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Physiologic implications of adding small amounts of carbon dioxide to the gas mixture during inhalation of xenon

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Summary. In addition to being a physiologically active tracer of CBF, xenon (Xe) in subanesthetic concentrations produces a relatively mild lowering of carbon dioxide (CO_2) in the blood and elevation of transcranial Doppler (TCD) velocity. The addition of small concentrations of CO_2 (0.4–1.2%) to the inhaled mixture produced no measurable effect on end tidal (P_{et}) CO_2 or TCD velocity. Cerebral blood flow (CBF) alterations induced by Xe are minimized by allowing $P_{et}CO_2$ to fall, permitting quantitative measurement of CBF by the Xe/CT CBF method.

Key words: Xenon – Transcranial Doppler – Normal control

Xenon (Xe), when used in concentrations greater than 80%, has been known for several decades to be an effective and safe inhalation anesthetic [1–5]. In recent years, Xe in subanesthetic concentrations (< 50%) has been used as a contrast medium during computed tomography in neurology and neurosurgery [6–11]. While inhalation of Xe at a concentration of 33% produces a rapidly reversible, pleasant, intoxicated feeling in most individuals, adverse reactions associated with Xe, including headache, nausea and vomiting, change in neurologic status, and seizures, do occur with a frequency of less than 0.7%. Elevation of cerebral blood flow (CBF) has been observed by many investigators [12–16], despite the concurrent observation that Xe inhalation is commonly accompanied by a 3–4 mm Hg reduction in end-tidal carbon tension ($P_{et}CO_2$) [12, 13, 17]. Because variations in CO_2 with their potential alteration of CBF may confound assessment of the impact of Xe on the latter, we have examined whether the addition of low concentrations of CO_2 (0.4–1.2%) would prevent reductions in $P_{et}CO_2$ or alter flow velocity of the middle cerebral artery (MCA), blood pressure (BP), or heart rate (HR), compared with the values observed during Xe inhalation without added CO_2.

Methods

Fifteen healthy adult subjects, 8 males and 7 females between the ages of 33 and 69 (49 ± 12) yr were recruited. None had a history of head injury, or of cerebrovascular, heart or lung disease. All gave signed, informed consent and received remuneration for their participation in accordance with the guidelines of the University of Pittsburgh's Institutional Review Board.

All subjects abstained from food and drink for at least 4 h prior to the study. Electrocardiogram (EKG) and 12 lead electroencephalogram (EEG) were recorded using surface electrodes. Sytemic arterial blood pressure (BP) was recorded using a Critikon Dynamap (Johnson and Johnson, Tampa, FL) calibrated against a mercury manometer. End-tidal xenon tension ($P_{et}Xe$) was monitored by a thermoconductivity analyzer, and $P_{et}CO_2$ was monitored by infra-red capnography. Oxyhemoglobin saturation was monitored by ear oximetry. CBF velocities were measured by transcranial Doppler (TCD).

Subjects were seated in a comfortable chair throughout the test session. Wearing a nose-clip, they initially breathed room air through a mouthpiece attached to a low dead-space, two-way non-rebreathing valve. After breathing pattern and $P_{et}CO_2$ stabilized, baseline data were recorded for 3–5 minutes, after which a valve was turned to permit inhalation of 33% Xe/67% O_2 (Trial 1) for up to 7 min. This gas mixture was chosen because it is the most widely used clinically. Subsequent similar trials were performed using 0.4% CO_2/33% Xe/balance O_2 (Trial 2), 0.8% CO_2/33% Xe/balance O_2 (Trial 3), 1.2% CO_2/33% Xe/balance O_2 (Trial 4). Thirty min rest periods separated the trials.

Subjects were watched at all times, and if they indicated any unpleasant side effects, inhalation of the Xe mixture was terminated immediately. Some subjects had a tendency to become inattentive, though still awake, during Xe inhalation and it was occasionally necessary to remind them to continue to use the mouthpiece. A trial was considered to be terminated if the subject inadvertently disconnected from the mouthpiece.

After each Xe inhalation trial subjects were verbally questioned about their response to Xe and asked to rate on a scale of 1–10 (1 = loved, 10 = hated) the degree to which they either liked breathing Xe.

$P_{et}CO_2$ data were analyzed on a breath-by-breath basis. Occasional breaths associated with expired CO_2 tracings that did not exhibit a definite and expiratory plateau were excluded from the analysis. BP and TCD were measured every minute during baseline data collection and xenon inhalation periods. Statistical analyses were performed using SPSSX, a standard statistical software package. Growth curve analysis was used to determine the time at which $P_{et}Xe$ reached equilibrium. Repeated measures, two way, multiple analyses of variance (MANOVA) were used to determine trial and time

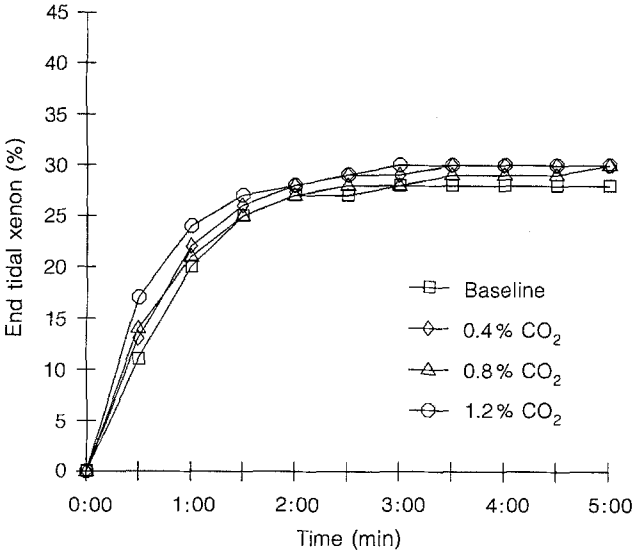

Fig. 1. Change in mean values of P_{et} Xe at 0.5 min intervals following initiation of inhalation

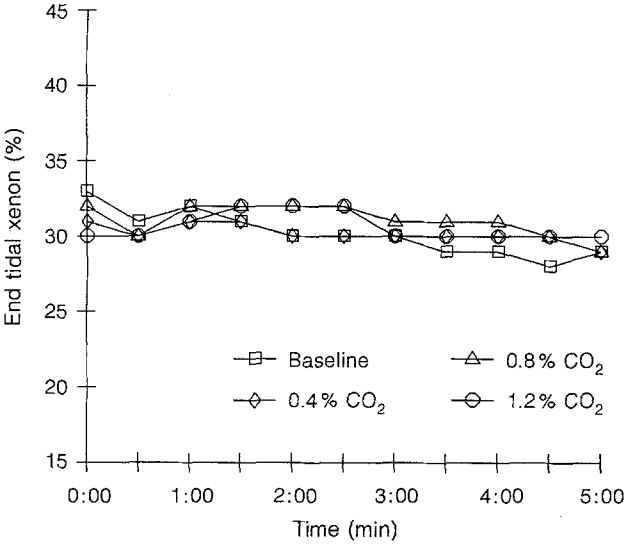

Fig. 2. Change in mean values of P_{et} CO_2 at 0.5 min intervals following initiation of inhalation

course differences from baseline. Statistical significance of differences was assigned at the $p \leq 0.05$ level. Data are presented as mean ± standard deviation. Since not all subjects were able to complete 7 min of Xe inhalation due to inability to maintain a tight seal about the mouthpiece, statistical analysis was performed only on the data collected during the first 5 min of inhalation. Three subjects were not able to participate in Trial 4 due to nausea.

Results

Three of the 15 subjects rated the Xe inhalation experience as more unpleasant than neutral. Two of these experienced nausea, but had pleasant sensations while breathing Xe, up to the time they began to feel ill. A third subject became nauseated during Trial 4.

In all subjects across all trials P_{et}Xe rapidly increased from 0 mm Hg at time zero to an equilibrium of

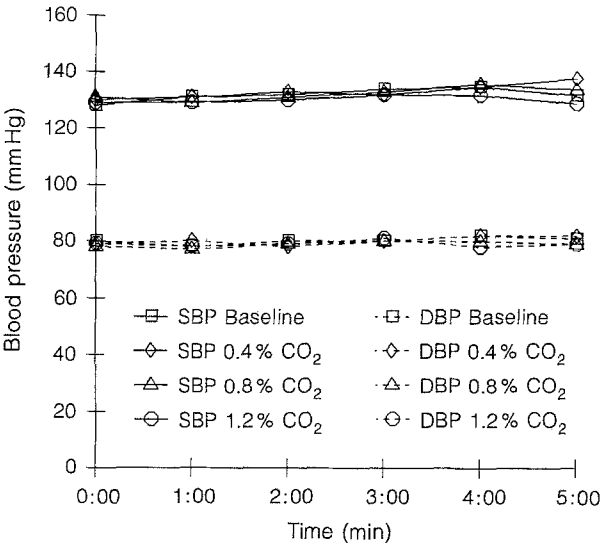

Fig. 3. Systolic (solid lines) and diastolic BP (dashed lines) during the 4 trials

28 ± 4 mm Hg in 2.5 min by growth curve analysis (Fig. 1). Following equilibration, mean P_{et}Xe fluctuated between 27 and 30 mm Hg during the remainder of all four trials. Because there were no significant differences in the P_{et}Xe curves or any other variables between the four breathing trials only data from Trial 1 are presented in Table 1.

$P_{et}CO_2$ decreased over time from 33 ± 6 to 29 ± 8 mm Hg during the first 5 min of Trial 1 (MANOVA, $p < 0.0001$) (Table 1). There was no difference in baseline $P_{et}CO_2$ or equilibration $P_{et}CO_2$ across the 4 trials (Fig. 2).

During Trial 1 systolic BP (SBP) did not change significantly from a baseline of 128 ± 11 mm Hg, nor did diastolic BP (DBP) change significantly from a baseline value of 80 ± 7 mm Hg (Table 1). There were no significant BP differences during the baseline and Xe inhalation periods within each trial or across the 4 trials (Fig. 3).

During Trial 1, HR did not change significantly from a baseline of 68 ± 8 beats per minute (Table 1). There were no significant changes within any trial or across the 4 trials (Fig. 4).

During Trial 1, TCD increased significantly from a baseline of 51 ± 16 to 61 ± 23 cm/s (20%) by 5 min after the initiation of Xe inhalation (MANOVA, $p < 0.0001$) (Table 1). This change was typical of that observed during all 4 trials, and although there is a trend towards increased flow velocity with increased CO_2 content, there were no significant differences between trials (Fig. 5). There was no correlation between TCD and $P_{et}CO_2$.

Discussion

This study confirms the observations that Xe is a tracer of CBF which is also physiologically active, tending to augment TCD recorded velocities despite an associated reduction of $P_{et}CO_2$. Our data do not confirm those of our earlier, less well controlled investigation which suggested that a reduction in $P_{et}CO_2$ may be minimized by adding

Table 1. Physiological responses to 33% Xe/67% O_2

Variable	Time (minutes)					
	BL	1.0	2.0	3.0	4.0	5.0
$P_{et}Xe$*						
mean	0	20	27	28	28	28
std dev		7	3	3	2	2
$P_{et}CO_2$*						
mean	33	31	30	29	28	27
std dev	6	8	8	8	8	9
TCD (cm/min)*						
mean	51	52	53	56	60	61
std dev	16	19	19	19	19	23
SBP (mm Hg)						
mean	127	131	132	134	135	132
std dev	11	13	17	18	21	21
DBP (mm Hg)						
mean	80	78	80	80	82	81
std dev	7	8	10	10	8	9
HR (beats/min)						
mean	68	70	66	67	68	67
std dev	8	11	9	9	10	9

* $p < 0.0001$ up to 5 min

$P_{et}Xe$ percent end tidal xenon, *$P_{et}CO_2$* percent end tidal carbon dioxide, *TCD* transcranial Doppler, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate

relatively small percentages (0.4–1.2%) of CO_2 to the inhalation mixture [18]. No significant alteration in $P_{et}CO_2$ or TCD velocities was observed in normal volunteers despite the addition of 0.4, 0.8, or 1.2% CO_2 to the 33% Xe/balance O_2 inhalation mixture.

Obrist et al. [Obrist WD, personal communication] found that addition of bursts of 0.5–5.0 cc/min 100% CO_2 was needed to stabilize $P_{et}CO_2$ during inhalation of 33% Xe. A relatively constant increase of 30.1 ± 16% and 41.4 ± 24% in CBF_{15} (weighted average of white and gray flows) and ISI (gray matter flow) respectively was observed when $P_{et}CO_2$ was stabilized [13, 19]. However, if $P_{et}CO_2$ was allowed to vary, as naturally occurs with Xe inhalation, CBF_{15} and ISI increased 16.7 ± 23% and 28.3 ± 34% respectively. Our data and those of Obrist et al. [Obrist WD, personal communication] support the speculation of Giller et al. [16] that hyperventilation with hypocapnia may in fact be useful in minimizing increases in CBF associated with Xe inhalation.

While alteration of CBF during the introduction of a diffusional tracer of CBF theoretically violates a basic premise of the Kety-Schmidt principle, computer simulation studies have shown that the effect on calculated flow values despite flow activation are minimized by our current Xe/CT CBF method [19, 20]. Fast flow information is obtained during the initial 2–3 min of Xe inhalation, prior to significant CBF activation, while slow flow, which requires a longer period of data acquisition, tends to be elevated. This elevation may be a function of the Xe tracer gas itself, the result is a minimal "false" elevation (< 5%) in measured flow even in the situation of maximal activation (45% activation). Future developments of the Xe/CT CBF method should allow use of lower concentrations (26%) of Xe with comparable image resolution.

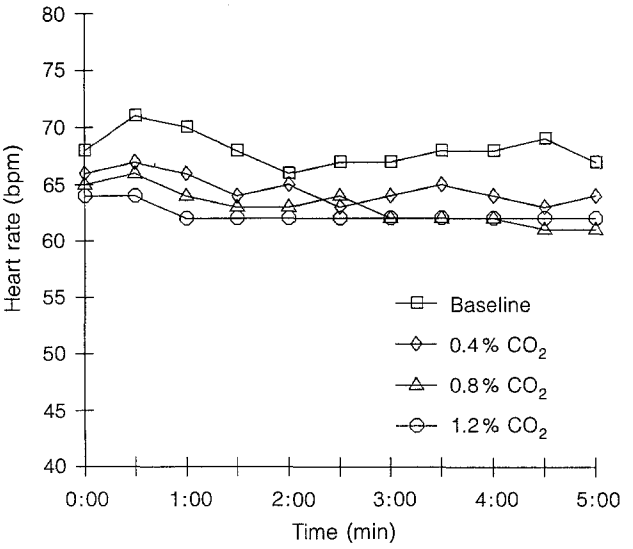

Fig. 4. Heart rate during the 4 trials

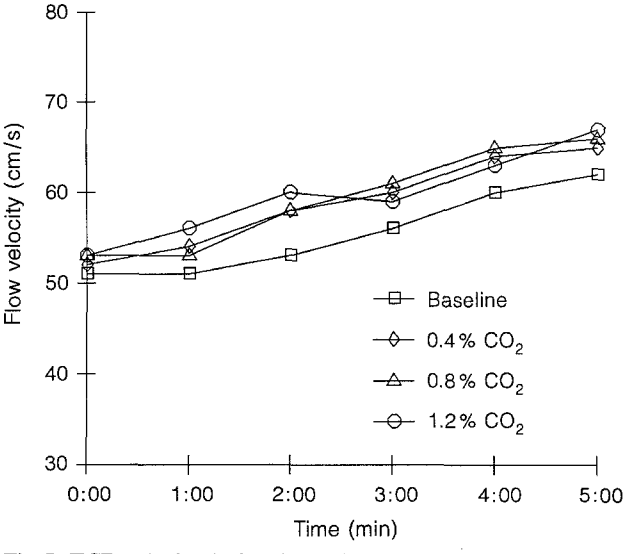

Fig. 5. TCD velocity during the 4 trials

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