Mapping Local Blood Flow of Human Brain by CT Scanning During Stable Xenon Inhalation

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SUMMARY Non-invasive methods are described for estimating local cerebral blood flows (LCBF) and partition coefficients (LX) during inhalation of 35% stable xenon gas (Xe*). After denitrogenation by 100% oxygen breathing, 35% Xe is breathed for 7–8 minutes to minimize subanesthetic effects. Mean changes in brain Hounsfield units extrapolated to 15 minutes were 7.7 units for white matter and 5.3 units for gray matter. They were measured from volumes 80 cubic mm (10 mm³ area × 8 mm length) or larger with an EMI 1010 scanner at 1 minute intervals. These data were used for computing LCBFs and LXs. Irradiation measured at the center of brain slices was 1 rad per minute. To calculate LXs about 6 exposures are necessary, thereafter, each 1 minute scan provides LCBF measurements for 2 adjacent 8 mm slices. Reproducibility for LCBF was r = 0.85 (p < 0.001). Mean LXs were 0.86 ± 0.08 for gray and 1.34 ± 0.10 for white matter. Normative mean flows (mls/100 g brain/min) were: basal ganglia = 79.6 ± 9.3, cortex = 82.3 ± 8.5, white matter = 29.2 ± 5.9, mildbrain tegmentum = 94.3 ± 14.8, cerebellar cortex = 80.1 ± 10.9, dorsal pons = 89.3 ± 4.7, brachium pontis = 35.0 ± 4.2. Subject finger exercises produced increases of LCBF in contralateral pre-central and post-central gyrus. Eye closure decreased flow values limited to the visual system. Gray matter flow values diffusely decreased in non-REM sleep but increased above normal in REM sleep. Cerebral infarction and hemorrhage resulted in zones of zero flow with borders having reduced LXs and low flows attributed to edema.

THE MOST WIDELY used methods for measuring regional cerebral blood flow (rCBF) include the 133Xe inhalation or intravenous injection methods. Because they are atraumatic they have largely replaced the intra-carotid 133Xe bolus injection method. They also have an added advantage of measuring gray and white matter flow of multiple regions of both hemispheres and brain stem-cerebellar regions rather than only that part of the hemisphere perfused by the injected artery.

However, there are some technical problems common to the use of radioactive tracers where emission from the brain is detected by the use of external probes. These problems include poor resolution due to Compton scatter, tissue overlap, and contamination by extracranial blood flow. As a result, the best resolution is seldom better than 7 cubic cm. There are additional problems that lessen the accuracy of rCBF measurements in abnormal brain because tissue: blood partition coefficients (solubility or μ) are not measured, and frequently are altered in abnormal brain. While modifications are being pursued at the present time to improve the resolution of the 133Xe inhalation method by single emission counting with a computer assisted tomograph of special design,™ improvements in resolution are not yet as satisfactory as those obtained by x-ray transmission computerized tomography. Best resolution provided by the EMI clinical CT scanner is circa 10 mm² area × 8 mm depth (80 cubic mm).

For these reasons, Drayer and associates, Kelcz et al., Haughton et al. and this laboratory have attempted to develop methods that take advantage of the excellent resolving powers of conventional x-ray transmission CT scanners by combining them with the contrast properties of stable xenon gas, which diffuses rapidly through tissues following its inhalation. Preliminary studies in the baboon model have indicated that local CBF (LCBF) can be measured with high resolution during inhalation of a sub-anesthetic mixture of 35% stable xenon (Xe*) in 65% oxygen. By inhaling low concentrations of the Xe* gas for 7–8 minutes, anesthetic effects may be minimized or avoided. A clinically applicable and non-invasive method for measuring LCBF and local λ (LX) values is now reported.

Methods Used For Xe* CT Scanning To Measure LCBF and LX

Measurements of LCBF and LX have been made in 37 carefully selected subjects including normal volunteers (N = 9), acute cerebral infarction (N = 4), chronic cerebral infarction (N = 2), cerebral hemorrhage (N = 2), carotid transient ischemic attacks (N = 4), verteobasilar insufficiency (N = 2), verteobasilar migraine (N = 1), brain tumor (N = 4), narcolepsy (N = 4), sleep apnea (N = 5).

There have been no complications. The measurements were carried out on both out-patients (N = 18) and in-patients (N = 19).

After signing informed consent* and fasting for 6
hours to avoid vomiting during the procedure, each patient was placed in the EMI 1010 CT Scanner. EEG, ECG, eye movements and chin EMG were monitored throughout and blood pressure was measured before and after each CBF measurement. Patients and volunteers who spontaneously fell asleep were encouraged to do so, in order that any effects of sleep on LCBF could be evaluated. A flat rubber facemask, designed to slide through a notch in the CT aperture, was selected to ensure a tight fit for each patient. The mask was fitted with valves and an aspiration pump to allow end-tidal sampling of PeO2, PeCO2 and PeXe.

The end-tidal Xe* was measured with a Gow-Mac thermoconductivity analyzer. The inspiratory and expiratory gas concentrations, calibrated in volumes percent, were recorded on a polygraph. Anesthetic tubing was used to deliver a mixture of 35% Xe* in oxygen from a gas tank fitted with valve controls and flow meters. A 35% Xe* mixture was found to be optimal after evaluating different Xe* concentrations in the first group of subjects. This mixture minimized subanesthetic effects and changes of the Hounsfield units of blood and brain were satisfactorily measured with the EMI scanner set at the 1 minute scanning mode. The Xe* mixture was inhaled from a small volume, continuous replenishment, partial rebreathing system with one-way valves at both intake and output and a 3-way stop-cock that could be interchanged rapidly from room air to 100% oxygen and to 35% Xe* inhalation. A pressure release valve, which opened above atmospheric pressure, insured that positive pressure did not develop. As soon as the subject was comfortably installed in the EMI scanner, 100% oxygen was breathed for 20 minutes to remove almost all nitrogen from the body. This was confirmed when the PeO2 values remained constant at 97% or greater. Preliminary denitrogenation is important, as this increases the rate and efficiency of tissue saturation with Xe* and avoids nitrogen build up in the partial rebreathing system. Valves were also fitted to the input and output tubing close to the mask in order to monitor the inspired and expired gas mixtures (PIO2, PIXe and PEO2, PEXe). Because xenon gas is expensive, the cost per series of LCBF and LA measurements for 2 back-to-back, 8 mm thick, slices of the brain was estimated to be $50–75. However, once LA was measured, LCBF measurements of the same region may be repeated after brief 3–4 minutes inhalation of Xe*, at a much lower cost, of about $25 for each measurement. This is because estimation of LA requires more prolonged inhalation, with consumption of twice the volume of Xe*, than is necessary for measuring LCBF.

In practice, 3 control scans were regularly made in order to establish baseline values in Hounsfield units for all regions of interest prior to beginning 35% Xe* inhalation, which was then continued for 7–8 minutes until brain and blood levels were saturated near to a plateau or could be extrapolated to a plateau. Inhalation intervals of 7–8 minutes were considered optimal in order to minimize sub-anesthetic symptoms, yet estimate A values with good reproducibility. Saturation curves expressed in ΔH units were then converted at 6–10 second intervals from the end-tidal Xe* values (assumed to be in equilibrium with the arterial blood) by methods to be described. The brain tissue ΔH was measured from selected regions of interest, for both gray and white matter. Gray matter ΔH changes usually approached equilibrium within 8 minutes but white matter ΔH changes require extrapolation to saturation at infinity.

If concentrations higher than 35% Xe* were used, respiratory slowing and restlessness were likely to ensue. There are differences in Xe* tolerance and a few patients described a feeling of light-headedness or numbness of the extremities during inhalation of 35% Xe* for 7–8 minutes. Since it is an anesthetic gas, inhalation of Xe* in mixtures above 45% for 6 minutes or longer produces temporary agitation, confusion, EEG slowing, and decreases of LCBF values by circa 20%, similar to reports in the baboon. If concentrations above 60% are used, loss of consciousness and anesthesia eventually will result.

The end-tidal (PexE) curve has been shown to be in equilibrium with the arterial blood. After conversion into ΔH for arterial blood, from PexE curves, the exact temporal relationships with serial CT scans of the brain were obtained, which are necessary in order to correct for recirculation and to calculate LA and LCBF values. End-tidal values for PexE, PeCO2, PeO2 and the timing of each scan were recorded on the polygraph (fig. 1). Usually about 5 one-minute scans were made during saturation and 3 during desaturation. However, irradiation may be minimized to a total of 5 scans, which will give satisfactory data for LCBF and LA measurements (2 control, and 3 between 2–8 minutes of Xe* inhalation). With the EMI 1010 scanner used, the measured irradiation to the center of the brain (measured with a phantom) is 1 rad per minute. There is virtually no exposure to other organs, and a series of LCBF measurements gave irradiation exposure to the head comparable to that occurring during standard cerebral angiography. Irradiation of the lens and cornea of the eye were avoided by appropriate positioning of the head.

For human use, the EMI 1010 CT unit was fitted with an 8 mm collimator. The x-ray beam was adjusted to 113 kVp (mean) and to 32 mA (mean) with a 60 second scanning mode. Two adjacent sections, 8 mm thick, were scanned with each exposure. Mean standard deviation in the steady state for the human brain measured by 3 repeated scans, prior to Xe* inhalation, was < 1.3 H unit for regions of interest 80 cubic mm or larger.

According to Kelcz et al.,11 reproducibility error measured as ΔEMI/ΔH for the EMI Mark 1 CT scanner they used, was circa 6.32 at 120 kVp. The improved EMI 1010 scanner used in the present
justed to 120 kVp and to 256 mA, during 11 sequential studies, when similarly tested with 11 serial 1 min notes and programs for computer analysis of LCBF and LX values.

Available from ASIS/NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, N.Y. 10017.

*See NAPS Document No. 03640 for 11 pages of explanatory notes and programs for computer analysis of LCBF and LX values. Available from ASIS/NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, N.Y. 10017.

**Copies of this latest computer program, using double integration of air and brain data points, are available on written request to the authors.
Polysurgical recording during CT Xe$^8$ CBF and LA measurements in a 41 year old male

**Fig. 1.** Polysurgical recording to show from above down: samples of EEG, EKG, BP and continuous graphs of end-tidal CO$_2$ (PcO$_2$), inspired oxygen (Pio$_2$), end tidal oxygen (PeO$_2$), inspired Xe$^8$ (Pixe$^8$), end-tidal Xe$^8$ (Pexe$^8$). CT scanning intervals are shown by the square wave signal at base of chart with time base in minutes.

mean intervals, for arterial blood; which can then be substituted for Ca (t) in the *in vivo* autoradiographic equation $C_v (T) = \lambda_{a,t} / \lambda_{a} C_o e^{(-\lambda_{a} T)} dt$ and/or in the monoexponential model of Obrist. $C_v (T)$ are the values for $\Delta H$ that are directly measured from regions of interest in brain tissue by CT scanning. Both *in vivo* autoradiographic and monoexponential models have been programmed for DEC 10 Computer analysis (NAPS Document No. 03640).

**Results**

Mean $\Delta H$ change for blood samples during inhalation of 35% Xe$^8$ in oxygen for 7-8 minutes in 9 normal volunteers was $6.0 \pm 1.0$ units (fig. 2) and for the total of all tested, N = 11 (9 normals, 2 patients), was $6.3 \pm 0.8$ units (fig. 3). Figure 2 summarizes mean $\Delta H$ values for the arterial blood plotted by indirect calculation from Pexe$^8$ values measured in 9 normal volunteers. Corresponding maximal $\Delta$ changes for white matter were $7.7 \pm 0.2$ and for gray matter were $5.3 \pm 0.4$ (extrapolated to tissue equilibrium at 15 min carried out by visual curve fitting) and after 2.4 minutes were $3.5 \pm 0.7$ and $2.6 \pm 0.6$ for white matter (fig. 4). For ethical reasons and to avoid possible side effects, prolonged inhalation of Xe$^8$ to complete tissue saturation for 15-30 minutes was not carried out, but

**Fig. 2.** To show reconstructed curve for arterial changes in mean $\Delta H$ units during 35% Xe$^8$ inhalation expressed as percentage change (y axis) with standard deviations plotted against time in minutes (x axis), recorded in normal subjects (N = 9). Corresponding mean 1 minute CT scanning intervals are also indicated in black on the x axis.
A H VALUES MEASURED AT SATURATION IN BLOOD OF HUMAN VOLUNTEERS BY DIRECT CT SCANNING DURING 35% Xe\textsuperscript{8} INHALATION (N = 11)

**FIGURE 3.** Mean ΔH units measured directly in blood samples at saturation in 11 subjects during 35% Xe\textsuperscript{8} inhalation.

was estimated by extrapolation of the actual plotted curves from 8 to infinity (fig. 4). This is important because the formula for calculation of Lλ values requires knowledge of ΔH changes in blood and tissue at saturation, during inhalation of an Xe\textsuperscript{8} mixture of known concentration.\textsuperscript{9,11,14} If λ is estimated before tissue saturation is complete, λ values may be underestimated. If concentrations of Xe\textsuperscript{8} exceeded 45–50%, as was tested in the first few subjects,\textsuperscript{14} mean LCBF values for white and gray matter were measurably reduced in the order of −20% (p < 0.001) due to sub-anesthetic effects of higher concentrations of gas.

**Normal Values For Human LCBF And λ**

Optimal scanning times, with the most satisfactory reproducibility, for calculating in vivo autoradiographic LCBF values from serial 1 minute scans, were found to be from the second to the fifth minute (mean 2.4 minutes for second scan and 4.1 for third scan) for both gray and white matter (fig. 5A,B). The methods used for calculating cerebral flow were based on theoretical considerations discussed by Kety\textsuperscript{9} and computer solutions of the Fick formula as reviewed by Obrist et al.\textsuperscript{1} Stable relationships were found to exist between arterial input and tissue curves between the second and fifth minutes. Measurements made during the first minute were overestimated because of misalignment of the head and air curves, delays in the rise time, errors in matching brain scans and blood ΔH changes, plus unsatisfactory signal-to-noise ratios. High values measured in the first minute would be expected if the air curve lags behind the head curve. LCBF values calculated at 4.1 minutes were in good agreement with those calculated at 2.4 minutes (fig. 5A,B). Saturation LCBF values calculated after 2.4 minutes (designated LCBF\textsubscript{S4}) were found to be in excellent agreement with LCBF values calculated during the first 4.5 minutes of desaturation using the monoeXponential formula (p < 0.001, \( r = 0.883 \)).

This correlation is illustrated in figure 6 where desaturation monoeXponential LCBF values (designated LCBF\textsubscript{ME}) show good correlation with saturation values, where both were measured in the steady state.

Normative values measured in 9 normal healthy volunteers are illustrated in tables 1 and 2. Reproducibility for LCBF measurements repeated in the steady state during 2 separate inhalations of Xe\textsuperscript{8}, 20 minutes apart, was \( r = 0.85 \) (p < 0.001). White matter LCBF values were in the range of 35.8 ± 6.1 and Lλ values were 1.29 ± 0.04, extrapolated to 15 minutes (table 1) and 29.2 ± 5.9 and 1.34 extrapolated to infinity (table 2). In the relaxed state, with the eyes open, occipital and frontal cortical values showed higher values than...
ESTIMATED OPTIMAL SCANNING INTERVAL DETERMINED FROM SERIAL 1 MINUTE AUTORADIOGRAPHIC LCBF MEASUREMENTS FOR A) GRAY MATTER AND B) WHITE MATTER IN NORMALS

FIGURE 5A AND B. To show optimal scanning intervals determined from serial 1 minute scans, with plots of mean LCBF values (with standard deviations), computed by the in-vivo autoradiographic method for white matter (A) and gray matter (B) in normal subjects. The optimal intervals for scanning appear to lie between 2.4 and 4.1 minutes.

Changes in LCBF During Activation And Sleep

These measurements recorded in the steady state with eyes open were compared to those measured when the eyes were closed in semi-darkness in 8 normal volunteers (fig. 7A,B) and during activity of either the left or right hand in 2 normal volunteers and 3 sleep apneics (fig. 8). During slow wave sleep measured in 8 subjects, all Fg values decreased. When the fingers were exercised there were significant increases in the contralateral sensory-motor cortex in the hand area.

The thalamus showed consistent regions of inhomogeneous flow. These regional differences in LCBF were attributed to different levels of activity of the various thalamic nuclei, since they appeared to correlate with LCBF values of their corresponding projection areas which were measured concurrently. For example, the visual cortex, pulvinar of the thalamus, geniculate bodies and colliculi showed relatively high flows with the eyes open. These regions decreased significantly when the eyes were closed (figs. 7B and 9). Likewise, the frontal cortex, dorsomedial and anterior nuclear regions of the thalamus showed high flows and these decreased during slow wave sleep in normal volunteers (N = 2).

Patients with sleep apnea, in the awake state, showed reduced gray matter flow values in frontal, temporal and occipital regions as well as in the thalamus, caudate, lentiform nucleus and lateral geniculate bodies compared to the awake state in normal volunteers. These patients also showed progressive reduction of gray matter flow during sleep stages I-III, with the most marked reductions in occipital cortex, basal ganglia, mid-brain, pons and cerebellum. Sleep apneics showed greater reductions of LCBF during non-REM sleep than normals. These findings are considered to be consonant with earlier observations reported with the 133Xe technique.25, 29

All 4 narcoleptics showed REM-onset sleep with diffuse increases of LCBF (+15 to 25%). Maximal increases were measured in pons and midbrain. These...
TABLE 1. Normative Values for LCBF<sub>24</sub> (mls/100g brain/min) and L<sub>K</sub> measured in normal, healthy volunteers while awake (N = 9, 8M IF)

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean BCEF&lt;sub&gt;24&lt;/sub&gt; ± SD</th>
<th>Mean L&lt;sub&gt;K&lt;/sub&gt; ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex</td>
<td>81.9 ± 7.3</td>
<td>0.89 ± 0.07</td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>79.5 ± 7.9</td>
<td>0.89 ± 0.05</td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>79.1 ± 6.1</td>
<td>0.88 ± 0.06</td>
</tr>
<tr>
<td>Occipital Cortex</td>
<td>82.6 ± 9.8</td>
<td>0.88 ± 0.06</td>
</tr>
<tr>
<td>Average Cortex</td>
<td>81.3 ± 8.5</td>
<td>0.89 ± 0.06</td>
</tr>
<tr>
<td>Average White Matter</td>
<td>35.8 ± 6.1</td>
<td>1.29 ± 0.04</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>79.6 ± 9.3</td>
<td>0.90 ± 0.05</td>
</tr>
<tr>
<td>Thalamus</td>
<td>84.2 ± 9.8</td>
<td>0.91 ± 0.07</td>
</tr>
<tr>
<td>Cerebellar Cortex</td>
<td>72.0 ± 17.0</td>
<td>0.88 ± 0.08</td>
</tr>
</tbody>
</table>

Mean Age 38.3 ± 10.8 yrs, MABP 84.8 ± 7.6 mm Hg, Mean PCO<sub>2</sub> 36.8 ± 3.2 mm Hg.

Measurements Of LCBF And L<sub>K</sub> IN Cerebrovascular Disease

All 6 patients with cerebral infarction and both patients with cerebral hemorrhage showed zones of zero flow which could be volumetrically estimated in 3 dimensions by measuring the horizontal area and the observations also appeared to be consistent with earlier reports of 133Xe measurements.8, 10

TABLE 2. Normative Values Measured by Single Compartment Analysis and Double Integration for Air to Brain Values in Normal Healthy Awake Volunteers Without Risk Factors (N = 9)

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean BCEF&lt;sub&gt;24&lt;/sub&gt; ± SD</th>
<th>Mean L&lt;sub&gt;K&lt;/sub&gt; ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex</td>
<td>81.5 ± 8.8</td>
<td>0.854 ± 0.07</td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>77.9 ± 7.6</td>
<td>0.839 ± 0.07</td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>81.5 ± 8.8</td>
<td>0.854 ± 0.07</td>
</tr>
<tr>
<td>Lateral Occipital Cortex</td>
<td>84.8 ± 7.0</td>
<td>0.842 ± 0.08</td>
</tr>
<tr>
<td>Striate Cortex</td>
<td>86.0 ± 7.9</td>
<td>0.877 ± 0.08</td>
</tr>
<tr>
<td>Caudate Nucleus</td>
<td>88.3 ± 4.4</td>
<td>0.908 ± 0.07</td>
</tr>
<tr>
<td>Lentiform Nucleus</td>
<td>85.1 ± 10.5</td>
<td>0.943 ± 0.107</td>
</tr>
<tr>
<td>Thalamus</td>
<td>85.8 ± 8.0</td>
<td>0.901 ± 0.06</td>
</tr>
<tr>
<td>Cerebellar Cortex</td>
<td>80.1 ± 10.9</td>
<td>0.977 ± 0.07</td>
</tr>
<tr>
<td>Midbrain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tectum, Tegmentum (Dorsal)</td>
<td>94.3 ± 14.8</td>
<td>0.884 ± 0.073</td>
</tr>
<tr>
<td>Cerebral Peduncle (Ventral)</td>
<td>41.7 ± 10.4</td>
<td>1.382 ± 0.051</td>
</tr>
<tr>
<td>Lateral Geniculate Body</td>
<td>106.2 ± 14.6</td>
<td>0.884 ± 0.082</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>90.4 ± 7.9</td>
<td>0.876 ± 0.065</td>
</tr>
<tr>
<td>Average Cortex</td>
<td>82.3 ± 8.5</td>
<td>0.862 ± 0.081</td>
</tr>
<tr>
<td>Average White Matter</td>
<td>29.2 ± 5.9</td>
<td>1.338 ± 0.102</td>
</tr>
</tbody>
</table>

*Data analyzed at infinity by special computer program developed for this purpose.

Figures 7A and B. To show LCBF<sub>24</sub> changes for the entire visual system (A) during eye closure in normal volunteers; with the eyes open the visual system shows increased regional flow which is statistically significant, (p < 0.01). Regional changes in the various components of the visual system are shown in B.
Percentage Change of LCBF during Voluntary Finger Exercises
(2 Normal Volunteers, 3 Sleep Apneics)

<table>
<thead>
<tr>
<th></th>
<th>Contralateral</th>
<th>Ipsilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentral</td>
<td>+27.4 ± 34.6%</td>
<td>-1.8 ± 17.3</td>
</tr>
<tr>
<td>Postcentral</td>
<td>n = 5</td>
<td>n = 4</td>
</tr>
<tr>
<td>Cortex</td>
<td>+6.9 ± 17.7%</td>
<td>+6.1 ± 21.5</td>
</tr>
<tr>
<td>n = 13</td>
<td></td>
<td>n = 12</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>-14.3 ± 0.1%</td>
<td>+7.4 ± 20.4</td>
</tr>
<tr>
<td>n = 2</td>
<td></td>
<td>n = 4</td>
</tr>
<tr>
<td>Anterior Mesial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal Cortex</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 8.** To show percentage increases (+27%) for LCBF of the contralateral pre- and post-central gyri during repetitive finger flexion and extension. The high standard deviation is due to minor head movement during exercise.

Known depth (8 mm) of adjacent scans. Areas of acute infarction and hemorrhage were surrounded by zones of reduced flow and reduced λ values which were attributed to changes in tissue solubility brought about by either edema or gliosis, which were estimated from the duration of the stroke.18, 19-21 Similar results have been reported from this and other laboratories, in previous studies following experimental cerebral embolism in the baboon during Xe* CT scanning.7, 9, 10, 12 Reduced λ values were reported in the baboon model where it was possible to continue inhalation of Xe* for 10 minutes or longer to assure saturation or near saturation of ischemic and edematous tissue which was not carried out in human subjects for ethical reasons.7, 9, 19

Reduced λ values were measured in ischemic zones not only in acute infarction but also in regions of chronic infarction, where gliosis was assumed to be the cause, since this has been shown to be the case in the baboon.9, 10 Figure 10 illustrates measurements of LCBF and λ in one of our patients with extensive, bilateral cerebral infarction from cerebral emboli of cardiac origin 2 years previously.

In an hypertensive patient with a clinical diagnosis of multiple lacunar infarctions, 2 separate zones measuring 2-3 cubic cm in volume were detected, both zones showed reduced flow and λ values which correlated with the expected anatomical loci based on the clinical neurological deficits. Neither of these zones was readily apparent in the plain CT scans although on retrospective review of the CT scans several low density lesions were detected.

In another patient with hemianopia and hemiparesis there was a zone of zero flow in the internal capsule and adjacent optic radiations. LCBF values were also reduced despite normal λ values in the ipsilateral visual projection systems including occipital cortex, pulvinar, lateral geniculate body and superior colliculi. These reductions of LCBF with normal λ values in the visual system remote from the infarction were attributed to deafferentation.

**Figure 9.** To illustrate brain maps of LCBF and λ measured in a 34 year old, right-handed, normal healthy male volunteer at rest with eyes closed in a darkened room. EEG showed alpha activity.
In patients with acute, severe hemispheric infarction or hemorrhage there were sometimes contralateral (mirror-image) reductions of Lx values in the opposite hemisphere associated with reduced flow values. These were attributed to diachisis and edema, consonant with previously reported measurements using the $^{133}$Xe inhalation method. Patients with transient ischemic attacks (TIAs) showed normal Lx values for both gray and white matter (n = 6). Patients with remote TIAs (3 weeks or longer since the ictus) showed a tendency to regional reduction of LCBF values appropriate to their symptoms. In patients with recent TIAs (within 2 weeks) some focal regions of hyperemia were also observed. In one patient with classic migraine, studied within 24 hours after a typical attack of photopsia and hemianopia lasting 30 minutes, there was marked hyperemia of the occipital cortex.

**Brain Tumor**

In patients with glioblastoma multiforme (N = 2) proven by biopsy, there were irregular, patchy but neighboring zones of both increased or decreased flow together with excessively high or low Lx values, measured within the tumor. Surrounding the tumor LCBF and Lx values were reduced. This was attributed to edema, which was noted around the tumor at surgical biopsy. This patchy and variable pattern of flow, particularly where high flow and Lx values exceeded the upper limits of normal co-exist, is different from any other condition so far examined, and is suspected of being pathognomonic for glioblastoma.

Two additional patients with low grade gliomas (grade I-III astrocytomas) were also examined. Their LCBF and Lx values were diffusely reduced within the solid tumor mass. In one of these patients with a history of focal seizures, a typical Jacksonian seizure occurred during the CT measurements. The seizure involved the right hand and spread to the arm. Flow values in areas of the motor cortex and lentiform nuclei involved by the seizure, but adjacent to the tumor were 57% higher than those measured in the opposite hemisphere.

**Discussion**

Methods are described for non-invasive 3 dimensional measurements of LCBF and Lx in human subjects by the use of the CT scanner which have a resolving power in the order of 80 cubic mm. Preliminary results are presented for normal healthy volunteers together with values measured in patients with
cerebrovascular disorders, sleep disorders and brain tumor which appear to lend support of the validity of the method and to its possible application for clinical research.

Inhalation of a mixture of 35% Xe\textsuperscript{133} in 65% oxygen appears to be the optimal concentration for minimizing any sub-anesthetic effects, yet sufficient to produce changes in absorption coefficients for the EMI scanner which exceed the signal-to-noise ratio. The admixture of 65% oxygen is estimated to produce a reduction of LCBF values not exceeding 5\%.

Compared to rCBF measurements by the \textsuperscript{133}Xe inhalation, intracarotid or intravenous bolus measurements, the resolving power of the CT scanner is superior. Problems of Compton scatter and extracranial contamination are avoided and inaccuracies due to tissue overlap (partial volume effects) are minimized. Nevertheless, present LCBF values are similar to normal values for gray and white matter previously reported in normal age-matched volunteers measured by \textsuperscript{133}Xe inhalation\textsuperscript{35} except that white matter values are higher. The high white matter flows are attributed to exclusion of extra-cerebral contamination, underestimation of L\textsubscript{X} values for white matter and tissue overlap, whereby some gray matter may be included in AH measurements of white matter involved. When L\textsubscript{X} were extrapolated to infinity L\textsubscript{X} values were higher and LCBF values were lower (table 2).

Higher flow values for the calcarine cortex were measured by Xe\textsuperscript{133} CT scans than with \textsuperscript{133}Xe measurements, due to better resolution. This finding is consonant with the high glucose consumption of human occipital cortex, which is increased further by visual stimulation, as measured by F\textsuperscript{18} labelled deoxyglucose infusions during positron emission tomographic scanning\textsuperscript{36–38}.

In general, LCBF values measured by the stable xenon CT method, shown in tables 1 and 2, are in good agreement with values reported by the \textsuperscript{133}Xe methods for gray and white matter.\textsuperscript{35} Occipital cortical flows tend to be higher than previously reported \textsuperscript{133}Xe values, possibly because of contamination by sagittal sinus or scalp flow and the anatomical in-folding of the calcarine cortex. Normally, CBF is tightly coupled with neuronal activity and metabolism. To further test the validity of the Xe\textsuperscript{133} LCBF measurements, activation tests were carried out. LCBF values were measured with the eyes closed in a darkened room and compared later in the same subjects with values measured when the eyes were open in a brightly lighted room. The visual systems showed a striking increase of +16.8\% (p < 0.01) whereas fronto-temporal cortical and basal ganglia showed no significant change. With the eyes open, LCBF values were higher in superior colliculi by +11.5\%, lateral geniculate body by +27.4\%, striate cortex by +11.3\% and lateral occipital cortex by +4.2\% compared to values measured with the eyes closed and alpha activity in the EEG (fig. 7). When subjects were asked to flex and extend the fingers LCBF values increased in the contralateral pre- and post-central gyrus by +34.8\% (fig. 8) compared to similar measurements made in the resting state. These Xe\textsuperscript{133} LCBF findings appear to be consonant with previous reports of regional increases of rCBF during brain activation measured by the \textsuperscript{133}Xe methods and may lead to considerable error. Improvement in making quantitative measurements of ischemia, infarction and edema in patients with stroke may have usefulness in future research, for evaluating the effects, if any, of medical and surgical therapy.

Presently reported L\textsubscript{X} values measured \textit{in vivo} and \textit{in situ} in patients with malignant brain tumors presented here appear to be consonant with abnormal L\textsubscript{X} values measured \textit{in vivo} in experimental brain tumors in dogs,\textsuperscript{39} as well as those measured \textit{in vitro} from specimens of brain tumor obtained at autopsy or surgical biopsy.\textsuperscript{11, 39, 49}

Presently reported L\textsubscript{X} values, measured \textit{in vivo}, of 0.86 for gray matter and 1.34 for white matter, are in reasonable agreement with values measured in post-mortem samples of brain tissue of 0.80 for gray matter and 1.5 for white matter, although white matter values are higher.\textsuperscript{11, 12, 40} Lower L\textsubscript{X} values for white matter measured by present \textit{in vivo} methods may be due to technical factors such as to incomplete saturation of white matter, or tissue overlap with gray matter or may, in fact, indicate slight differences between L\textsubscript{X} values for dead and living brain tissue. We suspect that the latter may be the case because of the remarkably small standard deviation for white matter of 1.34 ± 0.1. This may be expected to be larger if it were due to technical variation such as incomplete tissue saturation or gray matter overlap.

Possible errors introduced in LCBF measurements were tested by substituting L\textsubscript{X} values for white matter of either 1.29 or 1.5 in the autoradiographic formula, which was modified after Kety\textsuperscript{41–43}.

\[
\text{Ci}(T) = \frac{\text{Ki}}{\text{C}_{\text{a}}} (T - t) \frac{\text{e}^{-K_{\text{I}} T}}{\text{Ki}} dt
\]

where K\textsubscript{I} = \text{mF}/\text{X}. Resulting values for LCBF when actual ΔH changes for blood and brain measured in normals were substituted in the formula were then compared. For 24 white matter LCBF measurements in normal volunteers, using 1.29 for L\textsubscript{X} mean LCBF values in mls/100 g brain/min were 34.0 ± 5.7 and when 1.5 was substituted mean LCBF values were 33.4 ± 5.2. These are not significantly different.

Patients with cerebral infarction show zones of zero flow which may be readily recognized and quantitated in 3 dimensions with Xe\textsuperscript{133} CT. These tend to be overlooked with \textsuperscript{133}Xe inhalation and external counting, since they are recorded only as zones of reduced flow. LCBF values measured by CT scanning are more accurate, not only for these technical reasons, but also because L\textsubscript{X} values are actually measured rather than assumed. This does not affect measurements in normals but L\textsubscript{X} (and hence LCBF) may be greatly altered secondary to disease of the brain.\textsuperscript{4} L\textsubscript{X} values, for example, were found to be altered in brain edema, infarction and tumor. Short inhalation intervals of Xe\textsuperscript{133} may be insufficient to evaluate true L\textsubscript{X} unless the latest computer program described here is used to estimate L\textsubscript{X} values extrapolated to saturation at infinity. Such changes in L\textsubscript{X} are overlooked by the \textsuperscript{133}Xe methods and may lead to considerable error. Improved precision in making quantitative measurements of ischemia, infarction and edema in patients with stroke may have usefulness in future research, for evaluating the effects, if any, of medical and surgical therapy.
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