Xenon Enhanced CT for Analysis of Cerebral Integrity, Perfusion, and Blood Flow

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SUMMARY Enhancement of the brain substance for CT evaluation using inhaled Xenon is confirmed. This technique was applied to the study of the normal and the embolized adolescent baboon. Healthy cerebral tissue enhances symmetrically, while abnormal areas show significantly diminished enhancement. At maximal enhancement, an indication of gross comparative cerebral perfusion is obtained. By obtaining serial CT scans over a 10 minute time interval, the clearance rate of Xenon (cerebral blood flow) may be evaluated. Xenon-enhanced CT enables a visual and numerical analysis of both brain morphology and physiology.

SINCE THE INITIAL application by Kety and Schmidt, various techniques to measure cerebral blood flow have been utilized with varying success. Although intra-arterial methods appear reasonably reproducible, they may be difficult, time-consuming and morbid. Inulation techniques, though far less invasive, present difficulties in data analysis due to recirculation and extracranial activity. All radionuclide methods, whether done by intra-arterial injection or inhalation, are limited by the non-morphologic nature of isotope studies. This makes it difficult to distinguish precisely which brain locality has produced the externally detected activity.

The introduction of cranial computed tomography (CT) has enabled accurate morphologic definition of the brain and its surroundings. As the iodinated contrast agents routinely used for intravenous CT enhancement do not diffuse into the brain substance, they are not ideal for the measurement of cerebral blood flow. CT enhancement may also be obtained using diffusible Xenon administered by inhalation. Thus, problems generated by the third component of circulation external to the brain and by the lack of anatomic specificity are readily overcome by CT imaging. This preliminary study will describe a CT technique to define cerebral perfusion and cerebral blood flow in the nonhuman primate as monitored by Xenon-enhanced CT.

Methods

Experimental Subjects

Cerebral blood flow measurements were obtained on 2 adolescent baboons (Papio anubis/cynocephalus) weighing 7.8 and 8.6 kg. One animal was a healthy control with no evidence of neurologic dysfunction. The second baboon was studied 103 days following successful embolization of the left middle cerebral artery via injection of a silastic-tantalum embolus (205PE) through the left internal carotid artery. The position of the embolus was monitored by CT (fig. 1) as evidence of neurologic dysfunction. The second baboon was studied 103 days following successful embolization of the left middle cerebral artery via injection of a silastic-tantalum embolus (205PE) through the left internal carotid artery. The position of the embolus was monitored by CT (fig. 1) as

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FIGURE 1. Embolus, Left Middle Cerebral Artery. A silastic-tantulum embolus (arrow) is seen by CT in the location of the horizontal portion of the left middle cerebral artery. Angiography confirmed the presence of the embolus completely occluding the horizontal middle cerebral artery.

95%. Commercial (non-radioactive) Xenon was then added to the system. A concentration of approximately 80% Xenon was attained as estimated from the decrease in the measured oxygen concentration.

When the Xenon concentration equilibrated at 80%, an immediate CT scan (maximum Xenon) was performed at the same section level as the baseline. The inhalation of Xenon was then abruptly discontinued and replaced by the inhalation of 100% oxygen (5 liter flow rate). As the Xenon was washing out, serial CT scans (at the same cut level) were performed at 0.3, 2.0, 3.7, 5.4, 7.1, 8.8, and 10.5 minutes following discontinuing Xenon inhalation, i.e., 2.0 minutes means a scan was begun at 1 minute and 40 seconds and completed at 2 minutes and 20 seconds.

A matching image region in the anterior left and right hemispheres, including gray and white matter, was then compared both by visual (various window settings) and numerical (print-out averaging) methods to evaluate brain enhancement with Xenon. The mean and histogram were obtained from comparable 95 to 100 voxel regions in each hemisphere. These same regions were studied on each of the successive serial CT scans to produce a Xenon clearance profile. Cerebral blood flow (ml/100 gm per minute) was then analyzed by two methods:8

\[
\text{1. CBF} = \frac{\Delta H}{\Delta A} \times 100 \times \lambda \\
\text{2. CBF} = \frac{(0.693) \times \lambda}{T_w} \times 100
\]

The partition coefficient of Xenon (\(\lambda\)) was based on the hemoglobin level.8 No correction was made for recirculation, \(\text{Paco}_2\), phencyclidine HCl sedation, or halothane (1%) anesthesia.

Results

Baseline CT and Neurologic Condition

The baseline CT scan and neurologic status of the healthy, control baboon were normal. The successfully embolized baboon (embolus in horizontal portion of left middle cerebral artery) never showed any abnormality in his neurologic examination. The serial CT scans at 4, 7, 10, 45, and 103 days were repeatedly normal (fig. 2).

Xenon Brain Enhancement

In the control animal, the maximum CT enhancement at approximately 80% Xenon concentration was symmetric in the two cerebral hemispheres (table 1). Both deep and superficial brain substance seemed to enhance to the same degree at this level of Xenon inhalation. In the embolized baboon, there was definite asymmetrical enhancement of the two cerebral hemispheres at 80% Xenon concentration. The non-embolized right hemisphere had a maximal enhancement of 11.0 EMI units above baseline. The left hemisphere in the distribution of the left middle cerebral artery, both superficial and deep, showed diminished maximal enhancement (9.4 EMI units) as compared to the right. A small area in the left opercula region had an enhancement of only 7.8 EMI units. This poorly enhanced region was accentuated on the delayed (3.7, 5.4, 7.1, and 8.8 minute) serial washout scans (figs. 3, 4).

Cerebral Xenon Clearance

The cerebral clearance curves for Xenon were similar in both animals as calculated by both compartmental (TV4) and stochastic (H/A) methods (table 1). Due to scanner speed and processing limitations, only 3 early scans (Maximum, 0.3 and 2.0 minute) were available for the evaluation of the fast component of Xenon clearance (washout). Nevertheless, a distinct fast and slow component of cerebral blood flow was readily demonstrated (table 2). In addition, stochastic analysis defined the combined gray and white flow as similar in both hemispheres of both baboons. Using measure mode (WW 0, WL 27) reproductions, a visual assessment of the Xenon washout was also readily obtained (fig. 4).

Gas Analysis

The \(\text{Pao}_2\) and expired air \(\text{O}_2\) were never lower than 78 torr when breathing pure Xenon thus reflecting some leakage in the inhalation system. This was not of consequence as an approximately 80% Xenon concentration was more than adequate for CT enhancement and washout observations. In both baboons, the serial blood gas measurement made at the time of each washout CT scan showed a progressive increase in \(\text{Pao}_2\) and expired \(\text{O}_2\) concentrations (table 1). This increase in \(\text{O}_2\) reflects the decrease in Xenon concentration and coincided with the diminishing attenuation coefficient noted by CT scan. The \(\text{Paco}_2\) remained fairly constant in an essentially physiologic range (table 1).

Discussion

One of the early limitations of CT scanning was its primarily anatomic orientation. However, with the use of intravenous contrast enhancement, physiologic information can be derived.8 It has also been suggested that cerebral
blood volumes may be measured using intravenous enhancement. However, intravenous water-soluble contrast agents are not freely diffusible into the brain substance and are thereby inadequate for the evaluation of cerebral blood flow. Intrathecal contrast enhancement with metrizamide (Amipaque, Sterling-Winthrop Research

### TABLE 2. Xenon Enhanced CT Analysis of Cerebral Blood Flow (Compartmental Analysis)

A comparison of the blood flow curves in the right (no embolus) versus the left (embolus horizontal MCA) hemisphere using semilogarithmic analysis of the information in Table 1B and Figure 4. Although maximal perfusion of the right side is greater than the left, calculated cerebral blood flow (fast and slow component) was very similar.
FIGURE 3. Baseline CT (Before Xenon Enhancement) A. A CT section of the level of the lateral ventricles photographed at WW75 and WL28. B. A specimen radiograph of a baboon at a similar level to CT section plane showing the normal anatomic structures. C. The same CT section as in A now photographed using measure mode and WL27. D. A reversal photograph (measure mode, WL27) of Figure 3C (Baseline for Figure 4).
The diminished Xenon enhancement in the left middle cerebral artery distribution (embolus horizontal left MCA, fig. 1) as compared to the right is evident on all scans indicating diminished perfusion. The progressive diminution of Xenon enhancement in both hemispheres over a 10 minute clearance (washout) interval is readily demonstrated even by visual analysis of the scans. The complimentary numerical data (table 1) permits the calculation of cerebral blood flow. 

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Maximal Xenon Enhancement</th>
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<tr>
<td>0.0</td>
<td>Maximal Xenon Enhancement (estimated 80% Xenon concentration).</td>
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<tr>
<td>0.3</td>
<td>Following the inhalation of 100% oxygen to wash out the Xenon.</td>
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<td>2.0, 3.7, 5.4, 7.1, 8.8 and 10.5</td>
<td>CT scans show the progressive clearance of Xenon with 100% oxygen inhalation. By 10.5 minutes the CT has almost returned to the baseline appearance (see figure 3.)</td>
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Xenon-enhanced CT scanning appears to have 3 basic compartments using inhalation methodology; fast (predominantly gray matter washout), slow (predominantly white matter washout), and slower (predominantly extracerebral sources).

Actual brain imaging using radionuclides requires cyclotron-produced radionuclides introduced by intracarotid injection. Even with adequate collimation, the morphologic resolution of radionuclide techniques seems extremely limited when compared to CT scanning. Since non-labelled Xenon readily enhances the brain substance by freely diffusing across the blood-brain barrier, CT scanning provides a simple and reliable method for monitoring this enhancement. The presence and rate of clearance of Xenon from small regions of gray and white matter may be monitored by knowing the anatomy of the brain as defined by the CT scan. Even prior to the utilization of the numerical CT data, a visual analysis can separate the faster gray matter washout from the slower white (fig. 4) as well as compare the Xenon enhancement of the right versus the left hemisphere.
applications: (1) evaluation of capillary-brain tissue integrity, (2) evaluation of gross comparative cerebral perfusion, and (3) evaluation of cerebral blood flow.

1. A baboon with a cerebral embolus had repeatedly normal CT scans and clinical examinations. However, a Xenon enhanced CT scan revealed a small area of minimally perfused brain in the opercular region. The location of the abnormality was consistent with the characteristic location of infarction in the baboon following occlusion of the middle cerebral artery as documented by previous CT scan and pathologic studies. Therefore, Xenon-enhanced CT scanning appears to be an important adjunct to routine and enhanced CT scanning, especially when subtle tissue abnormalities of either gray or white matter are sought.

2. A symmetrical, bilateral, total regional brain perfusion should occur in a normal primate. The deep and superficial diminished enhancement in the distribution of the embolized left middle cerebral artery is expected even though the leptomeningeal anastomosis aids in the perfusion of a non-human primate hemisphere with vascular compromise. Thus, a simple technique is now available to evaluate the gross perfusion of comparable areas of the same brain. Potential applications include the evaluation of transient ischemic attacks, surgical vascular procedures, cerebral autoregulation, and cerebral edema.

3. The cerebral blood flow estimations as calculated using serial Xenon-enhanced CT scans correlated closely with those reported for baboons using the hydrogen clearance method. The findings of normal cerebral blood flow with chronic infarction in the baboon has been previously reported. The analysis obtained more accurately (i.e. consistent with previous nonhuman primate studies of cerebral blood flow) reflects the slow component of flow. This, however, is merely a limitation of scanner speed and the smallest size of a region of brain from which an accurate mean of attenuation coefficients may be obtained. Scans will be performed in from 2 to 10 seconds with newer CT scanners. This should enable the acquisition of multiple attenuation values during the initial 2 to 3 minutes permitting a more significant fast component analysis. The extracranial Xenon flow is obviously not a problem as CT scanning, especially when subtle tissue abnormalities of either gray or white matter are sought.

Xenon enhanced CT scanning has definite shortcomings with adverse reactions and value radiodiagnostically. Radiology 105: 580-582, (May) 1951

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Is There a Real Treatment for Stroke? Clinical and Statistical Comparison of Different Treatments in 300 Patients

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SUMMARY In the absence of universally accepted criteria for the medical treatment of stroke, we made a rigorously randomized comparative study of different treatments in 300 patients. One group of patients received only a general supportive treatment designed to ensure adequate supplies of water, electrolytes and calories, plus whatever was needed to prevent infection and correct extant associated pathology. Three other groups of patients were treated in the same way but were also given, respectively, one of the following medications: Hydergine (Sandoz) (a mixture of three ergot alkaloids), dexamethasone, and mannitol.

No statistically significant difference emerged among any of the treatment groups and the reference group in terms of objective therapeutic results. The authors concluded that, at least with the dosage used in this study, none of the treatments proved more useful than conventional supportive therapy in the first 10 days after a stroke.

TREATING PATIENTS with stroke is often unrewarding. As in other fields of medicine, the lack of a basic reference treatment for stroke has generated a multitude of drug therapies, each being thought of as a cure, only to be soon abandoned. It is likely that some deaths in the first several days after a stroke are due to cerebral edema around the infarcted area rather than to the infarct itself.1-3 Edema reaches its peak about 3 to 4 days after the stroke, and can be responsible for transtentorial herniation of the brain, rostrocaudal deterioration, and impaired cerebral blood flow. Drugs thought to reduce edema reduce intracranial pressure which can indirectly improve brain circulation. Those used in recent years include mannitol,4-7 corticosteroids,8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 and Hydergine9 22-23 each with conflicting reports of clinical effectiveness. We have studied these 3 therapies using 1) a large number of patients; 2) random selection for treatment; 3) each drug alone; 4) results from reliable clinical parameters; 5) data evaluated by a correctly designed statistical program.

Materials and Methods

We studied 300 patients with a diagnosis of stroke, hospitalized in the Emergency Medicine Division of the Policlinico Hospital in Milan, during 1974 and 1975. The mean age for the whole group was 71 years. There were 110 men (mean age 69) and 190 women (mean age 73). Of these 241 were diagnosed as having an ischemic stroke, 189 in the carotid artery territory, 40 in the vertebrobasilar territory. In 12 the classification was uncertain. At hospitalization, each patient was assigned randomly to one of the following 4 treatment groups:

Group A. These patients received adequate water and electrolyte replenishment by intravenous infusion for the first 48-72 hours, and then a suitable caloric intake, in the form of a special standard diet if necessary, administered by stomach tube. These patients also received suitable antibiotics and additional treatments, such as digitalis, diuretics, tracheal aspiration and instillation of mucolytic agents, and bedsore prevention.

Group B. These patients received the same treatment as those in group A, plus a proprietary mixture of dihydroergocornine, dihydroergocristine and dihydroergocryptine, 0.3 mg each (Hydergine) in a daily dosage of 6 ampoules representing 1.8 mg of each alkaloid in the mixture.

Group C. In group C received the same treatment as group A plus dexamethasone 24 mg daily, given in divided doses.

Group D. Patients received the same treatment as group A plus a solution of 20% hypertonic mannitol given i.v. 0.8-0.9 g/kg daily.

In all groups treatment was instituted between 3 and 24 hours after onset of symptoms. The period of observation was 10 days for all 4 groups.
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