Effect of Stable Xenon in Room Air on Regional Cerebral Blood Flow and Electroencephalogram in Normal Baboons

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Measurement of regional cerebral blood flow (rCBF) was performed in 6 healthy baboons during ventilation with 35% stable xenon in artificial air. rCBF was measured with the intraarterial xenon-133 method. EEG was recorded continuously. All CBF areas of interest over one hemisphere reacted in the same way. Mean flow increased during short-term exposure to stable xenon and decreased if stable xenon inhalation was continued for at least 24 minutes. EEG showed a decrease of α- and β-wave patterns a short time after the start of stable xenon inhalation without further changes over the period when rCBF finally decreased. CO2 reactivity increased in most animals, and autoregulation to mild arterial hypotension was significantly impaired with increased flow. It is concluded that 35% stable xenon in artificial air increases rCBF after short-term exposure and decreases rCBF after longer exposure. EEG changes were noted after short-term exposure. rCBF and EEG recovered rapidly after the end of stable xenon inhalation. (Stroke 1987; 18:643-648)

There is a great need for techniques to measure regional cerebral blood flow (rCBF) in patients under routine clinical conditions. Xenon in its radioactive form (133Xe) has been used for this purpose after intraarterial injection, i.v. administration, or inhalation. However, these techniques provide only two-dimensional flow maps and do not allow flow calculation in deeper parts of the brain.

Single-photon emission computed tomography (CT) with inhalation of 133Xe has not been proven yet to give high spatial resolution and cannot be used for local flow measurements in smaller brain tissue volumes. However, since nonradioactive xenon (stable xenon, Xes) absorbs x-ray radiation and thus may be detected with transmission CT, it may be used to measure rCBF. Several centers have introduced this technique with satisfactory results. Some of the groups report minor side effects, particularly if higher concentrations, such as 40–50% Xe, are used.

For routine purposes a method to estimate rCBF should be harmless and easy to perform. Since Xe in higher concentrations has been used as an anesthetic, it should be made clear whether lower concentrations that allow rCBF measurements affect clinical condition, blood flow, and other records such as the EEG. From our own unpublished data we realized that 50% Xe in room air causes serious changes in the EEG of baboons. Therefore we became interested in the question of whether Xe at the concentration routinely used for blood flow measurement can cause changes in the EEG and rCBF. Since anesthetic agents might affect autoregulation and CO2 reactivity, both mechanisms were also tested during inhalation of Xe.

Materials and Methods

Six adult baboons of both sexes weighing between 12 and 15 kg were used for the experiment. All animals survived the protocol. After i.p. injection of pentobarbital (25 mg/kg) while in the cage, the baboons were intubated and ventilated by nitrous oxide-oxygen (N2O:O2 3:1). Relaxation was achieved by repeated injections of pancuronium bromide (0.04 mg/kg). The first study of rCBF was started at least 6 hours after the single injection of barbiturate. Sufficient ventilation was achieved by a semiclosed ventilation apparatus and controlled by regular measurements of all arterial blood gases. One femoral artery and 1 femoral vein were cannulated with polyethylene catheters to continuously record the arterial blood pressure (aBP) and central venous pressure.

The left lingual artery was exposed by a cervical incision. A thin polyethylene catheter (o.d. 1 mm, i.d. 0.5 mm) was introduced into the lingual artery, with its tip at the orifice of the vessel. All arteries of the upper half of the common carotid artery except the internal carotid artery were transiently ligated, guaranteeing that all 133Xe which was injected through the polyethylene catheter entered only the internal carotid artery. In several experiments it was indicated that only negligible amounts of 133Xe contaminated the extracerebral cranial tissue.

The baboon was fixed in prone position in a stereotactic frame by 2 ear bars and a mouth piece. The frame also held the lead collimator for the detectors to record the 133Xe washout curves. Eight NaI detectors with a...
crystal diameter of 8 mm and a collimation of 14 mm were positioned over the left hemisphere, covering the territories of the anterior (3 detectors), middle (3), and posterior (2) cerebral arteries. In all experiments the peak radioactivity over the posterior cerebral artery territory was at least 60% of that over both other territories.

For the measurements of rCBF, 1.0–1.4 mCi $^{133}$Xe in 1.0 ml of normal saline was rapidly injected through the polyethylene catheter in the lingual artery. Saturating and desaturation were recorded by a multichannel analyzer (Wenzel, Munich). Desaturation was recorded for 8.5 minutes. Clearance curves were stored online and thereafter used for stochastic analysis to express flow in milliliters per 100 grams per minute.

After fixing the baboon in the stereotactic frame EEG electrodes were fixed over both sides of the skull in the frontal, temporal, parietal, and occipital positions (Figure 3). The EEG signals from bipolar recordings were stored directly on analog tape, recording the distribution into the classical EEG frequencies by filters. The outputs of the filters were conveyed to an analog-digital converter. A tact generator determined the interval time with a precision of ± 1 msec from each 0 pass. The events were classified according to the inter-val class and summed from the incidence of events in the class (β range, 23–13 Hz; α range, 13–8 Hz, θ range, 8–3 Hz, δ range, 3–0.5 Hz). The mean frequency, amplitude information, and electrical power equivalent (EPE) were determined, constituting the mean amplitude per unit time and providing information on the power spectrum.

Body temperature was measured by a rectal thermometer and controlled by a heat mattress at a temperature of 36–37°C. Central venous pressure was kept at 2–5 mm Hg. Steady-state Paco2 was kept at 34–38 mm Hg, and Paco2 at 80–125 mm Hg. Paco2 changes were induced by additional inhalation of CO2, which raised Paco2 by 10–16 mm Hg.

Protocol

During the steady state (normocapnia, normotension), rCBF (CBF 1) was measured. After recording the $^{133}$Xe washout curves, CO2 reactivity was measured during hypercapnia (CBF 2). aBP did not change significantly during this procedure. CBF 3 tested autorégulation with induced hypotension, aBP was lowered by a maximum of 25% by an infusion of sodium nitroprusside. In all instances aBP during hypotension was kept at 2–5 mm Hg. Steady-state Paco2 was kept at 2–5 mm Hg. During this autorégulation test, Paco2 was kept at the level achieved at CBF 1.

After measurement of CBF 3, nitrous oxide–oxygen was stopped and exchanged with 35% Xe8 in artificial air (20% oxygen, 45% nitrogen) without interposing another steady-state measurement to evaluate whether Xe8 interfered with the already existing autorégulatory response. Four minutes after the start of Xe8 inhalation, CBF 4 was measured during hypotension and normocapnia. During the recording of $^{133}$Xe desaturation at CBF 4, Xe8 inhalation was continued for another 4 minutes. After the end of the autorégulation tests another steady-state measurement was made to guarantee steady rCBF values (CBF 5) during nitrous oxide–oxygen inhalation.

CO2 reactivity was measured at CBF 6 during inhalation of Xe8 and CO2, 4 minutes after the start of Xe8 inhalation. After completion of CBF 6, ventilation was switched back to nitrous oxide–oxygen for at least 10 minutes.

Thereafter, rCBF was measured 4 (CBF 7), 16 (CBF 8), 27 (CBF 9), and 38 minutes (CBF 10) from the beginning of a 45-minute period of Xe8 inhalation. After completion of CBF 10, inhalation was switched to nitrous oxide–oxygen, and 3 minutes later CBF 11 was measured during normotension and normocapnia. Background activity at the beginning of each CBF study had returned to almost normal values.

Results

aBP, central venous pressure, and heart rate were not significantly altered by short-term or continuous inhalation of Xe8 during relaxation of the baboons. In 2 animals a slight reduction of aBP by 5–7 mm Hg was noted, beginning 9–16 minutes after the start of Xe8 inhalation.

During the steady state, rCBF over the frontal areas (2 of 3 detectors over the territory of the anterior cerebral artery) had a higher (12–16%) rCBF than all other detectors. This is in accordance with steady-state flow in most other baboons examined so far in our laboratory. However, since alteration of rCBF, CO2 reactivity, and autorégulatory capacity were almost homogeneous for all regions of interest (with some minor exceptions that did not change the overall trend) only mean regional values for all detectors are reported here.

During the steady state (CBF 1 and CBF 5), mean rCBF (mrCBF) was 39.9 ± 5.1 and 38.2 ± 4.6 ml/100 g/min corrected, using the individual regional CO2 reactivity factors (CO2-RF) calculated from CBF 1 and CBF 2, to a Paco2 value of 40 mm Hg. rCBF values from CBF 7 to 10 were corrected to a Paco2 value of 40 mm Hg using CO2-RF from CBF 5 and CBF 6. Data from CBF 11 were corrected with CO2-RF from CBF 2.

Mean CO2-RF was 0.43 ± 0.08 ml/100 g/min/mm Hg at CBF 2, which corresponded to a RF of 1.1 ± 0.4 % mrCBF/mm Hg. During inhalation of Xe8 (CBF 6), CO2-RF was calculated as 3.2 ± 0.8 % mrCBF/mm Hg. In 2 animals the increase in mrCBF during Xe8 and CO2 inhalation was less than during administration of CO2 alone. In 4 animals CO2-RF increased during Xe8 inhalation.

Figure 1 indicates mrCBF during the protocol (values of CBF 2 and CBF 6 are not included). During short-term inhalation of Xe8 (CBF 7), mrCBF rose from 38.2 ± 5.2 to 48.9 ± 11.2 ml/100 g/min. In 1 animal mrCBF decreased by 14.7% due to the regional decrease of rCBF in 6 of 8 regions of interest, whereas in all other animals mrCBF increased significantly. The maximal increase was to 63.2 ± 3.1 ml/100 g/min. During prolonged inhalation of Xe8 (CBF 8–11), mrCBF first increased to 48.9 ± 11.2 (at CBF...
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Figure 1. Mean regional cerebral blood flow (rCBF) and blood pressure (BP) before and during inhalation of 35% stable xenon (Xe) in room air. rCBF ± SEM as ml/100 g/min; BP as mm Hg. Individual CBF measurements were performed according to the protocol (see text). rCBF 2 and 6 are not included. The x axis indicates Xe inhalation until 133Xe was injected for the CBF study (except CBF = 1). Steady state, measurement during normocapnia and normotension with inhalation of nitrous oxide in oxygen (3:1) (CBF = 1). AR, measurement during inhalation of nitrous oxide in oxygen and mild systemic hypotension (autoregulation test) (CBF = 3); AR Xe, measurement during inhalation of Xe and mild hypotension (CBF = 4); CBF = 5, second steady state; CBF = 7-10, exposure to Xe; *, significantly different from CBF = 3 (p < 0.05); †, significantly different from CBF = 1 and CBF = 5 (p < 0.05); n.s., not significantly different.

7) and then decreased progressively to 24.3 ± 4.1 ml/100 g/min at CBF 10.

The difference between CBF 7, 8, or 10 and CBF 5 was significant (p < 0.01). CBF 9 (27 minutes after the start of Xe inhalation) was not significantly different from CBF 5 since the standard deviation was relatively large (rCBF = 36.3 ± 16.2 ml/100 g/min). Three minutes after the end of prolonged Xe inhalation (CBF 11), rCBF was 42.1 ± 9.8 ml/100 g/min, not different from CBF 5. However, in 2 animals rCBF had not returned to the steady-state level.

During nitrous oxide inhalation, mean aBP was 124.1 ± 13.2 mm Hg at CBF 1 and 97.3 ± 6.1 mm Hg at CBF 3. Mean blood pressure values are indicated in Figure 1. It is evident that blood pressure was not significantly altered by Xe inhalation.

The autoregulation test showed no significant increase in rCBF during ventilation with nitrous oxide-oxygen. This indicates normal regulatory processes although it has been reported that nitroprusside increases cerebral vascular diameter.18 During the autoregulation test with ventilation with Xe, rCBF increased to 54.8 ± 12.9 ml/100 g/min. In none of the animals did mrCBF remain unchanged or decrease. Cerebrovascular resistance during induced systemic hypotension and nitrous oxide-oxygen ventilation decreased from 3.1 ± 0.5 to 2.6 ± 0.7 mm Hg/ml/100 g/min. During Xe inhalation and induced hypotension, vascular resistance decreased from 2.7 ± 0.6 to 1.7 ± 0.5 mm Hg/ml/100 g/min. In 4 animals the change in cerebrovascular resistance caused by induced hypotension was bigger during Xe ventilation than during nitrous oxide-oxygen ventilation, while in 2 animals it was unchanged. However, in all 6 animals the change in ventilatory gases from nitrous oxide-oxygen to Xe decreased cerebrovascular resistance.

About 10-20 seconds after the start of Xe inhalation the EEG showed a significant decrease in α- and β-wave activity (Figures 2 and 3) with a tendency to slight recovery over the 45 minutes of Xe inhalation. Theta- and δ-wave activity increased slightly during this period. Such changes were noted over both hemispheres. Despite an initial increase in rCBF and a subsequent decrease, this EEG pattern persisted throughout the continuous inhalation of Xe. After the end of the Xe exposure, the steady-state pattern of the EEG returned again within 60 seconds.

Discussion

Nitrous oxide affects blood flow in the brain only to a minor extent at high concentrations. Therefore, we used a mixture of nitrous oxide and oxygen for ventilation and pancuronium bromide for complete relaxation to achieve constant hemodynamic conditions throughout the experiment.

The method of measuring rCBF by intravenous injection of 133Xe and recording the clearance curves by externally fixed detectors described here has been used in our animal laboratory for more than 10 years. During the surgery the common and external carotid arteri...
ies were treated carefully, and the internal carotid artery was never touched. Long-term studies with repeated measurement of rCBF over 24 hours have indicated that this technique does not alter rCBF. Therefore, the flow changes reported here are not due to the technique.

The study of basic blood flow during the steady state and of autoregulatory capacity and CO₂ reactivity in all 6 animals revealed similar values compared with those obtained in other baboons in our laboratory. None of the animals showed pathologic conditions before inhalation of Xe⁵. After Xe⁵ inhalation, CBF returned to normal within a few minutes and was not different from steady-state values. The normalization of rCBF at CBF 5 indicates that the possible vasodilatory effect of sodium nitroprusside was of rather short duration. Therefore, all changes in flow from CBF 7 to CBF 11 are not due to a hypothetical prolonged toxic effect of this substance.

Inhalation of 35% Xe⁵ in room air significantly increased mrCBF within 4 minutes. It may be argued that at CBF 7 (4 minutes after the start of Xe⁵ inhalation) Xe⁵ inhalation was continued for the total time of recording the clearance of ¹³³Xe (8.5 minutes) and that this prolonged inhalation of Xe⁵ increased the CBF. However, during testing of autoregulation (CBF 4) Xe⁵ was inhaled for only 4 minutes prior to the injection of ¹³³Xe and continued for 4 minutes during recording of the clearance curves. In pilot experiments, increase in CBF and alteration of EEG were also noted after short-term inhalation for 3 minutes during the steady state.

Gur et al²⁰ observed in 3 baboons a rather constant flow alteration. In our study there were no particular effects on single cortical areas but there were some variations between individual animals despite the fact that all animals had similar steady-state flow values, autoregulation, and CO₂ reactivity. In our opinion the effect of Xe⁵ on individual flow regulation is variable and not predictable and precludes the use of a constant factor to calculate the natural flow using inhalation of 35% Xe⁵ in room air. Junck et al²¹ reported that inhalation of 40% Xe⁵ in oxygen caused rCBF increases in rats only if inhalation continued for at least 2 minutes. Inhalation for 1 minute resulted in increased flow only when 80% Xe⁵ in oxygen was used. The increase in CBF in their protocol was a maximum of 96% above baseline values. This is similar to our experience, with a maximum increase of 79% in 1 animal. However, the signal-to-noise ratio of the CT scanners available today is not low enough to get sufficient increase of Hounsfield units with inhalation of 35% Xe⁵ for only 1 minute. Winkler et al²² evaluated a single breath of 100% Xe⁵ to study CBF with a CT scanner in patients. We have not checked the effect of this protocol on CBF in baboons.

Prolonged administration of Xe⁵ over 45 minutes resulted in a decline in CBF. Thirty-eight minutes after the start of inhalation, CBF was estimated to be 26.4 ± 10.7 ml/100 g/min below baseline values. Gur et al²³ also reported an initial increase and subsequent decrease of CBF in baboons after several minutes of inhalation. Similar experiences were reported by Meyer et al²⁴ in patients and were believed to be due to pharmacologic effects. Since the progressive decrease of CBF parallels the slowing of EEG over time, it seems rather unlikely that CBF decreases after an initial incomplete equilibration.²⁵

There were mild changes in Paco₂ during the protocol. The maximum change of 1 animal during continuous inhalation of Xe⁵ was 2.9 mm Hg. To avoid artificial effects due to changing ventilatory volume or ventilatory rate during Xe⁵ inhalation (which could interfere with the transport of xenon across the lung-blood barrier) the rate and volume of controlled respiration were not altered during the change from N₂O-O₂ anesthesia to Xe⁵ in air ventilation. All rCBF values were corrected by the individual regional CO₂ reactivity factor. Even if one considers this factor not very exact it does not explain the alteration of CBF during Xe⁵ inhalation. Since hypercapnia during Xe⁵ inhalation enhanced CO₂-RF, which leads to a stronger...
increase of flow compared with hypercapnia during nitrous oxide-oxygen exposure. Xe may act as a vasodilator. This is also known for halogenated anesthetics. The increase in CBF during mild hypotension may substantiate the uncoupling of CBF from metabolic regulatory processes with inhalation of Xe. The increase in rCBF caused by administration of Xe during mild hypotension (autoregulation test, CBF 4) indicated that Xe even breaks the autoregulatory action. If we had made another steady-state measurement between CBF 3 and CBF 4 we would not have gotten information on this topic.

We have not tested autoregulatory capacity and CO2 reactivity during prolonged exposure to Xe. However, it is unlikely that during the decline in CBF autoregulation and CO2 reactivity would return to normal. At present we are studying these effects and the effect of 35% Xe on rCBF and intracranial pressure in baboons with acute localized ischemia of the brain.

The change in CBF during inhalation of Xe may not be due to alteration of Paco2 because we have observed only minor changes in Paco2. During short-term exposure to Xe, Paco2 tended to decrease (by a maximum of 2.6 mm Hg in individual animals), and during prolonged exposure it tended to increase. However, there was never a change in Paco2 of >2.8 mm Hg during the protocol. These only mild spontaneous changes in Paco2 do not agree with our findings in young volunteers, who, during short-term inhalation of Xe in oxygen, sometimes experience remarkable decreases in Paco2 due to hyperventilation (Hartmann et al, unpublished data). The mild reaction to altered Paco2 in baboons may be due to artificial ventilation with nitrous oxide in oxygen and relaxation.
The EEG changes with an initial depression of α- and β-wave activity and an increase in slow wave activity have already been noted by Morris et al. and Cullen and Gross during xenon anesthesia in humans. Burst suppression was not noted by either them or us, in contrast to experiences with other inhalation anesthetics like ether or cyclopropane. The subsequent depression of brain blood flow during continuous inhalation of Xe did not result in further changes of the EEG. It is possible that xenon exerts the typical anesthetic excitatory effect resulting in EEG changes and at the same time it may increase flow with a limited duration of action. CBF reduction at the later stage of continuous exposure then might reflect the anesthetic effect.

The effect of Xe on CBF and EEG may be transient. A few minutes after the end of Xe inhalation, CBF had returned to normal, and the EEG showed a pattern similar to that observed during the steady state. In summary: We have observed in healthy adult baboons an increase in CBF, paralleled by slowing of the EEG. It is possible that xenon exerts the typical anesthetic excitatory effect resulting in EEG changes and at the same time it may increase flow with a limited duration of action. CBF reduction at the later stage of continuous exposure then might reflect the anesthetic effect.

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