite parasagittal region, involving superior sagittal sinus. Total removal of tumor was carried out 2 weeks prior to Xe-CT study. At the time of study there was a mild weakness in both lower
extremities, more marked on the left. Plain CT scan revealed a low density area in the left parasagittal gray matter. It is uncertain whether the slight hypodensity present in white matter is within the normal range or is the result of edema (fig. 4A). The extent of the edema became obvious during xenon enhancement. White matter of the right frontal lobe was enhanced to the same extent as normal white matter by 20 min, while increases of attenuation coefficients in white matter of other regions were small (fig. 4C). $L_A$ in edematous white matter was decreased to 0.6 to 0.9, together with decreased $K$ values, resulted in blood flow value of 7 to 17 ml/100 gm/min or 29% to 54% of normal white matter flow. On the other hand, $L_A$ of the right frontal white matter was 1.6, resulting in near normal flow of 28 ml/100 gm/min. The right interhemispheric gray matter appeared normal on plain CT, but blood flow study revealed markedly decreased perfusion, 17 ml/100 gm/min, compared with 39 in the left gray matter. This may explain the fact that weakness of lower extremity was exaggerated on the left.

**Discussion**

CBF measurements with CT have several advantages over conventional isotope methods. Since the isotope detector in the 133-xenon inhalation method sees structures in 2 dimensions across the head, the clearance curve may be contaminated by radioactivity from the opposite hemisphere (so-called cross-talk), or from structures adjacent to the focus (look-through), or from extracerebral sources. Thus if prefixed values were used, as is the case with 133Xe isotope methods, $L_A$ is not measurable so that assumed values of 0.8 for gray and 1.5 for white matter, are assigned with correction for hematocrit values for each patient. $L_A$ values for normal tissues obtained by the present “in vivo” method were close to those described above, which were originally derived from homogenized gray matter or white matter obtained post-mortem as an “in vitro” study. Therefore, the partition coefficient appear not to be influenced so much by viability of tissues but rather by their fat content.

Another advantage of the CT method is the capability of obtaining localized tissue: blood partition coefficients, which are impossible to measure by conventional isotope methods. Blood flow rate is a product of $K$ (flow rate constant) multiplied by $L_A$ (partition coefficient). In the $^{133}$Xe isotope methods, $L_A$ is not measurable so that assumed values of 0.8 for gray and 1.5 for white matter, are assigned with correction for hematocrit values for each patient. $L_A$ values for normal tissues obtained by the present “in vivo” method were close to those described above, which were originally derived from homogenized gray matter or white matter obtained post-mortem as an “in vitro” study. Therefore, the partition coefficient appear not to be influenced so much by viability of tissues but rather by their fat content. CT-phantom studies using xenon in equilibrium at atmospheric pressure in mixtures of known fat content demonstrated that change in attenuation factor was linearly related to fat content.

The fact that $L_A$ for white matter is 1.5 to 2.0 times that for gray matter is also considered to reflect the total lipid content of 7% for gray matter and 17% for white matter. $L_A$ values change in pathological brain tissues, as the composition is different from that for normal tissue. $L_A$ measured here varied from 0.3 to 0.7 in infarcted tissue, and 0.6 to 0.9 in edematous tissue. Thus if prefixed values were used, as is the case with isotope method, blood flow values derived could be artifically doubled or tripled.

Xenon enhancement has proven useful to differentiate abnormal tissue from normal tissue by utilizing differences of xenon solubility of various tis-
Fat concentration is diminished to various degrees in lesions of the central nervous system diseases such as multiple sclerosis, edema, or infarction. Multiple sclerosis plaques which are isodense and not detected by plain CT have been reported to be revealed with xenon enhancement. In the present report, as shown in figure 4, the extent of edema was more clearly defined after 20 minutes of xenon inhalation.

Clearance rates for either gray matter or white matter have been shown to be monoexponential or composed principally of one compartment. In the present studies, significant amounts of slow component were found to contaminate gray matter flow in two-compartment analysis. This may be partly due to the limited number of data points available or to the problems of curve fitting for gray matter, which contains more diverse flow rates than white matter. A more likely explanation is that the slow compartment found in gray matter was derived from partial-volume averaging with inclusion of adjacent white matter.

Anesthetic properties of xenon gas have been extensively studied in humans. The level of anesthesia achieved by high concentration of xenon has been reported to be sufficient for surgical purposes. The influence of the anesthetic property of xenon on CBF was assessed by Meyer et al. When 80% stable xenon was administered to unanesthetized baboons for intervals between 1.5 to 10 min, analysis of clearance curves revealed a progressive decline in CBF values with the longer time intervals. The authors recommended brief periods of inhalation or the use of xenon concentrations between 30%–50%. However, xenon concentrations used appeared to have little effect on CBF measured by our method since values obtained from the build-up curve are in good agreement with data obtained in awake subjects as reported by other authors using the 133-xenon method. The xenon concentrations were gradually increased and was 37 ± 5% at 5 min. The level of anesthesia was observed to be minimal around 5 min, when the data points are particularly critical in the determination of CBF values from build-up curve analysis. Therefore it is suggested that anesthetic effects may be minimized by using the build-up curve rather than the clearance curve, which avoids or minimizes any sedative effects of the preceding xenon inhalation. Furthermore, we were unable to obtain reliable estimates of CBF from clearance curves because of poor computer fit.

One of the drawbacks of our method is derived from respiratory changes induced by bronchospasm. In the early phase of this study, respiratory effects were encountered at times as a consequence of the high concentration of xenon, 70% or more, administered through a face mask. It was found later that sufficient enhancement could be achieved with fewer side effects by the inhalation of xenon in a 50% concentration. Bronchospasm, if it occurred, was easily reversed by aminophylline within one or two min following its detection by capnography. Changes in carbon dioxide tension have a great effect on the diameter of cerebral arteries and thus on blood flow. In our study, PaCO₂ was observed to change gradually in most cases during and after inhalation of xenon. However, the change was in the range of 2 to 3 mm Hg after 5 min when the data points were crucial to determine CBF values. Oxygen tension was also raised in a range of 170 to 240 mm Hg during inhalation of 50 to 70% xenon with supplemental O₂. However, other work suggests that oxygen tension in the range observed in the present method has no direct effect upon cerebral blood flow.

We tried rapidly increasing the concentration of inhaled xenon hoping to avoid bronchospasm, but this resulted in differences in xenon concentrations in blood and in the expired gas. Furthermore, a short period of xenon inhalation with extrapolation of the white matter curve to infinity makes estimation of λ unreliable, as equilibrium of xenon in gray matter takes only 10 min and that in white matter as much as 40 min. As our results showed, xenon inhalation of 20 min or more was required if calculations were to be based on the respiratory gas curve instead of blood samples. Estimation of the arterial xenon gas concentration from samples of end-tidal air was not always accurate. Arterial blood curves tend to lag behind the air curve to some extent, with the result that end-tidal xenon measurements overestimated arterial blood xenon concentration during inhalation and underestimated it during clearance. Kg values based on the air curve were consistently lower than those computed from arterial measurements. Since a high concentration of xenon is used, the exchange rate of the gas between blood and air at the pulmonary interface may be slow and require a significant length of time to come to equilibrium. Particularly in the presence of severe pulmonary disease, air curves may be an unacceptable substitute for the arterial blood concentration.

In our study, there is fair agreement between the end-tidal and arterial xenon curve in healthy young subjects. Patients who exhibited respiratory trouble during the study revealed large discrepancies between the two curves. In radioactive xenon studies of blood flow, the concentration in blood appears to parallel that in inspired or expired gas, possibly because of much lower concentration of xenon that are used.

Krypton is an inert gas with a high atomic number and therefore expected to be a gas that could be used for the enhancement of CT scans. In contrast to xenon, it has an advantage of not having a narcotic effect. We administered a krypton to one subject. Although the concentration of expired gas rose to 40% after 40 min, no enhancement was demonstrated either in blood or the head CT scan. The solubility of krypton in water, thus in blood, is one half that of xenon. Furthermore, krypton, with atomic number of 36, is one half as radiopaque as xenon. Small amount may be absorbed from the lungs into the body, but the concentration is insufficient to increase the attenuation coefficient.

An alternative method of performing CBF studies with an autoradiographic technique may have less limitations. Since autoradiography requires only a few serial scans, it not only reduces the total radiation dose but also enables multilevel scanning. We have also analyzed the collected data by an autoradiographic
technique that requires only three scans, i.e., a base line scan, an intermediate scan after 5 minutes, and a scan at equilibrium. Computation of K is much simpler as both input (xenon blood concentration) and output (head curve) functions are characterized as exponential. Although this method provided flow rates close to that found by curve fitting method, the overall error introduced is increased almost two-fold.

Xenon used in a closed rebreathing system required approximately 20 liters for each study. Each CBF measurement costs $200, which is twice the cost of 30 mCi of 133-xenon required for an inhalation study, both being imported in Japan. This method is expensive at present, since the market for xenon is rather limited. However, the cost should fall considerably with wider medical use since raw supplies of xenon in ambient air for purification and commercial production is inexhaustible.

Thus, the stable xenon CT method appears to have several advantages over conventional CBF measurement utilizing radionuclide techniques, and it can provide useful clinical and research information. For example, this study might be particularly helpful to determine the need for superficial temporal artery to middle cerebral artery bypass and to evaluate its benefits, along with angiographic studies.

Acknowledgements

The author wishes to express great appreciation to Dr. Walter D. Obrist, University of Pennsylvania, for the consultation, to Dr. Russel H. Patterson, Cornell Medical Center, for reviewing article and to Ms. Mari Iwai and Kumiko Saegusa for their secretarial assistance.

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Computed tomographic measurement of local cerebral blood flow by xenon enhancement.
H Segawa, S Wakai, A Tamura, N Yoshimasu, O Nakamura and M Ohta

Stroke. 1983;14:356-362
doi: 10.1161/01.STR.14.3.356

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