Effect of Stable Xenon on Regional Cerebral Blood Flow and the Electroencephalogram in Normal Volunteers

Alexander Hartmann, MD; Christian Dettmers, MD; Franz J. Schuier, MD; Hans Detlef Wassmann, MD; and Hans W. Schumacher

We evaluated the effects of breathing 35% stable xenon in 65% oxygen on regional cerebral blood flow and the electroencephalogram in 20 normal volunteers. We measured blood flow in 32 brain regions over both hemispheres with the xenon-133 intravenous injection technique in two protocols. In the first protocol (n = 10), a baseline study was followed by a second study during 5 minutes of breathing stable xenon; in the other protocol (n = 8), the baseline study was followed by a second study after 5 minutes of breathing stable xenon. Two volunteers were excluded due to excessive movements during the inhalation of stable xenon. Some of the remaining 18 volunteers had varying alterations of consciousness accompanied by electroencephalogram changes. After stable xenon inhalation the electroencephalogram returned to normal within 2-3 minutes. During stable xenon inhalation mean±SD PECO₂ dropped significantly from 39.4±4.4 to 33.7±5.4 mm Hg in the first protocol and from 39.4±2.6 to 34.8±4.1 mm Hg in the second protocol due to hyperventilation in 13 volunteers. Mean regional cerebral blood flow increased significantly by 13.5-25.4% without correction for PECO₂. In the first protocol regional cerebral blood flow increased by >12% in 11-14 (depending on the flow parameter) of the 20 hemispheres. In the second protocol regional cerebral blood flow increased by >12% in 9-13 of the 16 hemispheres. We conclude that cautious interpretation is necessary in the assessment of regional cerebral blood flow with 35% xenon-enhanced computed tomography.

Several reports have been published on the use of stable xenon (Xe) as a contrast agent for computed tomography (CT) of the brain. Since Xe is freely diffusible, it accumulates in the brain during inhalation and after inhalation is washed out in parallel with the blood flow. However, we know that high concentrations of Xe may alter consciousness and the electroencephalogram (EEG). Therefore, many groups use ≥35% Xe in O₂, which still permits a sufficient increase in Hounsfield units during inhalation to allow calculation of regional cerebral blood flow (rCBF). We previously conducted a study on six baboons that showed that rCBF and EEG were influenced by Xe. That study prompted us to study the effects of 35% Xe in 65% O₂ on rCBF and EEG in normal volunteers.

Subjects and Methods

We studied 20 volunteers of either sex aged 27-42 (mean±SD 33.4±3.1) years with no history or signs of central nervous system or other major disease. All volunteers underwent general medical and neurologic examination. We measured rCBF using the intravenous injection of xenon-133 and recording the clearance curves with a Novo 32 C cerebrograph (Hadsund, Denmark) as described by Obrist et al. We explained the technique and received informed consent from each volunteer in accordance with the university rules of ethics.

Thirty-two NaI detectors with a crystal size of ⅜ in. and a collimation of 20 mm were arranged in a helmet shape over the volunteer's skull. After recording the background or residual activity for 30 seconds in the first study and for 5 minutes in the second study brain tissue saturation was attempted by injecting approximately 25 mCi xenon-133 into one cubital vein over approximately 10-15 seconds. This xenon-133 saturation phase lasted for 60 seconds. Clearance of xenon-133 from the brain tissue was recorded for 10 minutes, and the data were stored on-line on a
Hartmann et al
Stable Xenon in Humans
183

FIGURE 1. Tracings of end-expiratory concentrations of CO₂ (top) and xenon-133 (bottom) in both cerebral blood flow studies of protocol A. Charts read from right to left. Right: baseline measurements during inhalation of room air; left: measurements during inhalation of stable xenon (Xe'). Background activity of xenon-133 was counted for 30 seconds in first study and for 5 minutes in second study (A). B, injection of xenon-133 into one cubital vein; C, calculation of initial slope index during clearance phase.

PDP 1103 V computer. The end-expiratory concentration of CO₂ (PᵦCO₂) was continuously followed by a capnograph and recorded on a plotter (Figure 1). The end-expiratory concentration of xenon-133 was continuously monitored for correction of recirculation. In the second study, which was started approximately 20 minutes after the end of the first study, the end-expiratory concentration of Xe' was continuously recorded by a Gow-Mac gas analyzer (Bound Brook, N.J.) (Figure 2). The Xe' was delivered as exactly 35% in 65% O₂ (Messer-Griesheim, F.R.G.) with no other gas constituents.

Cerebral blood flow (CBF) was calculated using three methods: the raw head curves were corrected for the xenon-133 background activity in the first study and for the remaining activity in the second study by recording for either 30 seconds or 5 minutes before the xenon-133 saturation phase began. A biexponential analysis of the corrected clearance curves was performed by using an iterative curve-fitting process, which yielded the rate constants K₁ and K₂.

Three flow parameters were calculated. Flow of the rapidly perfused (fast) compartment (Fᵢ), which represents primarily gray matter flow, was calculated as Kₓ × Aᵣ × 100, where Aᵣ is the partition coefficient of xenon-133 between blood and the gray matter. Initial slope index (ISI), which is a modification of the index as described by Risberg et al, was calculated from a deconvoluted clearance curve constructed from the biexponential analysis as 100 × monoexponential slope between 0.5 and 1.5 minutes. The ISI is

FIGURE 2. Tracing of end-expiratory concentration of stable xenon (Xe') during inhalation of 35% Xe' in 65% O₂. Chart reads from right to left. Inhalation of Xe' was started during counting of background activity of xenon-133 (A) and continued for 5 minutes. B, saturation phase, 60 seconds during which xenon-133 was injected intravenously; C, clearance phase, at end of Xe' exposure, curve of which was used for calculation of initial slope index.
dominated by perfusion of the fast compartment, but reflects perfusion of the slowly perfused compartment as well. Mean tissue flow (CBF15), which is expressed as a height over area index extrapolated to 15 minutes, was computed from the mean partition coefficient of the gray and white matter, the fractional flow of the fast and slow compartments, and the rate constants $K_1$ and $K_2$. CBF15 reflects clearance from both the fast and slow compartments as milliliters per 100 g per minute.

The EEG was continuously recorded according to university rules by needle electrodes placed over the frontal, precentral, posterior temporal, parietal, and occipital aspects of both hemispheres. The EEG signal was stored on Ampex tape and placed into a Schwarzer interval-amplitude analysis system, where it was distributed into the four classic EEG frequency ranges by a filter. The four filter outputs were conveyed to an analog-digital converter through a multiplexer. A quartz-controlled precision generator determined the interval time for each wave with a precision of ±1 msec from the zero passes. The events were classified into one of five intervals and summed between 1 and 5 minutes. The incidence of events was determined for five interval classes per EEG frequency range. The class gradation within the beta range (23–13 Hz) amounted to 2 Hz, that within the alpha (13–8 Hz) and theta (8–3 Hz) ranges to 1 Hz, and that within the delta range (3–0.5 Hz) to 0.5 Hz.

We measured the positive and negative amplitudes of every half-wave and listed them into one of 16 grades; we then summed them to determine the positive and negative absolute values of the total wave. The electrical power equivalent represents the electrical brain activity by summing the amplitudes in an EEG range and dividing the total by the measured time. This gives a mean amplitude per unit time in an EEG range, which is comparable to the EEG power spectrum.

We performed two protocols but did not use a double-blind design since all volunteers in our pilot

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**FIGURE 3.** Time schedules of protocols A and B. Background, counting of background activity for 5 minutes; Xe133, intravenous injection of xenon-133; ISI, clearance phase, curve of which was used for calculation of initial slope index.

**FIGURE 4.** Graph of mean ±SD electroencephalographic (EEG) changes in 10 normal volunteers in protocol A, expressed as electrical power equivalent (EPE) in classic EEG ranges before, during, and after inhalation of stable xenon (Xe85). Calculation of EPE was as described in text. Changes in alpha, beta, and theta ranges were significant.
studies were able to determine immediately whether they were breathing 35% Xe or room air and since routine conditions in our laboratory require that a patient undergoing Xe study be told that he will inhale a mild anesthetic gas for a certain period. During the rCBF study with Xe inhalation, one member of the laboratory staff talked quietly to the volunteers to soothe them if he noted restlessness.

Protocol A consisted of 10 volunteers. The first rCBF study was made during spontaneous respiration of room air. For the second rCBF study, inhalation of Xe was started during background recording 150 seconds before the injection of xenon-133 (Figures 2 and 3). During inhalation of Xe, the volunteers breathed via the cerebrograph from a bag containing 35% pure Xe in 65% pure O$_2$ and exhaled via the cerebrograph into a xenon trap connected to the exhaust system. Inhalation of Xe continued for 5 minutes and ended 90 seconds after the beginning of the xenon-133 clearance phase. The ISI was calculated from the xenon-133 clearance curve recorded immediately after Xe inhalation. Since the cerebrograph does not allow performance of CT at the same time, rCBF was not calculated with the Xe method. The studies had to be repeated in two volunteers since they reported nervousness shortly before the start of Xe inhalation. In all of the studies reported here, the volunteers were quiet, without any anxiety before Xe inhalation commenced.

In our earlier published studies in normal volunteers,$^{25}$ reproducibility of mean rCBF under constant conditions was 2.2±2.5%, provided that 20 minutes...
had elapsed from the end of the first to the start of the second study, leakage was monitored and completely prevented by a nose clamp and mouthpiece (instead of a mask), the laboratory was darkened, room noise was reduced, and the volunteer's eyes were closed. Each volunteer fulfilled the same requirements in the protocols reported here. However, according to our yearly reliability tests, a deviation of mean rCBF of >12% can be considered significant. In addition to statistical comparison of flow parameters using the two-tailed paired t test between protocols, the number of hemispheres in which mean rCBF changed by >12% was counted. We compared electrical power equivalent for the EEG frequency ranges between studies and protocols using two-way analysis of variance.

Results

Most volunteers reported subjective impressions during inhalation of Xe, with sensations beginning about 10–20 seconds after the start of inhalation. Ten subjects remained awake, eight became obtunded, and two (in protocol B) exhibited excessive movements ≤30 seconds after the start of Xe inhalation, causing the study to be stopped. These two subjects were excluded from the analysis. Four volunteers were cooperative throughout the entire study; two others showed inadequate behavior. Some subjects reported colored hallucinations or intense perceptions of acoustic and sensory stimuli.

In two volunteers in protocol B, EEG artifacts did not allow the calculation of electrical power equivalent; these volunteers were excluded from the analysis of EEG changes. By visual inspection the EEG showed changes in nine of the remaining 16 volunteers (Figure 4). Analysis showed a distinct decrease in electrical brain activity in the alpha and beta ranges shortly after the commencement of Xe inhalation. During the third minute of Xe inhalation, slight progressive increases in theta and delta wave activities were registered. These

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Mean±SD 39.4±4.4 33.3±5.4* 56.0±6.6 67.7±140.4 20.3±16.1 73.8±7.7 93.1±18.7* 25.4±17.1 45.9±5.4 53.2±11.2* 15.9±5.3

TABLE 1. Regional Cerebral Blood Flow Before and During Inhalation of 35% Xe in Normal Volunteers

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ink s, with sensations beginning about
changes (Figure 5) persisted throughout Xe inhalation. After Xe inhalation, the pattern returned to steady-state activity within 2–3 minutes. Analysis of variance indicated that changes in the alpha, beta, and theta wave activities from the steady state to Xe inhalation were significant (p<0.001), whereas the slight increase in the delta wave activity was not. Changes within EEG ranges between protocols A and B were not significantly different.

Table 1 lists PECO2, ISI, F1, and CBF15 and the percentage changes from the resting level for all subjects. Inhalation of Xe caused short-term hyper-ventilation of varying intensity in 13 subjects. The mean values for ISI, F1, and CBF15 in protocol B during the steady state did not differ from the corresponding values in protocol A. The mean percentage changes in all flow parameters for both protocols were significant (p<0.01, two-tailed paired t test). There were no significant differences (two-tailed unpaired t test) in percentage changes between protocols, indicating that even shortly after Xe inhalation (protocol B) CBF was altered. In 12 of 20 hemispheres in protocol A and nine of 16 hemispheres in protocol B, ISI increased by >12%. Such a change was found for F1 in 14 hemispheres in protocol A and 13 hemispheres in protocol B. CBF15 increased by >12% in 11 hemispheres in protocol A and 12 hemispheres in protocol B. These changes are of importance since they occurred despite a reduction in PECO2 in some volunteers. In no hemisphere was a significant reduction in CBF observed. No attempts were made to correct for CO2 differences between studies since it became evident from our experiences in baboons that CO2 reactivity might be altered by Xe inhalation. The CO2 data were recorded continuously by a capnograph, but it should be kept in mind that the reliability of PECO2 as reflecting PaCO2 decreases with hyperventilation. Obrist et al have calculated changes in CBF during Xe inhalation of 28.1% for CBF15 and 42.9% for ISI with Pco2 corrections. Using a CO2 reactivity factor of 3% CBF/mm Hg altered PECO2, we calculated increases for ISI of 42.1%, for F1 of 48.9%, and for CBF15 of 23% in protocol A. When PECO2 was corrected in protocol B, the increases were 29.4%, 38.6%, and 25.4%, respectively. A uniform pattern of rCBF changes during Xe inhalation could not be detected.
Discussion

Our results indicate that 35% Xe might exert an effect on consciousness, the EEG, and CBF. In pilot studies inhalation of 35% Xe for >5 minutes led to even more side effects.

Changes in CBF in animals have been reported by several authors. Meyer et al compared rCBF in gray and white matter derived from Xe-enhanced cranial CT in one group of baboons with rCBF derived from the intra-arterial xenon-133 technique in another group of baboons and found good correlations for the gray and less good correlations for the white matter. Our experiences in normal adult baboons revealed an increase in CBF after a few minutes of Xe exposure, followed by a reduction in CBF if inhalation continued. Only a few clinical observations have been made on rCBF alteration by Xe. Ip described an increase in rCBF after the inhalation of 50% Xe in one human. Obrist et al measured rCBF with the atrumatic xenon-133 technique before and during 6 minutes of 30–35% Xe inhalation; CBF increased significantly both with and without CO2 correction. In our 18 subjects, changes in flow parameters were variable. For example, ISI was altered by between —4.9% (not significant) and 58.7%. The influence of Xe on CBF did not differ between protocols. The high variability of CBF changes is probably due to the variable individual response, which is also indicated by the individual EEG changes. Even with correction for PECO2, the percentage change in CBF is not constant. An increase in noise during the second study is probably not the cause of the interindividual variation since test–retest studies with unchanged conditions have revealed a rather low mean change with a low standard deviation.

Quantitative EEG changes did not always parallel the CBF changes. One subject (no. 2) had a moderate reduction in alpha frequencies starting a few seconds after exposure to Xe. This subject’s F, changed to only a mild extent.

With respect to side effects, unpleasant dysesthesia, brief unresponsiveness, anxiety, and euphoria were reported by Yonas et al in subjects who inhaled 28–47% Xe for 3–6 minutes, confirming observations by others. Anesthetic effects were described long ago as 1951 by Collen and Gross with xenon concentrations as low as 20%. Meyer et al reported EEG changes if the Xe concentration exceeded 45% and loss of consciousness if the concentration exceeded 60%. Morris et al described EEG slowing and anesthesia at Xe concentrations of 80%. Burst suppression was not seen in our EEG tracings with 35% Xe.

As regards rCBF changes, we found no significant differences among individual areas of the brain. Gur et al reported on microsphere studies in three baboons and stated that 35–42% Xe in O2 leads to a significant CBF increase of approximately 17% with no influence of the tissue or site of measurement. However, recalculation of the published data reveals that CBF changes were 3.74%, 12.06%, 15.29%, and 18.50%, indicating that the CBF increase was inhomogeneous. Since Xe has some important characteristics for use as a contrast material in CT as well as for measurements of CBF, it should be investigated further with respect to its suitability for CBF measurement.

Acknowledgments

We acknowledge the substantial help of Dr. Yoshiyasu Tsuda and Dr. Karl Broich.

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**KEY WORDS** • cerebral blood flow • electroencephalogram • xenon
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doi: 10.1161/01.STR.22.2.182

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