Clinical Application of Stable Xenon CT-CBF Studies without Denitrogenation

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Abstract
Noninvasive and simplified methods for estimating regional cerebral blood flow (CBF) and regional partition coefficient (λ) using the inhalation of stable xenon (Xe\textsuperscript{s}) and computed tomographic (CT) scanning are described. Thirty percent Xe\textsuperscript{s} in 70% oxygen was inhaled for 240 seconds and exhaled for 160 seconds during serial CT scanning without denitrogenation in 26 patients with cerebrovascular diseases and four volunteer controls. During the investigation, the end-tidal Xe\textsuperscript{s} concentration was continuously monitored with a thermoconductivity analyzer to determine the build-up range (A value) and build-up rate constant (K value) of the artery by the curve fitting method. Calculated A and K values were corrected by the following formulae reported previously: for patients aged 0-20 years, \( A_e = 0.75A_a + 2.15 \), \( K_e = 0.67K_a + 0.69 \); 21-40 years, \( A_e = 0.56A_a + 3.24 \), \( K_e = 0.38K_a + 1.12 \); 41-60 years, \( A_e = 0.91A_a + 1.95 \), \( K_e = 0.38K_a + 1.32 \); over 61 years, \( A_e = 0.52A_a + 3.81 \), \( K_e = 0.31K_a + 1.55 \) (\( A_e \) and \( K_e \) were calculated with end-tidal Xe\textsuperscript{s} concentration, \( A_a \) and \( K_a \) were calculated by direct sampling of arterial blood). A CBF map (f map) and λ map made with corrected A and K values demonstrated reliable distribution. The CBF was high in the gray matter, low in the white matter, and much lower in the infarcted area. λ was high in the white matter, low in the gray matter, and much lower in the infarcted area. Eight patients were examined with and without denitrogenation. Both the f map and λ map with denitrogenation were compatible with those without denitrogenation. Xe\textsuperscript{s} CT-CBF studies without denitrogenation are useful in clinical neurosurgery and outpatients for estimating regional cerebral circulation.

Key words: cerebral blood flow, computed tomography, denitrogenation, stable xenon

Introduction
Three dimensional regional cerebral blood flow (CBF) measurement using stable xenon (Xe\textsuperscript{s}), an inert and diffusable gas, and computed tomographic (CT) scanning is widely used clinically because of its excellent spatial resolution and potential for determining regional partition coefficients. The Xe\textsuperscript{s} concentrations in arterial blood or in the end-tidal expired gas are measured, with the latter most commonly used at present.\textsuperscript{3,5,7,8,10,16} We have been developing and evaluating a method of analysis by which the build-up range (A value) and build-up rate constant (K value) can simultaneously be calculated from time-series data of short-term (4 minutes) inhalation of low-concentration Xe\textsuperscript{s} (30%).\textsuperscript{11,13} Denitrogenation, usually performed for 15-20 minutes before Xe\textsuperscript{s} inhalation, and the inhalation of pure oxygen may cause discomfort for the patient. This may cause movement resulting in the test being stopped, or images being difficult to interpret because of artifacts. Here, we report our newly developed three dimensional regional CBF measurement method using short-term inhalation of low-concentration Xe\textsuperscript{s} without denitrogenation.

Materials and Methods
The Xe\textsuperscript{s} CT-CBF measurements were performed 41 times in 30 subjects, consisting of 26 with ischemic cerebrovascular diseases in the acute (11 cases) and chronic (15 cases) stages and four healthy volunteers. The ischemic cerebrovascular diseases were internal carotid artery occlusion in six cases, middle cerebral artery occlusion or stenosis in 16, and perforating artery occlusion in four.

Two optional slices were selected as the region of interest in the head. The subjects inhaled room
air without denitrogenation followed by a mixture of 30% Xe and 70% oxygen for 240 seconds. Serial
scanning was performed a total of 6 times including 3 times in the washin process, twice in the washout
process of 160 seconds, and once before Xe inhalation. The program of serial scanning consisted of a
total of 12 scans consisting of 6 serial scans on each slice (Fig. 1). The Xe concentration in the end-tidal expired gas was continuously recorded by the thermoconducivity method, and the arterial A and K values were calculated from these time-series data. The Xe concentration in the arterial blood $C_a(t)$ or in the brain tissue $C_i(t)$ during the washin and washout processes was converted to the CT number on serial scans using the following equations:

$$h_a(t) = A_a(e^{-K_at(t-r)} - e^{-K_at})$$

where $\tau = t (0 < t < T)$ or $\tau = T (T < t) (T = 240$ seconds), $A_a$: build-up range, $K_a$: build-up rate constant in the arterial blood.

$$h_i(t) = A_i \left( g(t - \tau) - g(t) \right)$$

where $g(t) = e^{-K_i t} + K_i (e^{-K_i t} - e^{-K_at})/(K_a - K_i)$, $A_i$: build-up range ($\lambda_i A_a$), $K_i$: build-up rate constant in cerebral tissue.

The continuous time-series data of the Xe concentration in the end-tidal expired gas and the continuous time-series data in the Xe washin and washout processes were subjected to curve fitting by the least squares method, and the A and K values were calculated simultaneously by the following equations:

$$E_1 = \sum_{m=1}^{n} [h_a(t_m) - A_a(e^{-K_at_m} - e^{-K_at})]^2$$

$$E_2 = \sum_{m=1}^{n} [h_i(t_m) - A_i(g(t_m) - g(t)))]^2$$

where there were n measured values of $h_a(t_m)$ and $h_i(t_m)$. The A and K values which minimized the $E_1$ and $E_2$ values satisfied the condition $(\partial E/\partial A = \partial E/\partial K = 0)$.

In all cases, the arterial A and K values obtained from the Xe concentration in the end-tidal expired gas were adjusted by our correction formula.$^{12}$ Using these values the regional CBF ($f_i$) was calculated using

$$f_i = 100 \cdot \lambda_i \cdot K_i \quad (ml/100 gm/min)$$

where $\lambda_i$: partition coefficient of Xe.$^{13}$

Based on this principle, Xe CT-CBF measurements were performed a total of 41 times on the 30 subjects, and the accuracy of the partition coefficient ($\lambda$) map and CBF ($f$) map obtained were evaluated. The Xe delivery system used was the AZ-723 model (Anzai Sogyo, Tokyo, Japan) and the CT equipment was CT/T 9000 (Yokogawa Medical System, Tokyo, Japan).

In eight of the 30 subjects, Xe CT-CBF measurements with denitrogenation for 15-20 minutes using the AZ-721 model (Anzai Sogyo) were also performed 30 minutes after the measurements without denitrogenation using the AZ-723 model. The arterial A ($A_1$) and K ($K_1$) values obtained from the former measurements were compared with those values ($A_2$, $K_2$) obtained from the latter measurements.

**Results**

The $\lambda$ maps and $f$ maps obtained as a result of Xe CT-CBF measurements without denitrogenation in 30 subjects showed reliable distributions. In the $\lambda$ map, the distribution was high in the white matter, low in the gray matter, and even lower in the infarcted area. The distribution in the thalamus was intermediate between those in the white and gray matters. In the $f$ map, the distribution was high in the gray matter, low in the white matter, and even lower in the infarcted area. The increase in the CT number 240 seconds after the Xe inhalation was at least 3.6 Hounsfield units (HU) in the white matter, and the average for 41 measurements was 4.8 ± 0.6 HU. Figure 2 shows the A and K values obtained offline from time-series data of the Xe concentration in the end-tidal expired gas and the serial scans of a 34-year-old male volunteer.

In the eight cases where Xe CT-CBF measurements without and with denitrogenation were repeated using the AZ-721 and AZ-723, the relationship between $A_1$ and $A_2$ was $A_2 = 1.00 - A_1 - 0.0625$ ($n = 8, r = 0.965, p < 0.001$), which showed a significant positive primary correlation (Fig. 3 left). The relationship between $K_1$ and $K_2$ was $K_2 = 1.00 - K_1 - 0.0756$ ($n = 8, r = 0.992, p < 0.001$), which also showed a rather significant positive primary correlation, but $K_1$ was larger than $K_2$ in all cases (Fig. 3).
Figure 4 shows the Xe\textsuperscript{e} CT-CBF measurements without and with conventional denitrogenation in a 34-year-old male volunteer. We describe two representative cases.

Case 1: A 65-year-old male had a transient ischemic attack (TIA) with left hemiplegia and dysarthria. The symptoms completely disappeared in about 60 minutes. A CT-CBF study showed a low perfusion area in the watershed area between the right anterior and middle cerebral arteries, and in the right parietal region, but there were no abnormalities on CT scans (Fig. 5 left). Seven days after the TIA, improvement of the low perfusion area and basically bilateral symmetry were observed (Fig. 5 right). Cerebral angiography found 90% stenosis at the end of the horizontal portion of the right middle cerebral artery.

Case 2: A 42-year-old female was brought to our hospital immediately after the onset of a somnolent state and left hemiparesis. CT scans and an Xe\textsuperscript{e} CT-CBF study without denitrogenation were performed 5 hours after the onset. Although only a slight low-density area in the deep region of the right hemisphere was seen on CT scans, extensive low perfusion in a watershed area between the right anterior and middle cerebral arteries, and in the territory of the right middle cerebral artery were observed in the CBF study (Fig. 6). Cerebral angiography showed the right internal carotid artery occlusion.
Fig. 5 Case 1, a 65-year-old male of transient ischemic attack with left hemiplegia and dysarthria. left: Xe$^1$ CT-CBF study when the signs and symptoms had just disappeared, showing a relatively low CBF area in the watershed between the right anterior cerebral artery and ipsilateral middle cerebral artery, and in the right parietal lobe. right: Xe$^1$ CT-CBF study 7 days after the attack. \( f \) maps demonstrating no abnormal CBF area.

Fig. 6 Case 2, a 42-year-old female with left hemiparesis and somnolence. Xe$^1$ CT-CBF study 5 hours after the onset demonstrating a large low perfusion area in the right middle cerebral artery territory.

Discussion

Methods to obtain continuous time-series data of the Xe$^1$ concentration in the arterial blood include 1) the direct sampling of blood,\(^3\) 2) the shuttle method\(^9\) \textit{in situ} with direct scans of the intracranial carotid arteries simultaneously with head scans, and 3) measurement of the Xe$^1$ concentration in the end-tidal expired gas with a thermoconductivity analyzer.\(^2\)\(^6\) Using the third method, we prepared \( \lambda \) maps and \( f \) maps based on arterial \( A \) and \( K \) values with a correction formula measured by serial blood sampling.\(^1\)\(^4\) When the \( A \) and \( K \) values obtained by serial blood sampling are taken as \( A_a \) and \( K_a \) and those obtained from the Xe$^1$ concentration in the end-tidal expired gas as \( A_e \) and \( K_e \), the values were 1) \( A_e = 0.75A_a + 2.15, K_e = 0.67K_a + 0.69 \) for 0–20 years of age, 2) \( A_e = 0.56A_a + 3.24, K_e = 0.38K_a + 1.12 \) for 21–40 years, 3) \( A_e = 0.91A_a + 1.95, K_e = 0.38K_a + 1.32 \) for 41–60 years, and 4) \( A_e = 0.52A_a + 3.81, K_e = 0.31K_a + 1.55 \) for 61 or older. \( A_e \) and \( K_e \) values were obtained from the patient’s age and \( A_a \) and \( K_a \).
and were considered as the real A and K values. The important problem of whether or not the Xe concentration in the end-tidal expired gas accurately reflects the Xe concentration in the arterial blood could be solved by means of the correction formula, but the denitrogenation process before CBF measurement takes 15–20 minutes, and as the patients suffer discomfort at this stage the subsequent CBF measurements are often disturbed. Therefore, we devised a method of Xe CT-CBF measurement without denitrogenation to solve this problem.

It is well known that the increase of gas concentration in the pulmonary alveoli is generally slower when inhalation of an anesthetic gas is started without denitrogenation than after denitrogenation, so adequate denitrogenation is presently carried out before anesthesia.\(^1,4\)

When inhalation of 30% Xe and 70% oxygen mixture is started without denitrogenation, there should be a washout of nitrogen during the washin of Xe, and the Xe concentration in the pulmonary alveoli should decrease. \(^1,4\) However, the Xe concentration in the end-tidal expired gas and the increase in the head CT number showed adequate increases according to the results of the present study. A reliable distribution was also seen in the \(\lambda\) maps and \(f\) maps obtained on the basis of these results. In the \(\lambda\) map, the distribution was high in the white matter, low in the gray matter, and even lower in the infarcted area, while in the \(f\) map, it was high in the gray matter and low in the white matter. In eight of the 30 subjects, Xe CT-CBF measurements were performed both with or without denitrogenation, and the \(\lambda\) maps and \(f\) maps were almost the same as shown in Fig. 4. Since the \(\lambda\) maps and \(f\) maps matched the symptoms seen during the acute stage of cerebral infarction and TIA without any abnormalities on CT scans, it appears that Xe CT-CBF studies without denitrogenation provide a highly reliable, simple method of routine CBF measurements on an outpatient basis which is 15–20 minutes shorter than the conventional methods and reduces discomfort at this stage the subsequent CBF measurements.

References


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