Technical Comments

Elimination of Anesthetics from Rabbit Brain

A. M. Wyrwicz *et al.* have reported (*1, 2*) that the inhaled anesthetics halothane and isoflurane are eliminated slowly from the brain of rabbits and that the rates of elimination from rabbit brain are similar in the first several hours of recovery from anesthesia. Using nuclear magnetic resonance (NMR) spectroscopy, they found that 40 to 45% of the anesthetic originally present in brain was still present after 4 to 7 hours of elimination. Their values for halothane confirmed results from an earlier report by Divakaran and coworkers (*3*). Moss (*4*) then questioned "whether our most commonly employed anesthesia techniques really leave our patients 'awake' upon discharge . . . . there appears to be scientific and clinical evidence to suggest that patients' activity should be restricted for 2 days after even these short-acting anesthetics."

However, several results conflict with the above observations. A perfusion-limited model of elimination of inhaled anesthetics from brain (*5*) predicts a cerebral level of volatile anesthetic an order of magnitude less than that reported by Wyrwicz *et al.* Also, Cohen *et al.* (*6*) found in autoradiographic studies that 90% of intravenously injected radioactive halothane was eliminated from the brain within 20 minutes. Similarly, Wolff (*7*) reported a 97% elimination of halothane within 3 hours.

Because halothane undergoes considerable metabolism, some of the results indicating slow elimination may reflect the persistence of metabolites in brain rather than unmetabolized anesthetic (*1*). We avoided this problem by studying isoflurane. This volatile anesthetic resists biodegradation (less than 0.2% is metabolized). Our methods were similar to those of Wyrwicz *et al.* except for the method of analysis of isoflurane.

Cohorts of four to nine New Zealand White rabbits weighing 2.7 ± 0.4 kg were anesthetized with ketamine and xylazine. An endotracheal tube was inserted through a cricothyroidotomy and ventilation was controlled. Isoflurane (1.3%) was administered via a nonrebreathing system for 90 minutes and then discontinued. Anesthesia was maintained thereafter with ketamine and xylazine. Samples of arterial blood, inspired and end-tidal gases, and brain were obtained after 30 and 90 minutes of administration of isoflurane and after 10, 30, 90, and 270 minutes of elimination. Samples of fat and muscle were obtained after 90 minutes of administration and after 90 and 270 minutes of elimination.

Blood and inspired and end-tidal gas samples were analyzed with the use of methods described elsewhere (*8*). Brain, muscle, and fat tissues weighing 1 to 2 g were harvested. The tissues were immediately pressed between Teflon sheets to a thickness of less than 1 mm, weighed, frozen in liquid nitrogen, and sealed in a 600-ml glass flask. Each flask was baked at 80°C for 2 hours and then at 37°C for 15 minutes. The concentration of isoflurane in the flask was analyzed by gas chromatography. Partial pressures of isoflurane for blood and tissue were calculated from the concentration in the flask and the partition coefficient of isoflurane for blood or the specific tissue (*9*). Results from three animals in whom arterial carbon dioxide

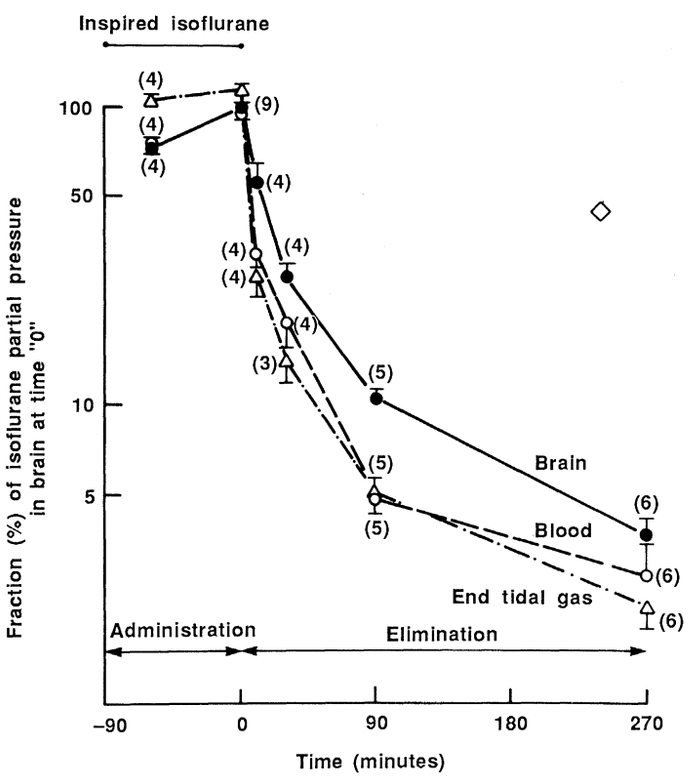

Fig. 1 (left). Partial pressures of isoflurane in blood, brain, and gases normalized to the average partial pressure in brain obtained after 90 minutes of administration of isoflurane (that is, at "time 0"). The mean and standard error of the mean are plotted for each cohort of rabbits. The number of rabbits in each cohort appears in parenthesis. Concentrations of isoflurane were determined by gas chromatography. Blood and brain concentrations were converted to partial pressures with the use of their respective partition coefficients (*9*). The diamond-shaped point represents the value reported by Wyrwicz *et al.*

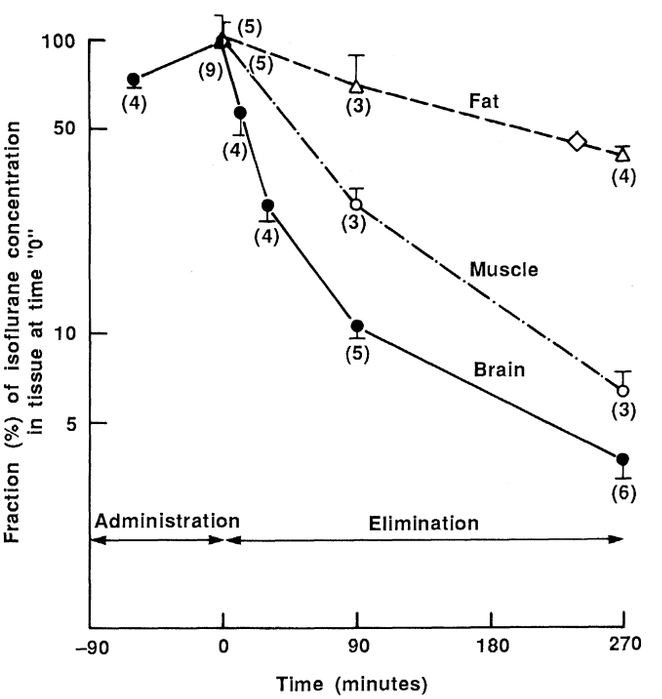

Fig. 2 (right). Concentrations of isoflurane in fat, muscle, and brain determined by gas chromatography and normalized to their respective average concentrations obtained after 90 minutes of administration of isoflurane (that is, at "time 0"). The mean and standard error of the mean are plotted for each cohort of rabbits. The number of rabbits in each cohort appears in parenthesis. The diamond-shaped point represents the value reported by Wyrwicz *et al.*

partial pressure did not fall within a range of 24 to 56 mmHg were excluded.

Partial pressures of isoflurane for all samples were divided (that is, normalized) by the mean partial pressure of isoflurane in brain after 90 minutes of administration. The partial pressures of isoflurane increased and decreased rapidly in brain, blood, and end-tidal gas (Fig. 1). The normalized value for brain decreased to 3.7% after 270 minutes of elimination. This value is an order of magnitude smaller than that reported at 240 minutes by Wyrwicz *et al.* (Fig. 1). Isoflurane partial pressures in brain increased and decreased at rates consistent with those predictable from known values for perfusion and solubility of isoflurane in brain. Our results imply that the patient given isoflurane (or halothane) will rapidly recover from anesthesia.

A possible criticism of our results is that isoflurane may have escaped from the brain before our transfer of the sample to the closed flask. However, comparison of partial pressures of isoflurane in blood and brain after 30 and 90 minutes of administration does not reveal a significant difference (Fig. 1). Unlike the samples of brain, the samples of blood were transferred anaerobically from vessel to flask; although the brain samples were susceptible to loss of anesthetic, the blood samples were not. The fact that blood and brain results were comparable after 30 and 90 minutes indicates that no appreciable amount of anesthetic was lost from the brain samples. Even if loss had occurred, were the loss proportional to anesthetic partial pressure, our findings would not be affected.

Several factors may account for the findings of Wyrwicz *et al.* If isoflurane is covalently bound to brain tissue, we would not have recovered all of the isoflurane in the brain. Contradicting this interpretation are the findings that isoflurane is not readily broken down to a compound that might form a covalent bond (*10*) and that nearly 100% of the administered isoflurane may be recovered in expired gas (*11*).

An alternative interpretation that would reconcile our results with those of Wyrwicz *et al.* is that isoflurane binds reversibly to sites in the brain. However, we found that solubility of isoflurane in rabbit brain follows Henry's law over a 100-fold range of anesthetic partial pressures (*9*). We would not expect this behavior if a large number of cerebral sites were saturated progressively by isoflurane.

Finally, the presence of isoflurane in a tissue adjacent to brain requires comment. In the rabbit, fat lies just behind the skull and under the mandible. Fat accepts 23 times as much isoflurane as does the brain (*11*, p. 15). Thus, the partial pressure of isoflurane in brain is five times greater than that in fat after 90 minutes of administration, but the concentration in brain is 6.5 times less than that in fat. After 270 minutes of elimination, 96% of the isoflurane has left brain, but only 60% has left fat (Fig. 2). The 60% decrease in the value for fat is comparable to the 55% reported by Wyrwicz *et al.* for brain. Thus it is possible that the focus of the NMR surface coil may have provided images of isoflurane in fat rather than brain.

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Response: Strum *et al.* report a rapid decrease of isoflurane levels in brain after exposure to this anesthetic and compare these results with our data for halothane (*1*), a different anesthetic agent that had a longer retention time. Retention times of these two compounds are not comparable, since isoflurane (as described in standard anesthesiology texts) is known to have a rapid onset and a short duration of anesthetic action compared with those of halothane. The studies of Cohen *et al.* (*2*) and by Wolff (*3*), cited by Strum *et al.* as giving results in conflict with ours, employed ^{14}C-labeled halothane introduced into a rat by intravenous injection. It was shown by Topham and Longshaw (*4*) that the distribution and retention time of intravenously administered halothane differ from those of halothane administered by inhalation. Therefore, neither the Cohen nor the Wolff studies are relevant to general anesthesia, where volatile anesthetics are introduced via the lungs.

Figure 1 shows typical elimination curves for halothane and isoflurane (*5*) measured noninvasively by us with fluorine-19 nuclear magnetic resonance (NMR) spectroscopy. These data show that isoflurane is eliminated from the brain more rapidly than is halothane. These results parallel those of Divakaran *et al.* (*6*), who have shown that halothane, when administered by inhalation, decreases to 50% of its initial concentration within 3 hours of the last exposure, which is consistent with longer retention. There is no conflict between our observations and those

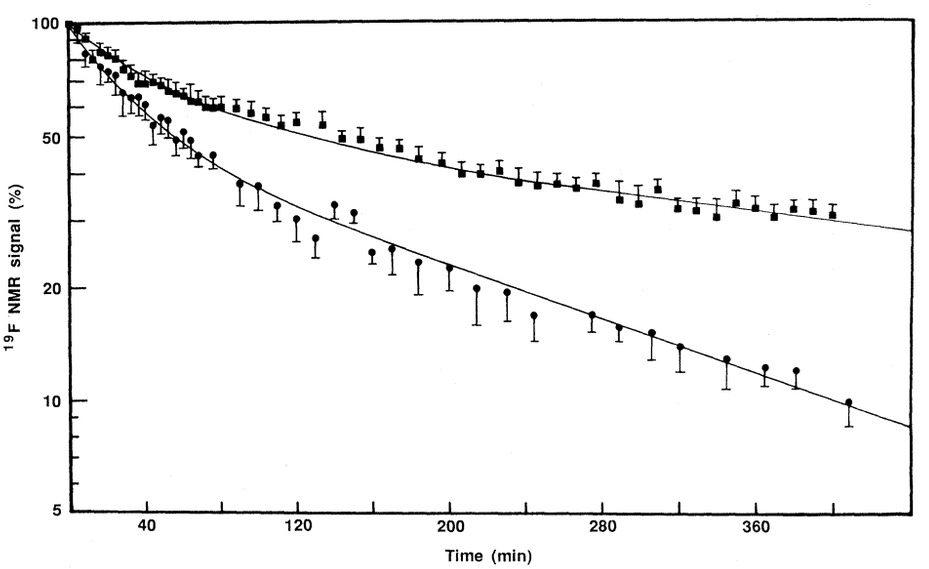

Fig. 1. Comparison of isoflurane (●) and halothane (■) elimination from rabbit brain measured in vivo with fluorine-19 NMR spectroscopy. Fluorine-19 signal areas expressed as percent signal remaining in the brain (after anesthesia) are plotted against time (points are means for $n = 6$ rabbits; the bars indicate standard error of the mean). Isoflurane decay curve was measured after 90 minutes of exposure to 1.5% isoflurane, and the halothane decay curve was measured after 90 minutes of exposure to 1% halothane. Only elimination for the first 7 hours is shown. Experimental details will be provided in (*5*).