

# Influence of Changes in Arterial Carbon Dioxide Tension on the Electroencephalogram and Posterior Tibial Nerve Somatosensory Cortical Evoked Potentials during Alfentanil/ Nitrous Oxide Anesthesia

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The effects of variation of arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>) on the electroencephalogram (EEG) and posterior tibial nerve somatosensory cortical evoked potentials (PTN-SCEP) during opioid/N<sub>2</sub>O anesthesia have not been well documented. We studied the effects of hypocapnia (PaCO<sub>2</sub> ≈ 23 mmHg) and hypercapnia (PaCO<sub>2</sub> ≈ 50 mmHg) during steady-state alfentanil/N<sub>2</sub>O anesthesia in 16 patients. EEG and PTN-SCEP were recorded continuously, while PaCO<sub>2</sub> was altered in 15-min intervals by varying the inspired CO<sub>2</sub> concentration. Hypocapnia caused significant increases in power in the delta, theta, and beta bands ( $P < 0.01$ ), with the greatest increase observed in the alpha band. Relative power increased in the alpha band but remained unchanged in the delta, theta, and beta bands. Median frequency and 95% spectral edge frequency were unaltered during hypocapnia. In contrast, hypercapnia caused a significant decrease of power in the alpha and beta bands, whereas delta and theta power remained unchanged. This was reflected in a significant decrease of the 95% spectral edge frequency, from 8.9 (6.7-11.6) to 7.0 (5.6-8.6) Hz. All EEG parameters returned to normal upon restoration of normocapnia. There was a significant negative correlation between power in the alpha band and end-tidal CO<sub>2</sub> in all patients ( $r = -0.47$  to  $-0.89$ ). PTN-SCEP latencies and amplitudes were not significantly different from control values during hypocapnia and hypercapnia. It is concluded that variations in PaCO<sub>2</sub> within the limits 20-50 mmHg produce substantial changes in the EEG power spectrum, especially in the alpha band (8-12 Hz), but do not alter PTN-SCEP. (Key words: Carbon dioxide; hypocapnia; hypercapnia. Monitoring: evoked potentials; somatosensory; electroencephalography.)

THE ELECTROENCEPHALOGRAM (EEG) and somatosensory evoked potentials (SEP) are frequently used to monitor nervous system pathways at risk during surgical procedures.<sup>1-8</sup> Because substantial variation in arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>) may occur in anesthetized patients, it is important to know how PaCO<sub>2</sub> influences these electrophysiologic recordings. There are several reports that

suggest that changes in CO<sub>2</sub> can alter the pattern of the EEG,<sup>9-15</sup> although the information is incomplete and apparently inconsistent. The effects of hypocapnia on the EEG during anesthesia with inhalational agents are well documented.<sup>12-15</sup> However, there have been no studies that quantify the effects of varying PaCO<sub>2</sub> on the EEG during opioid/N<sub>2</sub>O anesthesia. Similarly, although SEP are frequently used to monitor the integrity of the spinal cord intraoperatively, the influence of CO<sub>2</sub> has not been well documented. The purpose of this study was to investigate the effects of hypocapnia and hypercapnia on the EEG and posterior tibial nerve somatosensory cortical evoked potentials (PTN-SCEP) during alfentanil/N<sub>2</sub>O anesthesia.

## Materials and Methods

Eighteen patients, ASA physical status 1, undergoing elective surgery lasting longer than 2-3 h in which minimal surgical trauma and blood loss were expected (*e.g.*, dental surgery or vasovasostomy) were studied. All patients gave informed consent to participate in the study, which was approved by the local medical ethics committee. All patients were aged between 18 and 45 yr and were free from neurologic disease. None was taking any drugs known to affect the EEG or SCEP.

## ANESTHESIA

All patients were given diazepam 10 mg orally 1 h before arrival in the operation room. Anesthesia was induced with thiopental 3 mg/kg and with a loading dose of alfentanil 100 μg/kg given over 10 min. Pancuronium 0.1 mg/kg was given for muscle relaxation. Anesthesia was maintained with N<sub>2</sub>O 66% in O<sub>2</sub> and a continuous infusion of alfentanil 2 μg · kg<sup>-1</sup> · min<sup>-1</sup>. Additional pancuronium was given to maintain neuromuscular relaxation as indicated by train-of-four stimulation. An increase in heart rate or mean arterial blood pressure by more than 15% from the preinduction values was taken as an indication of inadequate anesthesia. If, at any time during the study, anesthesia was inadequate, an additional bolus dose of alfentanil, 1 mg, was given and the patient excluded from

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the study. During the operation, ECG, end-tidal CO<sub>2</sub>, intraarterial blood pressure, hemoglobin oxygen saturation (SpO<sub>2</sub>), and nasopharyngeal temperature were continuously monitored. All patients received lactated Ringer's solution. No fluids containing glucose were administered before or during the study period. To prevent hypothermia, infusion fluids were warmed to 38° C and a warming mattress was used.

Patients' lungs were ventilated with a Siemens Servo 900C ventilator equipped with rotameters for O<sub>2</sub>, N<sub>2</sub>O, and CO<sub>2</sub>. An open system with a fresh gas flow of 15 l/min was used. End-tidal CO<sub>2</sub> was analyzed using a mainstream capnograph (Hewlett-Packard 8534A) situated at the connector of the endotracheal tube. A two-point calibration procedure was performed before each session. After induction of anesthesia, ventilatory rate and minute volume were adjusted to obtain a steady-state end-tidal CO<sub>2</sub> tension of 20–22 mmHg for a period of 5 min. These ventilator settings were then maintained throughout the study.

During the study PaCO<sub>2</sub> was manipulated at constant minute volume by altering the inspired CO<sub>2</sub> concentration. The arterial to end-tidal CO<sub>2</sub> tension difference was taken into account during the CO<sub>2</sub> manipulations, which involved administration of CO<sub>2</sub> in the fresh gas flow. The study was begun after a period of at least 10 min of normocapnia and no earlier than 30 min after skin incision. After an additional 15-min control period of normocapnia, either hypocapnia or hypercapnia was induced according to a computer-generated list of random numbers. This was followed by a second normocapnic period of 15 min. Then a period of either hyper- or hypocapnia was induced, depending on the CO<sub>2</sub> concentration during the first period. This was followed by a third 15-min period of normocapnia.

Arterial blood gas analyses were performed 10 min after the start of each period. Blood samples were drawn in heparinized glass syringes, stored in ice, and analyzed within 15 min on an acid-base analyzer (ABL III, Radiometer, Copenhagen, Denmark).

#### EEG RECORDING

Two EEG channels were recorded continuously during the study period from F<sub>pz</sub>-C<sub>z</sub>' (2 cm behind C<sub>z</sub>) and F<sub>pz</sub>-O<sub>2</sub> (international 10–20 system), using Ag-AgCl colloid-attached disc electrodes, filled with electrode jelly. Electrode impedance was maintained below 2 kΩ. The EEG signal was amplified 20,000 times using Nicolet SM-200 EEG-amplifiers (Nicolet Instruments, Madison, WI), and the signal was filtered between 1 and 30 Hz (–3 dB). The EEG signal was displayed on an oscilloscope and was recorded with the ECG, arterial blood pressure waveform,

capnographic waveform, and temperature on a digital tape recorder (EDR 8000, Earth Data Limited, Southampton, UK), using 16-bit analog-to-digital conversion and a 256-Hz sampling rate.

#### EEG ANALYSIS

Four second epochs of digitally recorded EEG were subjected off-line to fast Fourier spectral analysis on a Nicolet Pathfinder II (Nicolet Instruments, Madison, WI), using Frequency Analysis Program V2.0. Epochs containing amplitudes greater than 200 μV were designated as artifact and automatically rejected. If the number of epochs containing artifact exceeded 15% of the total number of epochs during the study period, the patient was excluded from the analysis of the processed EEG. For each epoch the following parameters were derived from the power spectrum: total, delta-band (0.5–3.0 Hz), theta-band (3.25–8.0 Hz), alpha-band (8.25–13.0 Hz), and beta-band (13.25–30.0 Hz) powers, and 95 and 50% spectral edge frequencies (median frequency). A clinical neurophysiologist (EHB) who was experienced in the interpretation of intraoperative EEG patterns but blinded to the end-tidal and PaCO<sub>2</sub> data inspected the raw EEG to detect transient phenomena, such as the presence or absence of spike-wave activity, burst-suppression, and artifacts.

#### STATISTICAL ANALYSIS

Data from each 4-s epoch during the last 5 min of each CO<sub>2</sub> period were averaged and used in the statistical analysis. EEG spectral data were log-transformed to make the contribution to the total variance from each subgroup more uniform. Analysis of variance (ANOVA) for repeated measurements was used to test for changes among normocapnia, hypocapnia, or hypercapnia (BMDP statistical package, program 2V). A separate ANOVA was performed on the data from the three normocapnic intervals to detect any trend occurring over time during the study period. When the F-ratio of the analysis of variance reached  $P < 0.05$ , differences between normocapnia and hypocapnia or hypercapnia and between hypocapnia and hypercapnia were compared using paired *t* tests with the Bonferroni correction for multiple comparisons. The first normocapnic period of the study was used for comparison with hypocapnia and hypercapnia. When a spectral parameter changed significantly during both hypocapnia and hypercapnia, linear regression analysis was performed, and correlation between end-tidal CO<sub>2</sub> and that EEG parameter was calculated for each patient. The data sets used in each regression analysis consisted of 112 epochs of 40 s each. Results from the power spectral EEG analysis are presented as mean and 95% confidence intervals.

TABLE 1. Ventilatory and Hemodynamic Variables during Normocapnia, Hypocapnia, and Hypercapnia

	Normo 1	Hypo	Normo 2	Hyper	Normo 3
End-tidal P <sub>CO<sub>2</sub></sub> (mmHg)	38 ± 1.4	20 ± 1.3	38 ± 1.4	50 ± 2.6	39 ± 2.1
Arterial P <sub>CO<sub>2</sub></sub> (mmHg)	39 ± 2.3	24 ± 2.8	38 ± 2.9	50 ± 2.8	40 ± 2.9
Arterial pH	7.38 ± 0.02	7.54 ± 0.04	7.38 ± 0.02	7.29 ± 0.02	7.37 ± 0.02
Arterial P <sub>O<sub>2</sub></sub> (mmHg)	198 ± 28	180 ± 42	191 ± 38	199 ± 52	191 ± 40
MAP (mmHg)	92 ± 14	94 ± 11	92 ± 18	96 ± 16	96 ± 15
Heart rate (beats per min)	75 ± 13	77 ± 15	74 ± 15	76 ± 16	75 ± 15
NPT (°C)	35.6 ± 0.4	35.6 ± 0.5	35.6 ± 0.5	35.8 ± 0.5	35.8 ± 0.37

Results are mean ± SD. Number of observations: 16.  
Normo 1, Normo 2, Normo 3 = normocapnic control periods; Hypo

= hypocapnia; Hyper = hypercapnia; MAP = mean arterial pressure; NPT = nasopharyngeal temperature.

### SOMATOSENSORY EVOKED POTENTIALS RECORDING AND ANALYSIS

A Nicolet Pathfinder II system was used for stimulation and recording. Both posterior tibial nerves were stimulated at the ankle using constant-current square-wave pulses with a duration of 200  $\mu$ s and a frequency of 3.1 Hz. SEP were recorded from the scalp electrodes (C<sub>z</sub>'-F<sub>pz</sub>). The raw EEG signal was amplified 20,000 times and filtered between 5 and 250 Hz (-3 dB). For each waveform, 320 sweeps were averaged. Averages were made with 512 data points on a time base of 200 ms, giving a horizontal resolution of 0.4 ms. In all groups, PTN-SCEP were acquired continuously, starting 30 min after induction of anesthesia.

The continuous acquisition of SCEP waveforms was controlled by a computer program that automatically stored the waveforms on hard disk together with the values of mean arterial pressure, end-tidal CO<sub>2</sub>, and nasopharyngeal temperature derived from the patient monitor (Hewlett-Packard 3854A). Acquisition was automatically halted when diathermy was used. For each waveform,

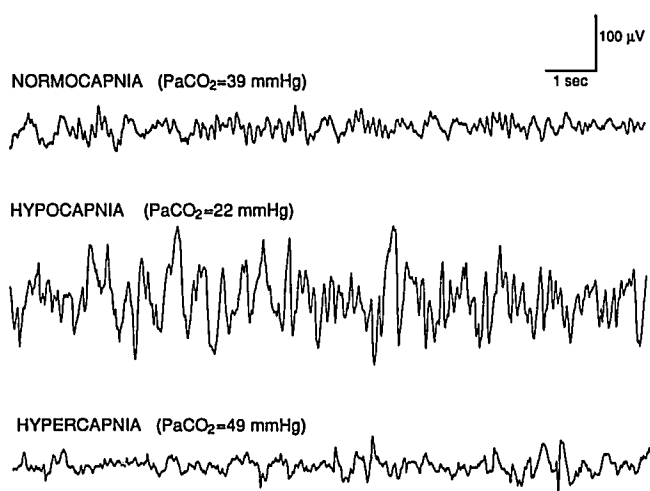


FIG. 1. Representative EEG traces from one patient during normocapnia, hypocapnia, and hypercapnia.

latencies and peak-to-peak amplitudes of primary cortical peaks P1 to N2 were identified using on-screen cursors. Data from two successive waveforms recorded during the last 5 min of each CO<sub>2</sub> period were averaged and analyzed with analysis of variance for repeated measurements (BMDP program 2V). Where appropriate, comparisons were made using paired *t* tests with the Bonferroni correction for multiple comparisons. All PTN-SCEP data are expressed as means ± standard deviation.

### Results

Eighteen patients entered the study. Their average age was 31.6 ± 7.4 yr, and their average height was 173.0 ± 7.6 cm. Average weight was 68 ± 15.0 kg. Two patients were excluded because additional analgesics were given during the study period. Table 1 shows end-tidal CO<sub>2</sub>

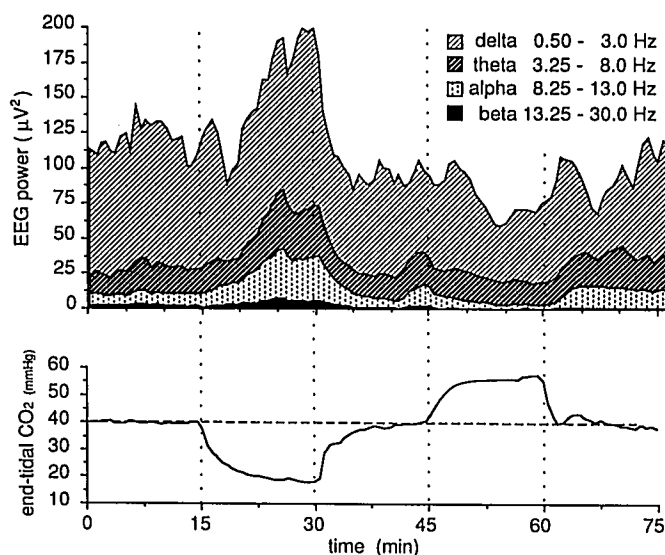


FIG. 2. Trendplot of delta, theta, alpha, and beta power versus time and end-tidal CO<sub>2</sub> versus time during CO<sub>2</sub> manipulations in one patient. Power values are stacked, showing the relative contribution of power in each band to total power (indicated by the upper line). Plots are smoothed (40-s moving average).

TABLE 2. EEG Spectral Parameters during Normocapnia, Hypocapnia, and Hypercapnia

	Normo 1	Hypo	Normo 2	Hyper	Normo 3
Delta power ( $\mu V^2$ )	85.5 (55.4-132.1)	137.2 (101.5-185.4)*	82.8 (55.1-124.3)	83.4 (58-110.9)†	82.9 (56.2-122.3)
Theta power ( $\mu V^2$ )	17.7 (10.7-29.3)	29.2 (19.2-44.4)‡	16.2 (11.1-23.7)	14.2 (8.8-22.9)†	17.0 (10.6-27.2)
Alpha power ( $\mu V^2$ )	5.5 (2.9-10.4)	15.1 (8.8-25.6)§	6.0 (3.1-22.4)	2.4 (1.1-5.1)§,¶	4.8 (2.1-11.1)
Beta power ( $\mu V^2$ )	2.1 (1.1-4.2)	4.0 (2.3-6.9)‡	1.5 (0.7-3.2)	0.6 (0.3-1.4)§,¶	0.9 (0.3-2.7)
Total power ( $\mu V^2$ )	120.7 (82.7-176.1)	193.3 (142.7-261.7)*	82.7 (55.1-124.3)	83.4 (58-119.9)†	82.9 (56.2-122.2)
Rel. delta power (%)	70.1 (61.1-80.6)	67.6 (61.6-74.3)	60.1 (63.8-77.0)	75.4 (68.9-82.6)	70.3 (62.3-79.4)
Rel. theta power (%)	14.8 (11.5-19.1)	16.7 (13.3-21.0)	16.7 (13.0-21.4)	16.0 (11.7-21.9)	17.7 (13.0-22.7)
Rel. alpha power (%)	5.5 (3.4-8.9)	9.0 (6.5-12.5)*	6.3 (3.9-10.2)	2.6 (1.4-5.1)§	5.0 (2.8-8.9)
Rel. beta power (%)	2.1 (1.0-4.6)	2.4 (1.5-3.9)	1.5 (0.7-2.9)	0.6 (0.3-1.3)§,†	0.9 (0.3-2.5)
Median frequency (Hz)	2.5 (2.0-3.2)	2.4 (2.2-2.7)	2.4 (2.0-2.8)	2.3 (2.0-2.7)	2.2 (1.7-2.9)
Spectral edge <sup>95</sup> (Hz)	8.9 (6.8-11.6)	9.7 (8.0-11.8)	8.8 (7.0-10.9)	7.0 (5.6-8.6)*,¶	8.1 (6.5-10.1)

Results are mean (95% confidence interval). Number of observations: 14.  
Normo 1, Normo 2, Normo 3 = normocapnic control periods; Hypo = hypocapnia; Hyper = hypercapnia.  
‡  $P < 0.05$  compared with Normo 1.

\*  $P < 0.01$  compared with Normo 1.  
§  $P < 0.001$  compared with Normo 1.  
†  $P < 0.05$  compared with Hypo.  
‡  $P < 0.01$  compared with Hypo.  
¶  $P < 0.001$  compared with Hypo.

tension, PaCO<sub>2</sub>, pH, arterial O<sub>2</sub> tension (PaO<sub>2</sub>), heart rate, mean arterial blood pressure, and nasopharyngeal temperature in the 10th min of each of the respective 15-min CO<sub>2</sub> periods. No statistically significant differences in heart rate, mean arterial blood pressure, nasopharyngeal temperature, or PaO<sub>2</sub> were observed among any of the five CO<sub>2</sub> periods.

EEG ANALYSIS

The EEG spectral data from 14 patients were analyzed. The raw EEG from one patient was lost because of a defective tape cartridge. One patient was excluded from the spectral analysis because more than 15% of epochs contained artifact. There were no significant differences between the two EEG channels. The data reported are those from the F<sub>pz</sub>-O<sub>2</sub> channel. Figure 1 shows representative EEG traces during normocapnia, hypocapnia, and hypercapnia in one patient. Figure 2 is a trend plot showing the contribution of power in the delta, theta, alpha, and beta bands to the total power during the five CO<sub>2</sub> periods in one representative patient. EEG spectral parameters are given in table 2. There were no significant differences in any of the spectral parameters among the three normocapnic control periods. During hypocapnia there were significant increases in total power and in power in the delta, theta, alpha, and beta bands. During hypercapnia there were significant decreases in alpha power, beta power, and 95% spectral edge frequency. The median frequency did not change during hypocapnia and hypercapnia. As for the relative fractions, only relative alpha power increased during hypocapnia and decreased during hypercapnia. Relative beta power was decreased during hypercapnia. Relative delta and theta power were unchanged during the CO<sub>2</sub> manipulations. Figure 3 shows power in the four frequency bands expressed as a per-

centage of power during the baseline normocapnic period. There was no difference between the EEG epochs from the first minute and epochs from the last minute of each 5-min period.

In each patient there was a negative correlation between power in the alpha band and end-tidal CO<sub>2</sub> tension. Individual correlation coefficients varied from -0.47 to -0.89 (average  $r = -0.85$ ). Beta power was correlated ( $r > 0.50$ ) with end-tidal CO<sub>2</sub> tension in 11 of 14 patients (average  $r = -0.76$ , range -0.20 to -0.82). In figure 4, the regression of log alpha and log beta power against end-tidal CO<sub>2</sub> tension in one patient is shown.

No burst suppression pattern or spike-waves were observed in the EEG of any patient at any time during the study period.

SOMATOSENSORY EVOKED POTENTIALS

Reproducible PTN-SCEP could be recorded in all 16 patients. PTN-SCEP latencies and amplitudes during the

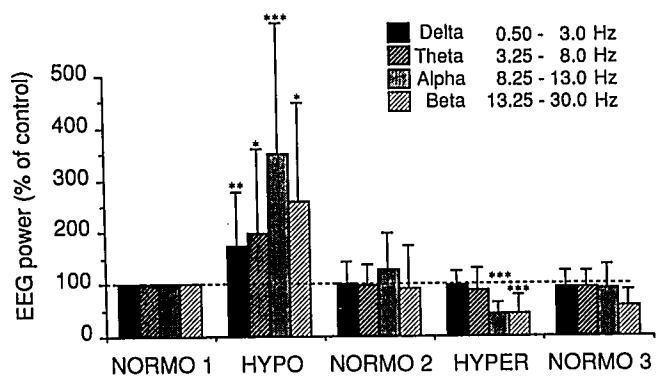


FIG. 3. Percentage change from normocapnic baseline period for power in the delta, theta, alpha, and beta bands during manipulation of end-tidal CO<sub>2</sub> (mean + upper 95% confidence limit).

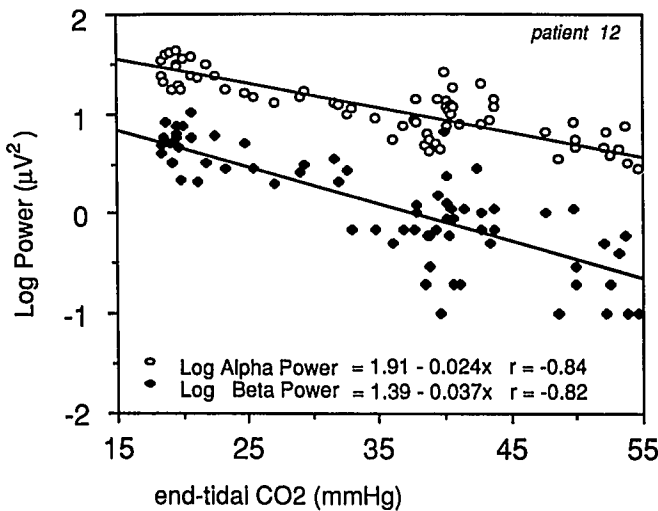


FIG. 4. Scatterplot of log alpha and beta band power versus end-tidal  $\text{CO}_2$  in one patient. Each datapoint is the average value of ten consecutive 4-s epochs.

normocapnic, hypocapnic, and hypercapnic intervals are given in table 3. There were no significant changes in the latency of any peak or in any peak-to-peak amplitude between the three normocapnic periods, and no significant changes in latency or amplitude during hypocapnia or hypercapnia compared with the baseline normocapnic period.

### Discussion

We have demonstrated that during alfentanil/ $\text{N}_2\text{O}$  anesthesia, variation of  $\text{PaCO}_2$  causes significant changes in the EEG power spectrum. These effects are greatest in the higher-frequency bands (alpha and beta). Since most emphasis is placed on high-frequency activity when the EEG is used to detect intraoperative cerebral ischemia or to assess anesthetic depth,<sup>1-6</sup> the changes we observed are clinically relevant.

The physiologic mechanisms underlying the  $\text{CO}_2$ -related changes in the EEG during anesthesia are unknown,

but several explanations are possible. These include cerebral hypoxemia, changes in anesthetic depth, brainstem-mediated reflexes, or changes in cellular function due to altered enzyme activity or change in intracellular calcium. We do not know to what extent these mechanisms might have been involved in our patients.

Hypocapnia-induced vasoconstriction can cause cerebral hypoxemia. There is a direct, linear relationship between cerebral blood flow and  $\text{PaCO}_2$  for  $\text{PaCO}_2$  between 20 and 80 mmHg<sup>1</sup>. Profound levels of hypocapnia ( $\text{PaCO}_2 < 20$  mmHg) decrease cerebral tissue  $\text{O}_2$  tension ( $\text{P}_{\text{O}_2}$ ) in dogs<sup>16,17</sup> as well as in humans.<sup>18</sup> Respiratory alkalosis increases the affinity of hemoglobin for oxygen (Bohr effect), which may further decrease cerebral tissue  $\text{P}_{\text{O}_2}$ . In one study, in awake hyperventilating subjects, end-tidal  $\text{CO}_2$  tension decreased to 15 mmHg, which produced marked EEG slowing.<sup>11</sup> In comparison to these investigations, it is unlikely that the degree of hyperventilation in our patients would have resulted in cerebral ischemia. In none of our patients did  $\text{PaCO}_2$  decrease to less than 20 mmHg. Furthermore, we did not observe any decrease in fast activity during hypocapnia, but rather noted increased activity in all power bands, suggesting increased cortical synchronization.<sup>19</sup>

Changes in anesthetic depth during hypocapnia or hypercapnia could also partly explain the observed EEG changes in our study. During anesthesia the cerebral metabolic rate for oxygen may be reduced,<sup>1</sup> and the baseline EEG will invariably be different from the awake state. Depending on the anesthetic agent(s) and doses used, there normally is a variable degree of delta and theta activity. Alfentanil  $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  used as the sole anesthetic for cardiac surgery produces a predominantly delta and theta EEG without any alpha and beta activity.<sup>20</sup> During inhalation of  $\text{N}_2\text{O}$  50–70%, alpha activity is attenuated and fast oscillatory activity appears at about 35 Hz.<sup>21</sup> In our study, during normocapnia, the EEG consisted predominantly of activity in the delta- and theta-frequency ranges, but alpha and beta activity accounted

TABLE 3. Latencies and Amplitudes of PTN-SEP during Normocapnia, Hypocapnia, and Hypercapnia

	Normo 1	Hypo	Normo 2	Hyper	Normo 3
Latency (ms)					
P1	42.4 ± 3.6	42.5 ± 3.7	42.6 ± 3.4	42.7 ± 3.8	42.4 ± 3.4
N1	49.5 ± 5.0	49.0 ± 5.0	49.3 ± 5.0	50.0 ± 5.1	49.1 ± 4.7
P2	66.2 ± 5.8	64.8 ± 5.5	65.5 ± 5.5	66.6 ± 7.3	65.0 ± 5.4
N2	93.8 ± 6.8	93.5 ± 6.6	93.1 ± 4.9	92.1 ± 6.9	92.4 ± 6.2
Amplitude (µV)					
P1N1	1.41 ± 1.70	1.26 ± 1.23	1.24 ± 1.30	1.39 ± 1.66	1.31 ± 1.15
N1P2	3.07 ± 1.66	3.11 ± 1.89	2.88 ± 1.72	2.85 ± 1.90	2.99 ± 1.78
P2N2	5.57 ± 2.81	5.60 ± 3.63	5.68 ± 3.72	5.26 ± 3.50	5.51 ± 3.46

Results are mean ± SD. Number of observations: 16.

Normo 1, Normo 2, Normo 3 = normocapnic control periods; Hypo = hypocapnia; Hyper = hypercapnia.

for 10–20% of total power. This pattern is consistent with anesthesia using 66%  $N_2O$  and a moderate-dose continuous infusion of alfentanil. Changes in  $pH$  may alter the availability of opioids by changing plasma protein binding or receptor kinetics. An increase in the free fraction of alfentanil would be expected to result in a stronger opioid effect on the EEG during hypercapnia, *i.e.*, increased delta and theta activity and decreased alpha and beta activity. However, plasma protein binding of alfentanil ( $pK_a$  6.50) is unaffected by changes in  $pH$  between 7 and 8.<sup>22</sup> In contrast, the percentage of free-fraction fentanyl and sufentanil increased significantly with lower  $pH$ . We are not aware of any reports on opioid receptor kinetics in which the influence of  $pH$  was systematically studied.

Patel and Mulsby<sup>23</sup> proposed a neuronal origin for both the EEG changes and the reduced cortical blood flow during voluntary hyperventilation: they suggested that these changes are mediated by the reticular activating and thalamocortical projection systems in the brainstem. Hypercapnia produces cortical arousal, and hypocapnia produces cortical hypoexcitability by a direct effect on mesencephalic structures.<sup>24</sup> Slow-wave activity can be produced experimentally by electrical stimulation of nuclei of the generalized thalamocortical projection system. In contrast, arousal stimulation suppresses this synchronization, leading to random firing.<sup>19,23</sup> This results in a lower-amplitude, higher-frequency EEG, due to cancellation of synaptic currents. Hypocapnia decreases activity in the mesencephalic reticular formation, and experimental lesions in the brainstem and thalamus can abolish the EEG response to hyperventilation.<sup>24,25</sup> Some of our data support the hypothesis that brainstem-mediated reflexes may be responsible for the observed EEG changes. During hypocapnia, power in all frequency bands increased, whereas during hypercapnia fast activity (alpha and beta power) decreased. There was a linear relationship between the changes in fast activity and the end-tidal  $CO_2$  tension over the entire range of end-tidal  $CO_2$  values observed.

PTN-SCEP during hypocapnia and hypercapnia were not significantly different from the baseline normocapnic period in our study. For the most part, these results are consistent with the findings of Schubert and Drummond,<sup>26</sup> who did not observe any changes in median nerve SEP amplitude when hypocapnia was induced by hyperventilation in patients anesthetized with  $N_2O$ /isoflurane. They observed small but statistically significant decreases in C2 (cervical) and cortical N1 and P1 latencies during hypocapnia. Tachibana<sup>27</sup> reported a lower amplitude of short-latency median nerve SEP in hyperventilated patients compared with patients in which normocapnia was maintained. However, only four patients were studied in each group, and latency was not reported.

Each different method of manipulating  $P_{aCO_2}$  to study

the effects on EEG and SCEP has its limitations. When acute hyperventilation is used to produce hypocapnia and volatile anesthetic agents are used, unless a steady-state has been reached, hyperventilation may result in increased anesthetic delivery and associated altered anesthetic states. We tried to avoid these errors by using a  $N_2O$ /opioid anesthetic technique and by manipulating end-tidal  $CO_2$  tension by varying the inspiratory  $CO_2$ , rather than by changing minute ventilation and respiratory rate. In this way hypercapnia could be induced without hypoventilation and the associated risks of hypoxia. However, this required continuous ventilation with a high minute volume, regardless of the desired end-tidal  $CO_2$ . We compared EEG and PTN-SCEP data obtained in the last 5 min of the hypocapnic, hypercapnic, and normocapnic study periods. Although we cannot be certain that a steady-state  $P_{aCO_2}$  was reached 10 min after the change in inspired  $CO_2$ , the lack of difference between EEG epochs in the first and last minute of each 5-min interval suggests that  $P_{aCO_2}$  levels were relatively stable at that time. It is much more likely that steady state conditions were present in our study than during acute voluntary hyperventilation, which can be sustained for only 3–5 min.

In conclusion, during alfentanil/ $N_2O$  anesthesia, changes in  $P_{aCO_2}$  have a significant influence on the EEG but not on the PTN-SCEP. During the  $CO_2$  manipulations, alpha and beta power varied inversely with end-tidal  $CO_2$ . There was no evidence of EEG slowing during hypocapnia to a  $P_{aCO_2}$  of 20 mmHg. This is in contrast to the EEG changes associated with voluntary hyperventilation in awake subjects, which are similar to those occurring during cerebral ischemia. The relation between EEG spectral parameters and end-tidal  $CO_2$  should be taken into account when processed EEG data during anesthesia are interpreted. PTN-SCEP are not significantly altered during hypocapnia and hypercapnia. Even when  $P_{aCO_2}$  changes between 20 and 50 mmHg, PTN-SCEP can be recorded and easily interpreted.

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