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*) in oxygen during CT scanning. After denitrogenation by 100% oxygen breathing, 35% Xe* is breathed for 7-8 minutes to minimize subanesthetic effects. Mean changes in brain Hounsfleld 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 x 8 mm), 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 ± 7.93, cortex = 82.3 ± 8.5, white matter = 29.2 ± 5.9, midbrain 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 gyri. 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.

For these reasons, Drayer and associates,1-10 Kelcz et al.,11 Haughton et al.12 and this laboratory13-18 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.

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

LCBF in contralateral pre-central and post-central gyri. 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.1,2 Because they are atraumatic they have largely replaced the intra-carotid 133Xe bolus injection method.3 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.4 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 λ) 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,5-6 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 mm³ area x 8 mm depth (80 cubic mm).

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*Since this manuscript was submitted an additional 17 subjects have undergone successful measurements without ill effect. These included pre- and postoperative measurements in patients undergoing STA-MCA by-pass procedures for internal carotid occlusion and therapeutic embolization of cerebral arteriovenous malformations (AVM).
XE* LCBF by CT Scans/Meyer et al.

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 face-mask, 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 opens 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 buildup 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, PexE* and PeO₂, PeCO₂, 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 λ 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 Standard Deviation CT scanner they used, was circa 6.32 at 120 kVp. The improved EMI 1010 scanner used in the present

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*Consent forms and protocol were approved by the institutional review board for human investigation of Baylor College of Medicine and the VA Medical Center. Houston, Texas.
studies, when similarly tested with 11 serial 1 min scans measuring a vial of iodine solution of 88 mg/100 ml, contained in a phantom, gave H values comparable to brain of 39.8 units and a $\frac{\Delta H}{SD}$ of 97.1. Since the higher the $\frac{\Delta H}{SD}$ becomes, the better the signal-to-noise ratio, the EMI 1010 scanner has a signal-to-noise ratio in the order of 14 $\times$ improved compared to the Mark 1 model. In 7 normal volunteers, this ratio calculated, in vivo, from the first 3 control brain scans prior to Xe* inhalation was 37.4. This indicates an excellent signal-to-noise ratio for the living brain, sufficient to measure reliably $\Delta H$ change during 35% Xe* inhalation, which has been a criticism of earlier scanners.0 This criticism of poor signal-to-noise ratio may be applicable to fourth generation, faster scanners. For example, we have tested a Model 8800 GE scanner, fitted with a 10 mm collimator and x-ray beams adjusted to 120 kVP and to 256 mA, during 11 sequential scans from a volume of a phantom measuring 7.7 cm$^3$ $\times$ 10 mm. Mean H values were 4.2 units, and the measured $\frac{\Delta H}{SD}$ was 9.4, indicating a signal to noise ratio that is less satisfactory than the EMI 1010 scanner.

$\lambda$ values were calculated from tissue and blood $\Delta H$ values estimated at saturation during inhalation of 35% Xe* by utilization of formulas originally proposed by Kelcz et al.11 but modified for indirect estimation of the $\Delta H$ of blood.0,18 LCBF values were determined by an in vivo autoradiographic formula originally proposed by Kelcz11 but modified and programmed for the DEC 10 Computer14 for each of the 1 minute scans measured during saturation. LCBF values were also measured during the first 4.5 minutes of desaturation by a monoeponential formula programmed for the DEC 10 Computer.14 $\Delta H$ changes for both tissue and blood were intergraded every 6 seconds in this program. This is a modification of the model of Obrist et al. using single compartmental analysis.0,18 Measured $\lambda$ values for each region of interest were used for all LCBF measurements. In collaboration with Dr. Walter Obrist of the Department of Neurosurgery of the University of Pennsylvania, a computer program has now been developed using a double integration method for the air curves to fit brain tissue $\Delta H$ curves and computation of $\lambda$ values at infinity. Raw data points for end-tidal Xe* and $\Delta H$ tissue change may be analyzed by this program, using the above principles, and both $\lambda$ and LCBF values are calculated by the computer, provided that at least 2 or more tissue $\Delta H$ measurements during either saturation or desaturation are entered. Results obtained are in good agreement but more accurate than data reported by in vivo autoradiographic analysis.14 The latest program provides more satisfactory fitting between tissue and air curves plus computation of $\lambda$ values to infinity, resulting in more uniform LCBF and true $\lambda$ values in regions of interest.** Data points representing changes in Hounsfield units for arterial blood in 9 normals, as shown in figure 2, were derived by conversion from the end-tidal Xe* curves measured on the polygraph during saturation and desaturation by means of the formulas originally described in the baboon14 with slight modifications for human use to be described shortly. This indirect method of plotting arterial $\Delta H$ curves was validated by direct serial CT scanning of blood samples concurrently measured in 11 of the human subjects. Saturation $\Delta H$ values for blood measured directly in these 11 subjects during 35% inhalation are illustrated in figure 3. Since correlation of indirect and directly measured $\Delta H$ values were satisfactory, it was not considered necessary to draw blood samples in later patients and volunteers. With knowledge of hematocrit, $\Delta H$ changes were calculated indirectly from the Pexe* curves in order to render the method non-invasive.

Detailed description of the method and theory for determination of maximal $\Delta H$ changes of blood having different hematocrits during inhalation of 35% Xe* has been reported elsewhere.14,18 The indirect method requires drawing blood samples during saturation and scanning them in a phantom. The indirect method does not require drawing blood samples and is achieved by converting Pexe* values to corresponding $\Delta H$ change in blood. In brief, changes in thermococonductivity values with respect to absolute end-tidal Xe* concentration, from 0 to 35%, are linear; likewise changes in Hounsfield units, measured directly from blood samples, with respect to changes from 0-35% Xe* concentrations are also linear. Thus, it is possible to calibrate the Pexe* saturation and desaturation curves directly recorded on the polygraph in terms of $\Delta H$ changes for arterial blood. The indirect $\Delta H$ calibration for Pexe* at saturation was converted to comparable arterial blood $\Delta H$ calibration at 35% Xe* saturation, by use of equation $\Delta H = \frac{5.15 \times 8 Xe* \times C}{\mu_x \mu_y Xe* X 100}$

where $\theta Xe^* = 0.0011 \times Ht (%) + 0.10$ and C = Percent mixture of Xe* used (35% in this case). The derivation of these equations will be found in references 11, 14, 19 plus the NAPS Document No. 03640 (see footnote). With our CT scanner, under the scanning conditions described; $\mu_x \mu_y Xe^*$ is $4.56 \times 10^{-2} \pm 0.73 \times 10^{-2}$, calculated from data derived by scanning human blood samples during saturation with Xe* of different concentrations. This empirically determined value closely approximated directly measured values by Kelcz et al.11 and renders indirect calculation of maximal $\Delta H$ at saturation possible non-invasively, i.e. avoids the necessity of drawing blood samples. The Pexe* curves recorded on the polygraph are now calibrated for estimating changes of $\Delta H$, at 6 or 10 sec-

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*See NAPS Document No. 03640 for 11 pages of explanatory notes and programs for computer analysis of LCBF and $\lambda$ 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.
**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 Pex$^8$ values measured in 9 normal volunteers. Corresponding maximal $\Delta H$ 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

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**POLYGRAPHIC RECORDING DURING CT Xe$^8$ LCBF AND $\Delta H$ MEASUREMENTS IN A 41 YEAR OLD MALE**

**FIGURE 1.** Polygraphic 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$^8$ (Pex$^8$). CT scanning intervals are shown by the square wave signal at base of chart with time base in minutes.

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**MEAN PERCENTAGE CHANGES IN HOUNSFIELD UNITS ($\Delta H$) OF ARTERIAL BLOOD CONVERTED FROM END-TIDAL Xe$^8$ CHANGES DURING INHALATION OF 35% Xe$^8$**

**FIGURE 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.
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A H VALUES MEASURED AT SATURATION IN BLOOD OF HUMAN VOLUNTEERS BY DIRECT CT SCANNING DURING 35% Xe8 INHALATION (N = 11)

FIGURE 3. Mean ΔH units measured directly in blood samples at saturation in 11 subjects during 35% Xe8 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 L\(\lambda\) values requires knowledge of ΔH changes in blood and tissue at saturation, during inhalation of an Xe8 mixture of known concentration.\(^9\) If \(\lambda\) is estimated before tissue saturation is complete, \(\lambda\) values may be underestimated. If concentrations of Xe8 exceeded 45–50%, as was tested in the first few subjects, 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 \(\lambda\)

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\(^9\) and computer solutions of the Fick formula as reviewed by Obrist et al.\(^1\) 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 LCBF4.1) 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\(_{4.1}\)) 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 Xe8, 20 minutes apart, was \(r = 0.85\) (\(p < 0.001\)). White matter LCBF values were in the range of 35.8 ± 6.1 and L\(\lambda\) 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

EXTRAPOLATED PLOTS TO 15 MINUTES OF CHANGES IN ΔH VALUES MEASURED IN GRAY AND WHITE MATTER AFTER 8 MIN. INHALATION OF 35% Xe8 IN A 41 YEAR OLD MALE WITH NORMAL NEUROLOGICAL EXAMINATION

FIGURE 4. To show plots (solid line) of mean ΔH changes, with standard deviation for gray (\(N = 18\)) and white matter (\(N = 8\)), recorded during 8 minutes of inhalation of 35% Xe8 in a 41-year-old male. The interrupted lines are extrapolated plots to saturation estimated at 15 minutes.
ESTIMATED OPTIMAL SCANNING INTERVAL DETERMINED FROM SERIAL 1 MINUTE AUTORADIOGRAPHIC LCBF MEASUREMENTS FOR A) GRAY MATTER AND B) WHITE MATTER IN NORMALS

CORRELATION OF IN-VIVO AUTORADIOGRAPHIC LCBF VALUES DURING SATURATION WITH MONOEXPONENTIAL LCBF VALUES DURING FIRST 4.5 MINUTES OF DESATURATION

**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.

Temporal and parietal. Basal ganglia and thalamic flow values were similar to or higher than those of the cortex. Slightly lower flow values were measured in the cerebellar cortex. High flows were also measured in the superior and inferior colliculi and pontine nuclei.

**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.11, 12

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 $LCBF_{14}$ (mls/100g brain/min) and $Lk_{15}$ Measured in Normal, Healthy Volunteers While Awake ($N = 9, 8M 1F$)

<table>
<thead>
<tr>
<th>Component</th>
<th>Mean Age 38.3 ± 10.8 yrs</th>
<th>Mean PeCO$_2$ 36.8 ± 3.2 mm Hg</th>
<th>$LCBF_{14}$ (N)</th>
<th>Mean Value ± SD</th>
<th>$Lk_{15}$ (N)</th>
<th>Mean Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex</td>
<td>30</td>
<td>81.9 ± 7.3</td>
<td>0.89 ± 0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>19</td>
<td>79.5 ± 7.9</td>
<td>0.89 ± 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>9</td>
<td>79.1 ± 6.1</td>
<td>0.88 ± 0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital Cortex</td>
<td>25</td>
<td>82.6 ± 9.8</td>
<td>0.88 ± 0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Cortex</td>
<td>83</td>
<td>81.3 ± 8.5</td>
<td>0.89 ± 0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average White Matter</td>
<td>55</td>
<td>35.8 ± 6.1</td>
<td>1.29 ± 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>21</td>
<td>79.6 ± 9.3</td>
<td>0.90 ± 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>36</td>
<td>84.2 ± 9.8</td>
<td>0.91 ± 0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar Cortex</td>
<td>8</td>
<td>72.0 ± 17.0</td>
<td>0.88 ± 0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Midbrain

- Tectum, Tegmentum (Dorsal) 24 79.8 ± 12.9 0.91 ± 0.09
- Cerebral Peduncle ( Ventral) 3 33.0 ± 4.0 1.21 ± 0.08

Pons

- Tegmentum (Dorsal) 3 89.3 ± 4.7 0.91 ± 0.09
- Brachium Pontis ( Ventral) 4 35.0 ± 4.2 1.29 ± 0.03

observations also appeared to be consistent with earlier reports of $^{133}$Xe measurements. 81, 82

Measurements Of LCBF And $Lk$ 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

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Mean Age 38.3 ± 10.8 yrs</th>
<th>Mean PeCO$_2$ 36.8 ± 3.2 mm Hg</th>
<th>$LCBF_{14}$ Mean Value ± SD</th>
<th>Mean $Lk_{15}$ Mean Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex</td>
<td>31</td>
<td>82.3 ± 8.5</td>
<td>0.871 ± 0.085</td>
<td></td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>35</td>
<td>81.5 ± 8.8</td>
<td>0.854 ± 0.070</td>
<td></td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>8</td>
<td>77.9 ± 7.6</td>
<td>0.839 ± 0.071</td>
<td></td>
</tr>
<tr>
<td>Lateral Occipital Cortex</td>
<td>16</td>
<td>84.8 ± 7.0</td>
<td>0.842 ± 0.080</td>
<td></td>
</tr>
<tr>
<td>Striate Cortex</td>
<td>12</td>
<td>86.0 ± 7.9</td>
<td>0.877 ± 0.082</td>
<td></td>
</tr>
<tr>
<td>Caudate Nucleus</td>
<td>8</td>
<td>88.3 ± 4.4</td>
<td>0.908 ± 0.070</td>
<td></td>
</tr>
<tr>
<td>Lentiform Nucleus</td>
<td>7</td>
<td>85.1 ± 10.5</td>
<td>0.943 ± 0.107</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>27</td>
<td>85.8 ± 8.0</td>
<td>0.901 ± 0.069</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Cortex</td>
<td>6</td>
<td>80.1 ± 10.9</td>
<td>0.977 ± 0.074</td>
<td></td>
</tr>
<tr>
<td>Midbrain</td>
<td>16</td>
<td>94.3 ± 14.8</td>
<td>0.884 ± 0.073</td>
<td></td>
</tr>
<tr>
<td>Lateral Geniculate Body</td>
<td>12</td>
<td>106.2 ± 14.6</td>
<td>0.884 ± 0.082</td>
<td></td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>8</td>
<td>90.4 ± 7.9</td>
<td>0.876 ± 0.065</td>
<td></td>
</tr>
<tr>
<td>Average Cortex</td>
<td>102</td>
<td>82.3 ± 8.5</td>
<td>0.862 ± 0.081</td>
<td></td>
</tr>
<tr>
<td>Average White Matter</td>
<td>49</td>
<td>29.2 ± 5.9</td>
<td>1.338 ± 0.102</td>
<td></td>
</tr>
</tbody>
</table>

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

LCBF$_{14}$ VALUES (mls/100g brain/min) FOR TOTAL VISUAL AND OTHER SYSTEMS COMPARED DURING EYES CLOSED VERSUS EYES OPEN IN AWAKE NORMAL VOLUNTEERS ($N = 8$)

<table>
<thead>
<tr>
<th>Component</th>
<th>Eyes Closed</th>
<th>Eyes Open</th>
<th>A%</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual System (Superior Colliculi, Lateral Geniculate Body, Striate Cortex)</td>
<td>84.3 ± 11.6</td>
<td>94.0 ± 26.7</td>
<td>+11.5%</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Frontal Cortex</td>
<td>81.5 ± 32.2</td>
<td>103.8 ± 19.0</td>
<td>+27.4%</td>
<td></td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>80.0 ± 5.4</td>
<td>89.0 ± 9.9</td>
<td>+11.3%</td>
<td></td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>81.3 ± 11.3</td>
<td>84.7 ± 10.8</td>
<td>+4.2%</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 7A AND B.** To show $LCBF_{14}$ 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.
% CHANGE OF LCBF$^*_v$ 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 ± 34.8%</td>
<td>n = 5</td>
</tr>
<tr>
<td>Postcentral</td>
<td></td>
<td>n = 4</td>
</tr>
<tr>
<td>Cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>+ 6.9 ± 17.7%</td>
<td>n = 13</td>
</tr>
<tr>
<td>Anterior Mesial</td>
<td>- 14.3 ± 0.1%</td>
<td>n = 2</td>
</tr>
<tr>
<td>Frontal Cortex</td>
<td></td>
<td>n = 4</td>
</tr>
</tbody>
</table>

**Figure 8.** To show percentage increases (+27%) for LCBF$_{con}$ 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 $\lambda$ 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. $^{18,15}$ Similar results have been reported from this and other laboratories, in previous studies following experimental cerebral embolism in the baboon during Xe$^*$ CT scanning. $^{7,15}$ Figure 10 illustrates measurements of LCBF and $\lambda$ 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 $\lambda$ 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 $\lambda$ values in the ipsilateral visual projection systems including occipital cortex, pulvinar, lateral geniculate body and superior colliculi. These reductions of LCBF with normal $\lambda$ values in the visual system remote from the infarction were attributed to deafferentation.

**Figure 9.** To illustrate brain maps of LCBF$_{con}$ and L$\lambda$$_{con}$ measurements in a 34-year-old, right-handed, normal healthy male volunteer at rest with the eyes closed in a darkened room. EEG showed alpha activity.

<table>
<thead>
<tr>
<th>$\text{Xe}^*$ values</th>
<th>Mean left hemispheric $Fg$ = 83</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Xe}^*$ values</td>
<td>Mean right hemispheric $Fg$ = 89</td>
</tr>
<tr>
<td>$\text{Xe}^*$ values</td>
<td>Mean left hemispheric $Fg$ = 70</td>
</tr>
<tr>
<td>$\text{Xe}^*$ values</td>
<td>Mean right hemispheric $Fg$ = 74</td>
</tr>
</tbody>
</table>

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. $^{7,10,15}$

Reduced $\lambda$ 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. $^{7,10}$ Figure 10 illustrates measurements of LCBF and $\lambda$ in one of our patients with extensive, bilateral cerebral infarction from cerebral emboli of cardiac origin 2 years previously.
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 diaschisis and edema, consonant with previously reported measurements using the $^{18}$Xe inhalation method.\textsuperscript{10}

Patients with transient ischemic attacks (TIAs)

LCBF and LI values in a 55 year old hypertensive, diabetic male with history of myocardial infarction and embolic infarction of both cerebral hemispheres 2 years earlier. 4 days prior to CBF, seizure with worsening of symptoms. On examination, right hemianopia, partial left hemianopia, Wernicke's dysphasia, left parietal lobe signs, apraxia, and mild right hemiparesis were observed.

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 L\(\Lambda\) values, measured within the tumor. Surrounding the tumor LCBF and L\(\Lambda\) 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 \(\Lambda\) 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 L\(\Lambda\) 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 L\(\Lambda\) 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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure10}
\caption{To illustrate values for LCBF\(\lambda_{14}\) and L\(\lambda_{15}\) mapped in a 55-year-old hypertensive diabetic male with a history of myocardial infarction and subsequent embolic infarction of both cerebral hemispheres, 2 years earlier. He had a seizure 4 days prior to CBF with temporary worsening of his symptoms. On examination, there were right hemianopia, partial left hemianopia, Wernicke's dysphasia, left parietal lobe signs, apraxia, and mild right hemiparesis: A. CT Scan at the level of the thalamus and caudate nuclei. B. CT section with LCBF and L\(\Lambda\) values mapped at a higher level to show 3-dimensional extent of the infarction.}
\end{figure}
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 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 EM1 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%. 44

Compared to CBF measurements by the 133Xe 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 133Xe inhalation 45 except that white matter values are higher. The high white matter flows are attributed to exclusion of extra-cerebral contamination, underestimation of LX values for white matter and tissue overlap, whereby some gray matter may be included in AH measurements of white matter involved. When LX were extrapolated to infinity LX values were higher and LCBF values were lower (table 2).

Higher flow values for the calcarine cortex were measured by Xe CT scans than with 133Xe 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 F18 labelled deoxyglucose infusions during positron emission tomographic scanning. 48-50

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 133Xe methods for gray and white matter. 46 Occipital cortical flows tend to be higher than previously reported 133Xe 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 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 cortex 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 contra-lateral pre- and post-central gyrus by +34.8% (fig. 8) compared to similar measurements made in the resting state. These Xe LCBF findings appear to be consonant with previous reports of regional increases of CBF during brain activation measured by the 133Xe. 31, 32

Presently reported LX values measured in vivo and in situ in patients with malignant brain tumors presented here appear to be consonant with abnormal LX values measured in vivo in experimental brain tumors in dogs, 11 as well as those measured in vitro from specimens of brain tumor obtained at autopsy or surgical biopsy. 31, 39, 97

Presently reported LX values, measured 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. 1, 3, 8, 11 Lower LX values for white matter measured by present 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 LX 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 LX 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 LX values for white matter of either 1.29 or 1.5 in the autoradiographic formula, which was modified after Kety51, 52, 54 Ca(T) = mF /X. Resulting values for LX 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 LX, 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 CT. These tend to be overlooked with 133Xe 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 LX values are actually measured rather than assumed. This does not affect measurements in normals but LX may be greatly altered secondary to disease of the brain. 4 LA values, for example, were found to be altered in brain edema, infarction and tumor. Short inhalation intervals of Xe may be insufficient to evaluate true as unless the latest computer program described here is used to estimate LX extrapolated to saturation at infinity. Such changes in LX are overlooked by the 133Xe 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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Mapping local blood flow of human brain by CT scanning during stable xenon inhalation.
J S Meyer, L A Hayman, T Amano, S Nakajima, T Shaw, P Lauzon, S Derman, I Karacan and Y Harati

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