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The Nonlinear Responses of Cerebral Metabolism to Low Concentrations of Halothane, Enflurane, Isoflurane, and Thiopental

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The relationship between cerebral oxygen consumption (CMR_{O_2}) and anesthetic concentration has been assumed (based upon isolated measurements) to be approximately linear at concentrations less than 1 MAC. The shapes of the anesthetic dose–response curves for both CMR_{O_2} and cerebral blood flow (CBF) were examined by multiple measurements made at small, progressive concentration increments from 0 to 2 MAC halothane (six dogs), enflurane (six dogs), and isoflurane (six dogs), and during a constant 23 mg/kg/hr infusion of thiopental (six dogs). The EEG was continuously recorded and changes in EEG patterns from "awake" to "anesthetic" were correlated with changes in anesthetic concentration, CBF, and CMR_{O_2}. The significance of changes in the slopes of regression lines for CMR_{O_2} before, during and after changes in EEG patterns from "awake" to "anesthetic" were then determined.

Contrary to previous inferences, CMR_{O_2} dose–response curves were found to be nonlinear at anesthetic concentrations less than 1 MAC for all anesthetics studied. CMR_{O_2} decreased precipitously until a stable "anesthetic" pattern was observed on the EEG; thereafter, CMR_{O_2} decreased at a markedly reduced rate. The onset of this change occurred at concentrations well below MAC for the inhalational anesthetics. With the thiopental infusion, CMR_{O_2} decreased most rapidly during the first 25 minutes.

With halothane and enflurane, CBF was maximal during the period of transition in the EEG from an "awake" to an "anesthetic" pattern. CBF was elevated at all concentrations of isoflurane studied. CBF decreased rapidly during thiopental infusion until the EEG pattern changed from "awake" to "anesthetic" and then more slowly. The results demonstrate that the change in the EEG to an "anesthetic" pattern, which occurs at concentrations well below MAC, is accompanied by an abrupt metabolic depression. It is speculated that these events coincide with the onset of functional depression. (Key words: Brain, blood flow; Brain, electroencephalogram; Brain, oxygen consumption; Anesthetics, volatile, halothane; Anesthetics, volatile, isoflurane; Anesthetics, volatile, enflurane; Anesthetics, intravenous, thiopental.)

THE EFFECTS of various inhalational and intravenous anesthetics on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) have been the subject of many investigations.[1–7] In these studies, CBF and CMR_{O_2} were measured at only a few isolated anesthetic concentrations, from which dose–response curves were constructed. These constructed curves all imply a linear response at anesthetic concentrations less than 1 MAC. McDowall[1,2] reported CBF and CMR_{O_2} at 0.5, 2, and 4 per cent end-tidal halothane in the dog. Theye and Michenfelder[4] reported CBF and CMR_{O_2} in the dog at sagittal sinus blood partial pressures of halothane of less than 1.0, 2.8–5.7, and 6.6–9.9 mm Hg. Michenfelder and Cucchiara[6] studied CBF and CMR_{O_2} in dogs at end-tidal enflurane concentrations of less than 0.1, 2.2, and 4.2 per cent. Likewise, Cucchiara *et al.*[7] reported CBF and CMR_{O_2} values at end-tidal isoflurane concentrations of less than 0.1, 1.5, and 2.5 per cent. Altenburg *et al.*[5] infused thiopental continuously in dogs (23 mg/kg/hr) and reported CBF and CMR_{O_2} before infusion and after total doses of 23 and 46 mg/kg.

Recently, we have observed (unpublished) the abrupt onset of EEG "anesthetic" patterns occurring at less than 1 MAC with halothane and enflurane in monkeys and man. We postulate that loss of awareness may occur coincidentally with these EEG changes. This suggests the possibility that the cerebral metabolic depression associated with these anesthetics may also be abrupt rather than having the approximately linear response previously assumed.

The present study was designed to determine the shapes of the anesthetic dose–response curves for CBF and CMR_{O_2} by repeating measurements at multiple small concentration increments of halothane, enflurane, isoflurane, and thiopental. The EEG was recorded to correlate changes in EEG pattern with changes in CBF and CMR_{O_2} for the anesthetic agents studied.

Methods and Materials

Twenty-four fasted, unmedicated dogs (weights 18 to 24 kg) were anesthetized with halothane (1 per cent; 12 dogs), enflurane (2.5 per cent; six dogs), and isoflurane (1.5 per cent; six dogs) in nitrogen (60 per cent) and oxygen. MAC in two dogs from each group had been determined one day prior to experimentation by the method of Eger *et al.*[8] and did not differ significantly from previously published results for the dog.[9,10] Succinylcholine (40 mg) was administered intravenously prior to the placement of a cuffed endotracheal tube and thereafter at 150 mg/hr. Cannulas were placed in the femoral artery for blood sampling and pressure determinations, in the

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femoral vein for replacement of blood, and in a cephalic vein for drug administration and core temperature measurement. Another cannula was placed percutaneously in the lumbar subarachnoid space for local anesthetic infusion. The vagus nerves in the neck were then isolated. Ventilation was controlled with a Harvard pump to maintain Pa_{CO_2} between 37.5 and 42.5 torr. Dogs were then placed in a prone position.

CBF in 15 dogs was measured by a direct method previously described.[11-13] This method includes isolation and posterior cannulation of the sagittal sinus and diversion of blood flow to an external collection and reinfusion system. The collected blood represents venous drainage from the anterior, superior, and lateral portions of both cerebral hemispheres (approximately 54 per cent of total brain weight).[12] In nine dogs, this technique was further modified by a midline division and dual cannulation of the sagittal sinus such that flows from the anterior and posterior portions of the cerebral hemispheres were separated and measured. The sagittal sinus was cannulated anteriorly at the ethmoidal veins and posteriorly above the torcula with diversion of blood to separate external collection systems and a common reinfusion pump. The sagittal sinus was occluded with oxidized cellulose (Surgicel) packs placed in the ethmoidal veins anterior to the anterior cannula, midway between the cannulas, and posterior to the posterior cannula (just above the torcula) to separate venous drainage. Postmortem injection of multicolored vinyl acetate into anterior and posterior cannulas delineated the separation of areas drained.

Epidural and core temperatures were maintained at 37.0 ± 0.1 C and 37.0 ± 0.5 C, respectively, by means of heating lamps and pads. Pa_{O_2}, Pa_{CO_2}, *p*H, and sagittal sinus blood P_{O_2} (Pss_{O_2}) were determined by electrodes (I.L.) at 37.0 C. Arterial pressure was transduced by strain gauge. End-tidal concentrations of volatile anesthetics were determined with an infrared analyzer (Beckman) calibrated individually for each agent. Sagittal sinus blood concentrations of volatile anesthetics were determined by gas chromatography.[15] Hemoglobin (Hb) and oxyhemoglobin (HbO_2) concentrations were measured in an I.L. CO-oximeter (Model 182) calibrated for dog blood. Oxygen content was calculated from dissolved O_2, Hb, and per cent O_2 saturation in the usual manner.[16] CMR_{O_2} was calculated as the product of CBF and the arterial–sagittal sinus blood O_2 difference. A continuous four-channel unilateral EEG was recorded from anterior, middle, lateral, and posterolateral epidural electrodes with reference to an indifferent ear electrode.[8]

After completion of the surgical preparation, the vagus nerves were sectioned in the neck and tetracaine (15 mg in 4 ml of 10 per cent dextrose in water) was administered every 30 minutes through the lumbar subarachnoid catheter. This assured minimal catecholamine release and absence of undesirable vagal effects on the heart at low anesthetic concentrations. Lidocaine (10 ml of a 1 per cent solution) was injected into the skin and muscle of the head. The volatile anesthetic was discontinued for one hour before control values were measured in each group at 0.1 per cent end-tidal anesthetic concentration. During control value measurements and subsequent experimentation, an electrical stimulus (4.5 v; 1 Hz) was delivered to the skin overlying the mandible. This, along with taping the eyes and plugging the ears, provided a relatively constant, reproducible background stimulus.

Following control determinations of EEG, CBF, and CMR_{O_2} (ten measurements over 30 minutes), the dogs were divided into four groups of six dogs each (halothane, enflurane, isoflurane, and thiopental + 0.1 per cent end-tidal halothane). Dogs in the halothane group received increasing inspired concentrations of halothane such that the measured end-tidal concentration increased at a rate of 0.05 per cent every 5 minutes to 1.1 per cent, and thereafter, at increments of 0.10 per cent every 5 minutes. Dogs in the enflurane and isoflurane groups similarly received increasing inspired concentrations of enflurane and isoflurane such that measured end-tidal concentrations increased by 0.10 per cent every 5 minutes. Dogs in the thiopental group received a continuous infusion of 23 mg/kg/hr thiopental while their end-tidal halothane concentrations were maintained at 0.10 per cent. EEG patterns, CBF, and CMR_{O_2} were recorded at 5-minute intervals for each dog for the duration of the experiment. For all six dogs in the halothane group and one dog in each of the other groups, CBF and CMR_{O_2} were separated into anterior and posterior components. The points of EEG change from "awake" to transitional ("shifting") patterns and from "shifting" to "anesthetic" patterns were determined by inspection of rhythm, amplitude, and frequency. Determinations were made without knowledge of either anesthetic concentrations or CMR_{O_2} values. High-frequency, low-amplitude activity (15 ± 5 Hz; $5 \times 10^{-5} \pm 4 \times 10^{-5}$ v), was classified as an "awake" pattern, while onset of persistent lower-frequency and higher-amplitude activity (10 ± 8 Hz; $30 \times 10^{-5} \pm 15 \times 10^{-5}$ v), particularly in the frontal lead, was classified as an "anesthetic" pattern. "Shifting" patterns showed alternation between "awake" and "anesthetic" characteristics.

The significances of changes in CMR_{O_2} before, during, and after the change in EEG pattern were determined for each group of dogs by a randomized block analysis of variance.[16,17] Basically, the slopes of regression lines drawn for individual dogs for CMR_{O_2} versus anesthetic concentration during the three EEG levels ("awake," "shifting," and "anesthetic") were compared with one another to identify significant differences in mean slope. Composite dose–response regression line equations (six dogs each) were also calculated by the method of least squares.

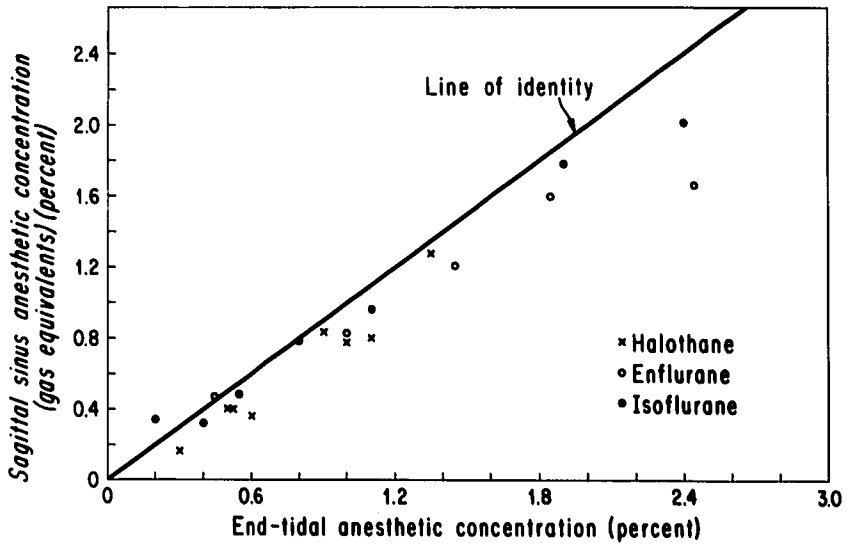

FIG. 1. The correlation between sagittal sinus blood anesthetic concentrations (converted to gas-phase equivalents) and end-tidal anesthetic concentrations for halothane, enflurane, and isoflurane. Sagittal sinus blood concentrations are plotted against end-tidal concentrations and data points are compared with a line of identity.

Results

Arterial blood-gas values, temperatures, and hemoglobin concentrations did not differ significantly among anesthetics or from initial values as the concentration of each agent was increased (table 1). Mean arterial blood pressure decreased progressively as anesthetic concentration increased. Pressures remained above 60 torr for halothane, enflurane, and thiopental and above 50 torr for isoflurane throughout the observation period.

End-tidal concentrations of halothane, enflurane, and isoflurane were correlated with simultaneously measured sagittal sinus blood concentrations (fig. 1). The slopes of regression lines drawn for mean sagittal sinus anesthetic concentrations (mg/ml converted to gas-phase equivalents)[18] were 90 per cent of end-tidal concentration for halothane, 70 per cent for enflurane, and 85 per cent for isoflurane. Because intercepts of these lines were similar, the difference between end-tidal and sagittal sinus blood concentrations of anesthetic was less at low end-tidal concentrations. Plasma thiopental concentrations measured in a previous study during a continuous thiopental infusion identical to that used in this study also correlated well (r = .98) with the total dose of drug infused.[5]

EFFECTS OF HALOTHANE

CBF remained on or above a regression line determined by Takeshita *et al.*[12] (representing the effects of time alone on CBF in this preparation) for the duration of the observation period (fig. 2). Maximum increase in CBF (23 per cent) occurred between end-tidal concentrations of 0.55 and 0.70 per cent.

Onset of changes in EEG tracings from an "awake" to a transitional ("shifting") pattern was found at 0.50 ± 0.01 (SE) per cent halothane (0.57 MAC) and onset of changes from a "shifting" to an "anesthetic" pattern at 0.63 ± 0.03 per cent (0.72 MAC) (fig. 3). Changes in CMR_{O_2} with increasing end-tidal concentrations of halothane were nonlinear. The rate of negative change of CMR_{O_2} was most rapid during the transitional period. The

TABLE 1. Blood-gas, Temperature, and Hemoglobin Values (Means ± SE)

	Arterial Blood-gas Values				Temperature (C)		
	P_{O_2} (torr)	pH	P_{CO_2} (torr)	Buffer Base mEq/l	Atrial	Dural	Hemoglobin (g/dl)
Halothane	195.5 ± 5.1	7.39 ± .02	39.5 ± 1.1	48.0 ± 1.1	36.9 ± 0.1	37.0 ± 0.04	13.7 ± 0.1
Enflurane	207.9 ± 11.1	7.37 ± .01	40.1 ± 0.7	47.4 ± 1.0	36.3 ± 0.2	37.0 ± 0.04	13.6 ± 0.4
Isoflurane	164.7 ± 9.8	7.36 ± .01	41.0 ± 1.7	44.2 ± 1.1	36.6 ± 0.4	37.0 ± 0.04	14.3 ± 0.1
Thiopental	165.9 ± 11.3	7.38 ± .01	39.8 ± 0.2	47.2 ± 0.8	36.8 ± 0.2	37.0 ± 0.04	14.5 ± 0.1

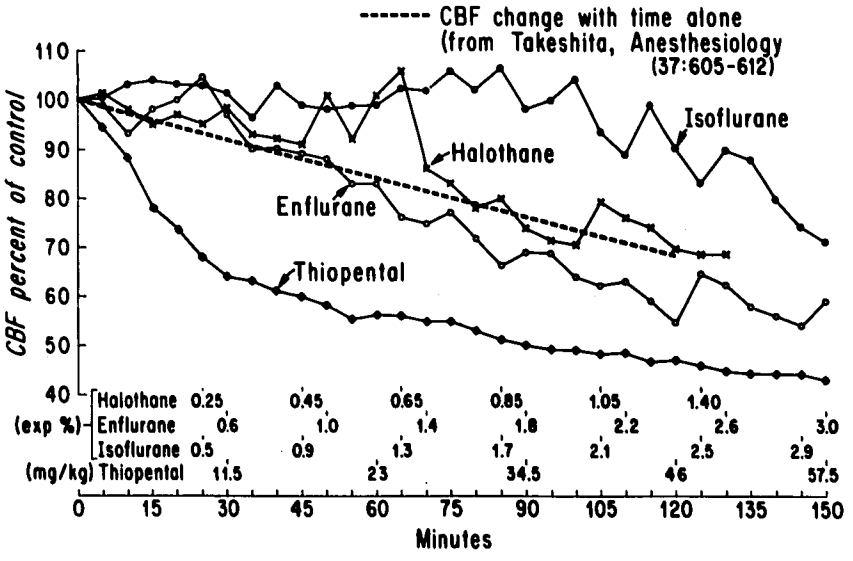

FIG. 2. Cerebral blood flow (per cent of control) plotted against end-tidal anesthetic concentrations of halothane, enflurane, and isoflurane, and total dose (mg/kg) of thiopental infused. Data points are compared with a regression line (Takeshita *et al.*[12]) for the effects of time on CBF.

negative slopes of regression lines for CMR_{O_2} at increasing anesthetic concentrations below and above the transition from "awake" to "anesthetic" EEG patterns were similar, while the negative slope during the transition period was significantly increased ($P < 0.001$, before versus during; $P < 0.002$, during versus after). No change in slope was found for increasing halothane concentrations after onset of an "anesthetic" pattern, through MAC, or at greater concentrations of halothane.

Contributions to the total CMR_{O_2} change by anterior and posterior portions of the brain were similar. Posterior CMR_{O_2} was greater (NS) than anterior CMR_{O_2} during most of the observation period.

Effects of Enflurane

Linearly increasing end-tidal concentrations of enflurane had less effect on CBF than halothane. For concentrations of enflurane greater than 0.70 per cent, CBF closely paralleled the time–effect regression line. At end-tidal concentrations below 0.70 per cent, CBF was increased above the time–effect regression line and was maximal at 0.50 per cent (12 per cent above the regression line) (fig. 2).

Changes in EEG tracings were less well defined for enflurane than for halothane or isoflurane. A "shifting" pattern occurred between 0.58 ± 0.08 (.26 MAC) and 0.93 ± 0.08 (.42 MAC) per cent (fig. 4). Changes in CMR_{O_2} with increasing end-tidal concentrations of enflurane were also nonlinear. The negative slopes of regression lines for CMR_{O_2} at increasing anesthetic concentrations during both "awake" and "shifting" periods were similar. However, both were significantly more negative than the slope of the CMR_{O_2} regression line after onset of an "anesthetic" pattern ($P < 0.005$). As with halothane, the slope of this portion of the curve did not change at increasing concentrations of enflurane through or above MAC. For enflurane, the contributions of anterior and posterior portions of the brain to the total CMR_{O_2} change were also not different.

EEG spike activity was not seen at any concentration of enflurane studied.

Effects of Isoflurane

The effect of isoflurane on CBF differed from that of either halothane or enflurane. CBF was significantly increased above the time–effect regression line at all end-tidal concentrations studied. At end-tidal concentrations less than 2.1 per cent, CBF remained near 100 per cent of its initial control value (uncorrected for the effects of time on the preparation). At 2 per cent, CBF was 31 per cent greater than the time–effect regression line value (fig. 2).

Changes in the patterns of EEG tracings and CMR_{O_2} regression lines with isoflurane were qualitatively similar to those seen with halothane. EEG changes from "awake" to "shifting" patterns were seen at 0.43 ± 0.03 per cent end-tidal isoflurane (.29 MAC) and changes from "shifting" to "anesthetic" patterns at 0.70 ± 0.04 per cent (.47 MAC) (fig. 5). Regression line slopes for the rate of decline in CMR_{O_2} during the "shifting" period, however, were significantly greater ($P < 0.008$, before versus during; $P < 0.001$, during versus after). As with halothane and enflurane, no change in the rate of CMR_{O_2} decline was seen at concentrations of isoflurane near or above MAC. Anterior and posterior cerebral contributions to the total CMR_{O_2} change were also not different.

Effects of Thiopental

The effects of an infusion of 23 mg/kg/hr thiopental on CBF and CMR_{O_2} were unlike those seen with any volatile agent studied. CBF rapidly declined to 20

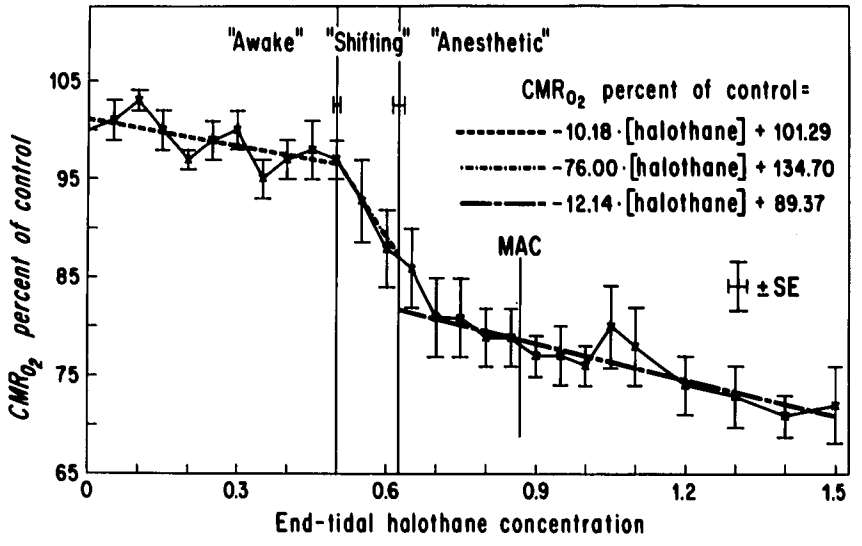

FIG. 3. The effects of halothane on CMR_{O_2}. CMR_{O_2} (per cent of control) is plotted versus end-tidal halothane concentration. Regression lines for changes in CMR_{O_2} are drawn for each EEG-determined area.

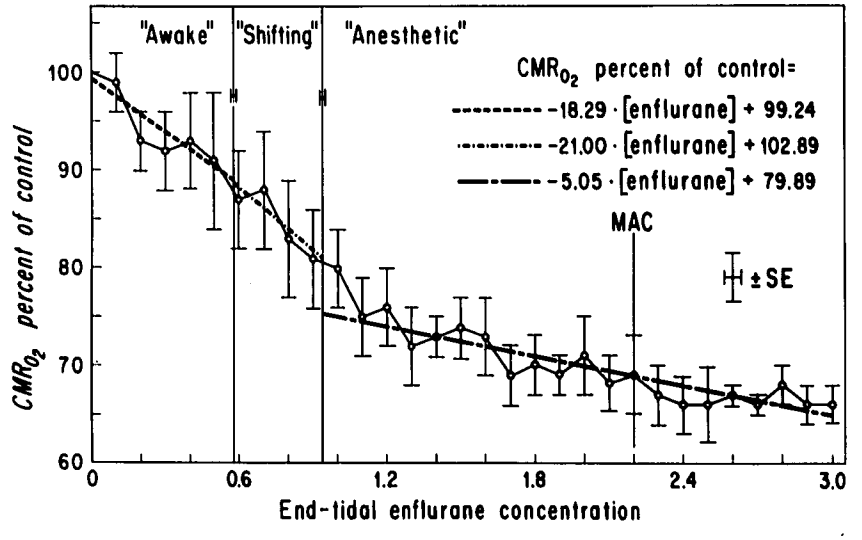

FIG. 4. The effects of enflurane on CMR_{O_2}. CMR_{O_2} (per cent of control) is plotted versus end-tidal enflurane concentration. Regression lines for changes in CMR_{O_2} are drawn for each EEG-determined area.

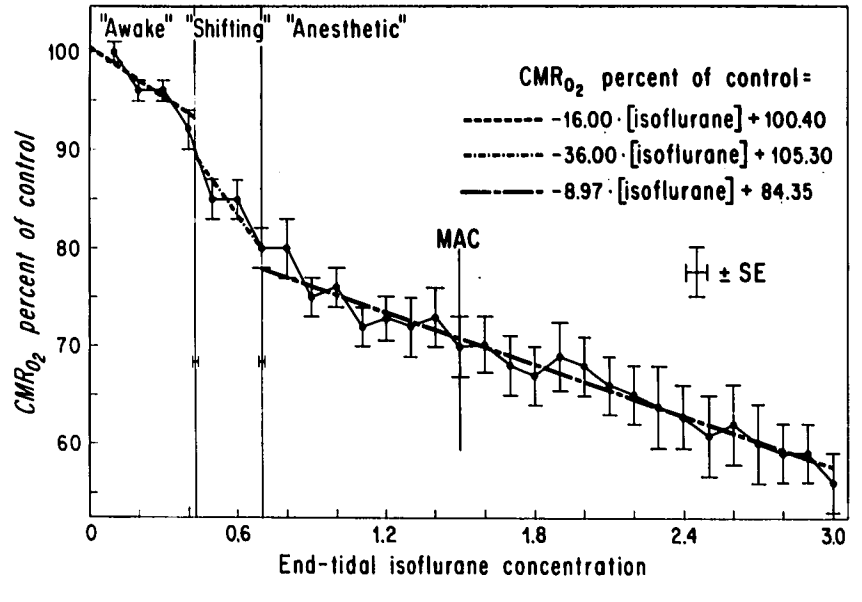

FIG. 5. The effects of isoflurane on CMR_{O_2}. CMR_{O_2} (per cent of control) is plotted versus end-tidal isoflurane concentration. Regression lines for changes in CMR_{O_2} are drawn for each EEG-determined area.

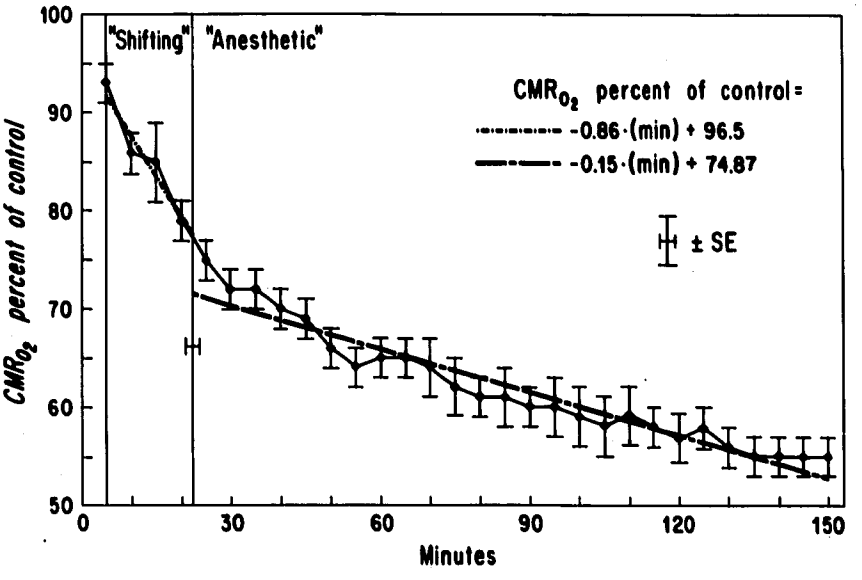

FIG. 6. The effects of thiopental on CMR_{O_2}. CMR_{O_2} (per cent of control) is plotted versus total dose of thiopental infused. Regression lines for changes in CMR_{O_2} are drawn for each EEG-determined area.

per cent less than the time–effect regression line and remained depressed for the duration of the infusion. After three hours of thiopental infusion, CBF was 43 per cent of its initial control value (fig. 2).

The changes in EEG tracings from "awake" to "shifting" patterns were variable in their occurrence but always apparent within 5 minutes of beginning the infusion. Changes from "shifting" to "anesthetic" patterns were also variable (21.7 ± 2.5 minutes after beginning infusion) and more difficult to recognize than the changes seen with volatile agents (fig. 6). Before and during the "shifting" period, CMR_{O_2} rapidly decreased to 77 per cent of control. With onset of an "anesthetic" pattern, the rate of CMR_{O_2} decline was less rapid and significantly different from before or during the "shifting" period ($P < 0.002$).

Discussion

The effects of random isolated end-tidal concentrations of halothane, enflurane, and isoflurane on CBF and CMR_{O_2} have been reported.[1,2,4,6,7] The results of this study quantitatively corroborate these reports and, in addition, describe the dose–response curve to 2 MAC for each of these anesthetics, based on measurements made at multiple small concentration increments.

Contrary to previous inferences, the CMR_{O_2} dose–response curves were found to be nonlinear at concentrations less than 1 MAC for all agents studied. Further, the points at which the slopes of the CMR_{O_2} response curves changed were found to coincide with changes in simultaneously recorded EEG patterns. This correlation suggests a relationship between cerebral function as reflected by EEG pattern and cerebral metabolism as reflected by CMR_{O_2}. For halothane and isoflurane, CMR_{O_2} decreased at a significantly greater rate during the transition period of the EEG pattern from "awake" to "anesthetic." For enflurane, CMR_{O_2} decreased at a significantly greater rate before and during the EEG transition period compared with the "anesthetic" period. For all inhalational agents studied, the major component of metabolic change between 0 and 2 MAC occurred at anesthetic concentrations well below 1 MAC. No change in the slopes of CMR_{O_2} dose-response curves was found at anesthetic concentrations near, at, or above MAC.

As a possible point on the anesthetic dose–response curve, the onset of the EEG "anesthetic" pattern is appealing since it is localized, reproducible, and presumably relates to a functional effect of anesthesia. MAC is used as the standard of potency for comparison of different anesthetic agents. It would seem reasonable to use the onset of this EEG change as another point for comparison of anesthetic potencies. We speculate that the loss of awareness associated with anesthesia takes place either within the EEG "shifting" period or at the onset of the "anesthetic" pattern at end-tidal anesthetic concentrations well below MAC.

The comparison of MAC values determined in the absence of spinal anesthesia with EEG "shifting" pattern anesthetic concentrations determined in the presence of spinal anesthesia in the same dogs may be questioned. However, the anesthetic concentrations at which we observed EEG "shifting" patterns correlated well with those previously observed in dogs without spinal anesthesia (unpublished data). The ratios of "shifting" pattern anesthetic concentrations to MAC in those dogs were identical to the ratios seen in the present study. Further, since the magnitude of change in CMR_{O_2} between 0 and 1 MAC was the same as that previously found in dogs not given spinal anesthesia,[4,6,7] there is no suggestion that spinal anesthesia altered the cerebral response to general anesthesia.

The results seen with a constant thiopental infusion were of interest as they relate to the possible use of barbiturates in the treatment of cerebral hypoxic injuries.[19] As with the inhalational agents, the major metabolic depression associated with a thiopental infusion occurs early and at a low total dose. If the depression in CMR_{O_2} is the major mechanism for protecting ischemic brain, then only moderate doses should be needed. Yet, Smith *et al.*[20] have suggested that massive doses of barbiturates are necessary to provide protection against cerebral hypoxic injuries. If this is so, then mechanisms other than metabolic depression alone must be involved.

Shapiro *et al.*¶ have recently reported regional differences in cerebral hemispheric metabolic rate for glucose at 0.9 per cent halothane in monkeys. Their results indicate significantly greater metabolic depression in the parieto-occipital regions compared with frontal regions. In the dog, we could find no significant difference between anterior and posterior CMR_{O_2} responses to increasing concentrations of halothane, enflurane, isoflurane, or thiopental. This lack of confirmation of the findings of Shapiro *et al.* may relate to the lack of frontal-lobe development in the dog.

Observed changes in CBF in this study were affected by the decrease in mean arterial pressures associated with increasing anesthetic concentration, as well as by the known effect of time on CBF in the immobilized dog.[12,21] However, when corrected for these factors, values obtained at 1 MAC were comparable to changes at 1 MAC previously reported for halothane, enflurane, and isoflurane.[4,6,7] The large (35 to 40 per cent) increases in CBF reported for halothane by McDowall[1,2] were not observed. Changes in CBF after one and two hours of a constant (23 mg/kg/hr) thiopental infusion correlated well with those reported by Altenburg *et al.*[5]

In summary, the results of this study underscore the potential for error introduced by connecting isolated data points and assuming that the intervening relationship is linear. Such is not the case for CMR_{O_2} at anesthetic concentrations below 1 MAC. This study also suggests a new point on the anesthetic dose–response curve. The transition of the EEG to an "anesthetic" pattern reflects a change in neuronal function. Easily measurable and reproducible, this transition relates to a simultaneous metabolic response to the anesthetic and presumably to a behavioral, functional effect of anesthesia. Further investigation is needed to determine whether loss of awareness does indeed occur during this EEG transition period.

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