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# Effects of Inhaled Stable Xenon on Cerebral Blood Flow Velocity

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The effects of inhaled stable xenon gas on cerebral blood flow were studied with 23 transcranial Doppler examinations performed in 13 normal volunteers while breathing, 25, 30, or 35% xenon for 5 min. Doppler velocities from the middle cerebral artery rose significantly during inhalation in 85% of subjects and 78% of studies and decreased significantly in 15% of subjects and 17% of studies. These different velocity responses may represent different responses of pial vasculature to xenon. The mean velocity rise among those studies showing a significant increase was  $38 \pm 3.6\%$  (SEM). The velocity rise began 2 min after the start of xenon inhalation and increased rapidly, so that the velocities measured at the four times at which scans were obtained in our xenon CT protocol (0, 1.5, 3, and 5 min after the start of xenon inhalation) were significantly different. A consistent fall in the pulsatility of the Doppler waveform as the velocity increased provided evidence for xenon-induced vasodilatation of the small-resistance vessels as the cause of the increase in flow velocity. Most subjects became mildly hyperventilated, so that the observed changes could not be attributed to hypercapnia.

Inhalation of 25, 30, or 35% xenon for 5 min induces a delayed but significant rise in cerebral blood velocity. This suggests that cerebral blood flow itself may be rapidly changing during the process of xenon CT scanning. These changes may compromise the ability of the xenon CT technique to provide reliable quantitative measurements of cerebral blood flow.

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The measurement of cerebral blood flow (CBF) by xenon-enhanced CT methodology has become an important diagnostic tool in a variety of clinical situations [1-10]. Alterations in CBF detected by xenon scans have correlated well with the known behavior of CBF, and a determined research effort continues to develop the xenon technique into a quantitative tool [11-18]. Xenon itself, however, is known to affect CBF in animals and humans [19-23]; such efforts may have serious implications for the interpretation of flow values derived from the xenon scan. Previous investigators have measured CBF changes during xenon inhalation chiefly with  $^{133}\text{Xe}$  injection or microsphere methods, which can only be performed intermittently and have a poor time resolution. Therefore, the exact time course of any changes in CBF during xenon inhalation under the conditions of a typical xenon CT study have been unclear.

Standard xenon CT protocols use CT scans obtained during xenon inhalation to calculate CBF by measuring the time course of the xenon enhancement [2, 4-7, 24]. If a significant change in CBF were to occur during inhalation, the flow and lambda values might change in an unpredictable fashion, which would have profound implications for the use of xenon CT scanning for quantitative or serial studies.

A technique of transcranial Doppler sonography has recently been developed whereby blood velocity in the basal intracranial arteries can be measured noninvasively by means of an ultrasound probe held to the scalp [25, 26]. Trends in

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**TABLE 1: Changes in Doppler Velocities After Inhalation of Xenon Gas**

Case No.	Age (years)	Sex	% Xenon Concentration/Change in Doppler Velocity <sup>a</sup>
1	53	M	25↑, 30↑
2	37	F	25↑
3	30	M	25↑, 30↑
4	31	M	25↑, 30↑
5	31	M	25↑, 30↑
6	30	M	25↑, 30↑
7	36	M	25↑, 30↑, 35↑, 35↑
8	34	M	25↓, 30↓, 35↓
9	37	F	30↓
10	34	M	30↑
11	27	M	30↑
12	32	M	30↑
13	27	M	30↑

<sup>a</sup> ↑ = increase; ↓ = decrease; ↕ = no change.

middle cerebral artery (MCA) velocities obtained in this manner correlate with changes in hemispheric CBF, and the velocity can be measured continuously for prolonged periods [27–30].

The purpose of this report was to investigate the moment-to-moment changes in the CBF velocity during conditions approaching a typical xenon CT study in clinical practice.

## Subjects and Methods

### Subject Population

Twenty-three studies were performed in 13 normal volunteers 27–53 years old (mean,  $34 \pm 7$  years). There were 11 men and two women; no subject took medication or had a history of cardiovascular or cerebrovascular disease (Table 1).

### Xenon Inhalation

Each subject was studied while seated and breathing through a mask connected to an XBF xenon delivery system (Picker International, Cleveland, OH) that displayed continuous readings of end-tidal carbon dioxide, end-tidal xenon, and end-tidal oxygen. After 5–10 min of baseline recordings, xenon gas was administered at specific concentrations for 5 min. Subjects were observed and end-tidal carbon dioxide monitored to ensure an airtight mask seal.

### Transcranial Doppler Measurements

Transcranial Doppler measurements were taken from the M1 segment of the left MCA as described by Aaslid et al. [25, 26] with the use of an EME TC2-64 Doppler device attached to the head with an AMP-2 headband and probe (Carolina Medical Electronics, Inc., King, NC). Mean velocity was read directly from the Doppler device. For each measurement, the Gosling pulsatility index was calculated as systolic minus diastolic velocities divided by mean velocity. This index is a measure of the pulsatile energy of the velocity waveform, and is generally elevated during downstream (pial or arteriole) vasoconstriction [25].

### Study Protocol

MCA mean velocity, Gosling pulsatility [31], end-tidal carbon dioxide, and end-tidal xenon were recorded every 30 sec throughout each study. After 5 min of baseline recording, the subjects were asked to hyperventilate and hypoventilate, and a carbon dioxide vs MCA velocity curve was constructed. Xenon gas was then adminis-

tered at concentrations of 25%, 30%, or 35% (Table 1). Seven subjects inhaled two or more xenon concentrations; each study was separated by at least 30 min. Recording continued for 5–8 min after the end of xenon inhalation until baseline readings were regained. The xenon was well tolerated with only minor feelings of lightheadedness and minimal respiratory irregularities. The velocity readings were not visible to the subjects at any time during the studies.

## Results

### MCA Velocity

A statistically significant rise in MCA velocity ( $z$  test,  $p < .001$ ) was seen in 18 (78%) of the 23 studies and in 11 (85%) of the 13 subjects. No velocity change was seen in 4% of the studies, while a significant velocity decrease was seen in 17% of the studies and 15% of the subjects ( $z$  test,  $p < .001$ ). A typical study is shown in Figure 1.

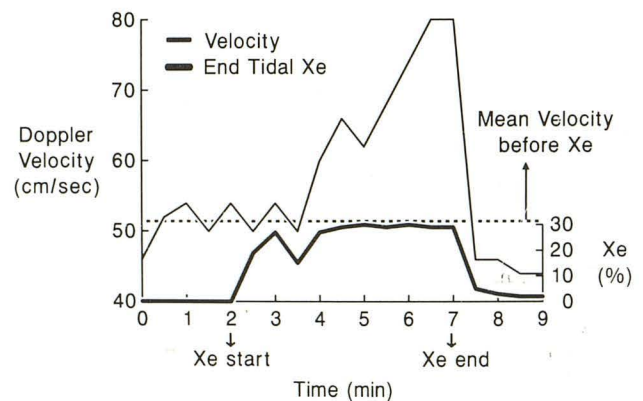
The mean velocity increase in those studies showing a significant velocity increase was  $38 \pm 3.6\%$  (SEM) (range, 14–69%).

### Differences Between Xenon Concentrations

Six of the studies done with 25% xenon and 10 done with 30% xenon showed some velocity elevation from baseline. In two (33%) of the six with 25% xenon and in nine (90%) of the 10 with 30% xenon, this elevation exceeded 30%; that is, studies at 30% xenon were three times as likely to show a velocity elevation exceeding 30% than those at 25% xenon. Furthermore, the seven patients studied at both 25% and 30% xenon concentrations showed 11% greater velocities at 30% concentrations ( $p < .05$ , matched  $t$  test) (Fig. 2).

### Velocity Rise Delay

The onset of the MCA velocity rise did not begin until about 2 min after the beginning of xenon inhalation (Fig. 1). In studies done with 25% xenon, the mean delay was  $2.1 \pm 0.32$  min (SEM). In studies done with 30% xenon, the mean delay was  $1.9 \pm 0.16$  min (SEM).



**Fig. 1.**—Mean middle cerebral artery velocities and end-tidal xenon readings during inhalation of 30% xenon in one patient. Velocity rise begins 2 min after start of xenon inhalation and continues throughout inhalation for a peak increase of 57% above baseline values. Note sharp fall in velocity at end of inhalation. End-tidal xenon curve indicates appropriate xenon delivery.



### Time Course of Velocity Rise

A popular xenon CT protocol calls for scans to be obtained before the onset of xenon inhalation and at 1.5, 3, and 5 min after the beginning of xenon inhalation. Accordingly, the maximum velocities attained during the time intervals from 0 to 1.5, 1.5 to 3, and 3 to 5 min after the start of xenon inhalation were recorded for each xenon concentration tested (Fig. 3). There was a statistically significant rise in velocity as time progressed at all three xenon concentrations ( $p < .05$ , analysis of variance, all concentrations;  $p < .01$ , individual  $t$  tests at 25% and 30%).

### Pulsatility

There was a statistically significant decrease in Doppler waveform pulsatility ( $p < .01$ ,  $z$  test) in 17 of the 18 studies in which velocity rose during xenon inhalation (Fig. 4). The mean decrease in pulsatility was 30%. The pulsatility drop preceded the velocity rise by  $0.73 \pm 0.22$  min (SEM), and the change in pulsatility was delayed from the start of xenon inhalation by about 1 min. The time taken for pulsatility to return to baseline levels after xenon inhalation ended was highly variable ( $1.2 \pm 0.33$  min, mean  $\pm$  SEM), with a range of 0 to greater than 4 min.

### Effect of Carbon Dioxide

Most of the subjects showed respiratory irregularities and mild hyperventilation during the studies. With the use of the

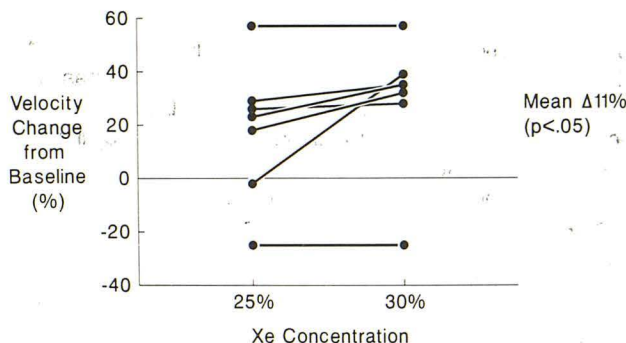


Fig. 2.—Changes in middle cerebral artery velocities in seven patients studied with both 25% and 30% xenon.

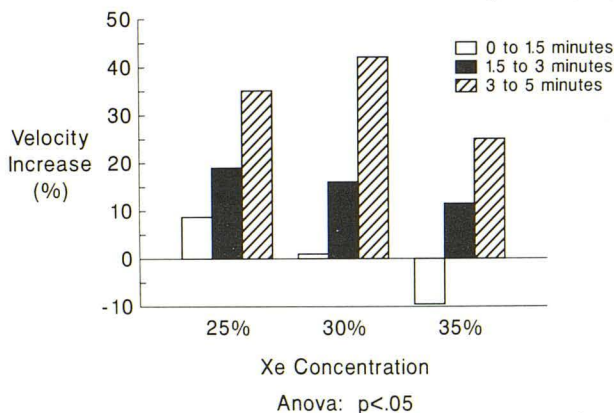


Fig. 3.—Mean middle cerebral artery velocity changes in 18 (78%) of 23 studies showing velocity increases by 5 min. Velocity increases significantly over the three time intervals during a 5-min xenon inhalation.

carbon dioxide velocity curves constructed at the beginning of each study, the measured velocity change could be compared with the expected velocity change (Fig. 5). For example, the transcranial Doppler study of the subject represented in Figure 5, done before xenon inhalation, showed mean velocities of 40, 49, and 51 cm/sec over the end-tidal carbon dioxide ranges of 30–31, 32–33, and 34–35%, respectively. Plotting these velocity values whenever the end-tidal carbon dioxide was in the corresponding ranges yielded the expected velocity curve in Figure 5. The measured change was 35–60% higher than the expected velocities using either peak velocity or mean velocity during the last 2 min of inhalation.

### Blood Pressure and Pulse

Pulse was monitored during each study and did not vary significantly, with the exception of one study that was not completed because of progressive tachycardia. It is well documented that inhaled xenon does not significantly alter blood pressure [32–36]. Accordingly, blood pressure was measured in only one study and did not vary before, during, or after this study.

### Discussion

The xenon-induced changes in CBF that have been reported in both animals and humans depend on the concentra-

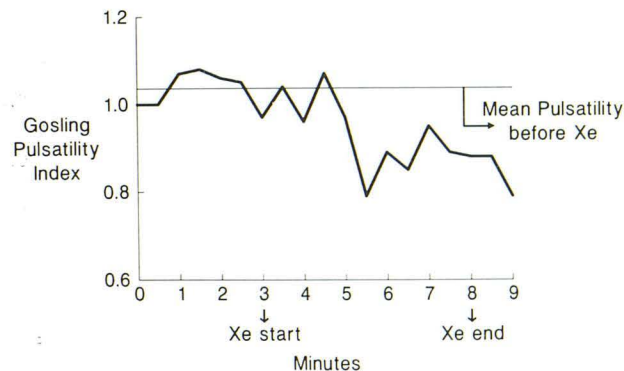


Fig. 4.—Pulsatility changes seen during typical study with 25% xenon. Onset of decrease occurs 2 min after beginning of xenon inhalation.

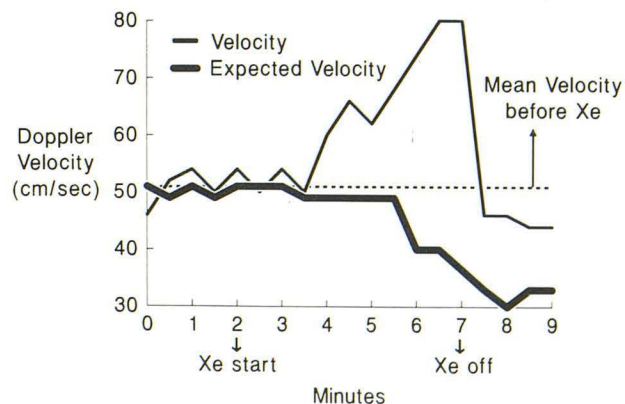


Fig. 5.—Measured mean middle cerebral artery velocities plotted with velocities expected for measured end-tidal carbon dioxide, based on measured carbon dioxide vs velocity curves. Measured velocity is significantly higher than expected, indicating that effects are not due to changes in carbon dioxide tension.



tion of inhaled xenon, the duration of inhalation, and the particular animal model; previous findings are summarized in Table 2. These studies indicate that although administration of xenon at high concentrations or for prolonged periods results in a fall in CBF, the inhalation of 35–40% xenon for 4–5 min leads to a 15–40% rise in CBF. Furthermore, two studies suggest that the flow rise might not begin until 1–2 min after the beginning of xenon inhalation [5, 22]. However, inferences regarding the precise time course of the CBF rise in humans cannot be made with confidence from animal studies, as the time course may be grossly affected by interspecies differences in xenon kinetics, which are largely unknown. Furthermore, intermittent  $^{133}\text{Xe}$  and microsphere measurements have poor time resolutions and cannot accurately measure the time course of the CBF rise.

The technique of blood velocity measurement in the basal cerebral arteries by transcranial Doppler sonography has been refined to allow reliable estimates of CBF. The Doppler velocities are not true velocities and do not correlate with actual CBF values. However, for a fixed probe angle and vessel diameter, it has been shown that changes in the Doppler velocity are directly proportional to changes in blood flow through the insonated vessel to within 5–15% [25–30, 38, 39]. Furthermore, under normal conditions, flow through the MCA reflects hemispheric CBF, and the MCA diameter changes only minimally with changes in blood pressure and carbon dioxide tension [28, 38]. Therefore, we have used Doppler signals from the MCA as a reliable estimate of CBF changes during xenon inhalation.

Transcranial Doppler velocity can be measured continuously in real time, and so is ideal for charting the exact time course of MCA velocity changes during relatively short periods. Furthermore, the Doppler waveform pulsatility index provides a continuous indication of the state of the tissues, as increases in pulsatility generally indicate vasoconstriction of small vessels [25, 31].

Although the effects of xenon on the caliber of the MCA have not been measured directly, it is unlikely that xenon induces a significant change in diameter. A diminished diameter would tend to produce a fall in CBF, contrary to the rise observed in several studies. Furthermore, a velocity rise of 40% would require a decrease of 30% in the cross-sectional area of the MCA. In a review of transcranial Doppler studies of vasospastic arterial segments and of arteries feeding arteriovenous malformations, a velocity increase of 40% was

associated with a mean pulsatility decrease of only 6% in the spastic segments but of 39% in the arteriovenous malformations. Similar data were found in transcranial Doppler studies of an artificial model of a vascular segment (Giller CA, unpublished data). This suggests that the observed mean increased velocity of 38% during xenon inhalation was a consequence of a decrease in distal resistance (i.e., pial or arteriolar vasodilation) rather than MCA narrowing.

Our results suggest there is a 38% rise in cerebral blood velocity during xenon inhalation with a high intersubject variability. Inhalation of 30% xenon produces a slightly greater and more frequent velocity rise than 25% xenon. Both the velocity increase and the pulsatility decrease begin about 2 min after the start of xenon inhalation, suggesting that the velocity increase is due to xenon-induced dilatation of small-resistance vessels. The velocity increases steadily and significantly during the 5-min period of xenon inhalation, so that flow velocities are significantly different at the various times in the xenon CT protocol that the scans are obtained.

Respiratory irregularities are not uncommon during xenon inhalation [23–36, 40–42]; most of our subjects became mildly hypocapnic. The observed velocity increase therefore was not due to changes in carbon dioxide tension; indeed, it may have been attenuated by hyperventilation. Our impression was that moderate hyperventilation provided protection from the xenon-induced velocity rise, and it is known that carbon dioxide and xenon have additive effects on CBF [23]. This suggests that moderate hyperventilation is necessary for paralyzed, intubated patients who cannot spontaneously hyperventilate in order to avoid dangerous elevations in CBF and intracranial pressure.

A delay between the start of xenon inhalation and the velocity rise was seen in most of our studies and has been noted in animals [5, 22]. Similar delays in EEG activity have been reported in humans [43]. In an interesting study in which parameria were subjected to various partial pressures of dissolved xenon gas, severe effects on membrane function were seen at threshold levels of xenon; these correlate with concentrations producing narcosis in multicellular organisms [44]. It is possible that the delays in transcranial Doppler velocity and pulsatility changes are due to sudden membrane effects at the molecular level once a xenon threshold has been reached.

Although the first 2 min of xenon inhalation were relatively free of changes in cerebral blood velocity, reliable calculation

**TABLE 2: Previous Findings on the Effects of Xenon on Cerebral Blood Flow**

Study Population/Source	% Xenon Concentration	Duration (min)	% Change in CBF	Technique
<b>Animal</b>				
Gur et al. [5]	Unknown	2	No change	Unknown
	Unknown	8	–25	Unknown
Gur et al. [21]	35–42	2–5	+12	Microsphere
Junck et al. [22]	40	1	No change	$^{14}\text{C}$ IAP
	40	2	+81	$^{14}\text{C}$ IAP
	80	1 or 2	+100	$^{14}\text{C}$ IAP
Dettmers et al. [19]	35	10	+22	$^{133}\text{Xe}$ injection
	35	>10	–50	$^{133}\text{Xe}$ injection
<b>Human</b>				
Meyer et al. [6]	45	Unknown	–20	$^{133}\text{Xe}$ inhalation
Ip [37]	50	Unknown	+56	$^{133}\text{Xe}$ inhalation
Obrist et al. [23]	30–35	3	+28	$^{133}\text{Xe}$ injection
Dettmers et al. [19]	35	5	+13	$^{133}\text{Xe}$ injection



of flow requires accurate knowledge of the xenon tissue saturation curve, which can be derived only from scans obtained at later times when cerebral blood velocity (and perhaps CBF) is rapidly changing. Even though significant errors can also arise with use of early scans [6, 7, 16], examples have nevertheless been reported in humans in which flow values from early and late scanning do not differ [45]. This agreement has been attributed to a diffusion effect that counteracts the effect of a flow increase [46]. Agreement has also been reported between flow values obtained at 2.4 and 4.1 min in six humans breathing 35% xenon [6]; Kishore et al. [15] suggested that flows derived from different combinations of early and late xenon CT scans resulted in similar flow values but did not give human data [15]. The exact effects of xenon on xenon CT values and on the optimal time for scan acquisition remain unclear.

The potential effect of xenon on xenon-derived CBF values can be seen from consideration of the flow calculation algorithm. This algorithm uses CT and end-tidal xenon data to produce an approximate xenon tissue saturation vs time curve. This curve ascends fairly rapidly to a stable value (at large time values), which is called  $\lambda$ . The steepness of ascent is related to the rate constant, and flow is equal to the product of  $\lambda$  and the rate constant [24]. An increase in CBF during xenon inhalation will cause a steepening and distortion of the xenon tissue saturation vs time curve so that the curve-fitted (Kety) solution to it will yield a falsely high  $\lambda$  value. The corresponding rate constant and flow may be falsely high, low, or unchanged, depending on the exact alteration of the saturation curve. For example, an increase in selected gray-matter saturation values conceivably may lead to a Kety solution identical to that of white matter; that is, a solution with a high  $\lambda$  value but lower flow. Preliminary computer simulations assuming a rise in CBF during inhalation have confirmed the calculation of both significantly falsely high and low flow values for various choices of scanning times. Further computer simulation and analysis of human xenon CT scans is ongoing to investigate these surprising changes, and will be the subject of another report.

If inhaled xenon induces a true rise in CBF, intuition suggests that the only possible effect on xenon CT flow values should be false elevation. Indeed, it has been suggested that such a flow activation would even accentuate the measurement of low flow and might be important only as a scaling error [1, 21, 47]. However, as just discussed, the effect of a CBF rise may be to actually decrease the calculated flow values. Furthermore, four studies in two of our subjects showed a statistically significant decrease in MCA velocity during xenon inhalation. Insofar as cerebral blood velocity is proportional to CBF, these data suggest that in some individuals, xenon may produce a significant decrease in CBF at standard conditions (i.e., 30% xenon for 5 min). Such an effect has been documented at higher concentrations and longer inhalation periods [6, 7], and may be related to the efficacy of xenon as an anesthetic agent. Therefore, it cannot be safely assumed that the only possible effect of xenon is to increase CBF; in some individuals xenon may actually induce a decrease in CBF. The reliability of the xenon CT technique in detecting both low and high flow states may need to be reassessed in light of the potential of xenon to unpredictably increase or decrease CBF.

The effects of xenon on abnormal tissue are understood

even less well. While it is known that tumors, arteriovenous malformations, and ischemic tissue may have vastly altered vasoreactivities, the responses to xenon have not been studied systematically. Differing reactivities to xenon may have profound implications for interpretation of xenon CT flow studies performed serially, since tissue characteristics may change dramatically as the disease process evolves. Furthermore, even an effect on CBF of 20–30%, especially if focal, may significantly alter the interpretation of the xenon CT scan; changes of this magnitude are routinely taken as evidence of tissue pathology and are of the same magnitude as those produced in provocative studies with agents such as acetazolamide [1, 48]. We reiterate that the differential effects of xenon on CBF in abnormal tissues are completely unknown.

The conditions of our studies were arranged to closely simulate the conditions of a typical xenon CT study in that the subjects received explanations in the same fashion as patients would and could not see the Doppler readings during the studies. Although anxiety is known to affect CBF, we do not believe the reactions of our subjects were significantly different from those of patients. Furthermore, the sharp fall in velocity at the end of xenon inhalation and the drop in pulsatility (rather than a rise) are compelling evidence against a psychogenic, autonomic origin for the observed changes.

Xenon CT measurement of CBF remains an important clinical tool, and numerous reported examples show a close correlation between xenon CT flow values and known CBF changes in a multitude of clinical situations. We are concerned, however, that quantitative comparison of xenon CT flow values among patients or in a single patient examined serially may be confounded by a significant alteration of CBF during the scanning process, and that the high variability of this response to xenon may prevent routine numeric correction. Further investigations into the effect of xenon on xenon CT flow values in humans will be enlightening.

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