In vivo fluorine-19 magnetic resonance spectroscopy of cerebral halothane in postoperative patients: Preliminary results

ARTICLE *in* MAGNETIC RESONANCE IN MEDICINE · DECEMBER 1993

Impact Factor: 3.57 · DOI: 10.1002/mrm.1910300605 · Source: PubMed

In Vivo Fluorine-19 Magnetic Resonance Spectroscopy of Cerebral Halothane in Postoperative Patients: Preliminary Results

D. K. Menon, G. G. Lockwood, C. J. Peden, I. J. Cox, J. Sargentoni, J. D. Bell, G. A. Coutts, J.G. Whitwam

This study reports the use of ^{19}F MRS to study halothane in the brain of eight patients recovering from halothane anesthesia of short duration. Resonances attributable to halothane were observed up to 90 min after withdrawal of the anesthetic agent. The signal-to-noise ratio for an unlocalized spectrum acquired using a 6 cm surface coil was typically 20 with data collection times of 2 min. In seven patients a single resonance was seen with a mean (±SD) chemical shift of +43.3 (±1.8) ppm, referenced to NaF at 0 ppm. This resonance exhibited a T_1 value of between 0.5 and 1 s, and a T_2^* (estimated from the linewidth of the resonance) between 3.5 and 10 ms. In one patient two resonances were observed with chemical shifts of +38 and +41 ppm. Because we cannot exclude the possibility that this was due to field inhomogeneity, the significance of the last finding is uncertain. However, phantom studies show that the chemical shift of halothane in different environments (such as water, olive oil, methanol, and lecithin) can vary to an extent that accounts for the two resonances seen in our patient. These results demonstrate the feasibility of *in vivo* ^{19}F MRS studies of fluorinated volatile agents in humans. The potential for clinical ^{19}F MRS of fluorinated anesthetics is discussed.

Key words: human brain; fluorinated volatile anesthetic agents; *in vivo* fluorine-19 magnetic resonance spectroscopy; halothane.

INTRODUCTION

There have been no direct measurements of cerebral halothane levels in humans, and pharmacokinetic studies have inferred halothane levels in the brain on the basis of blood levels and tissue-blood partition coefficients, obtained from experiments on postmortem tissue samples (1). *In vivo* fluorine-19 magnetic resonance spectroscopy (^{19}F MRS) can detect and quantify fluorine-containing compounds in the tissues of living animals (2) and human subjects (3), and has been used to study the pharmacokinetics and metabolism of halothane (4–6), isoflurane (7), and desflurane (8) in experimental animals. There appear to be areas of disagreement between different groups with respect to findings in animal models (9–11); consequently, it is difficult to extrapolate results of these reports to provide a basis for planning human studies. This preliminary report, which outlines the use of ^{19}F MRS to study halothane in the brain of patients recovering from general anesthesia, was designed to provide preliminary information such as T_1 and T_2 values of cerebral halothane in humans, and possibly provide some information regarding the time frame during which halothane was detectable with ^{19}F MRS after a routine general anesthetic.

METHODS

The subjects participating in this study consisted of eight female patients, who were free of systemic illnesses (American Society of Anesthesiologists (ASA) Grade I), aged 25 to 45 (mean 36) years, who were undergoing minor gynecological procedures without significant postoperative pain. None had been exposed to halothane within 6 months of the study day. After premedication with metoclopramide 10 mg (by mouth) and glycopyrrolate 0.6 mg (intramuscularly) 1 h prior to surgery, anesthesia was induced with propofol 2 mg · kg^{-1} and maintained with halothane in oxygen, administered via a coaxial Mapleson D (Bain) system and face mask. In addition to routine monitoring (ECG, noninvasive blood pressure monitoring and pulse oximetry), expired end-tidal carbon dioxide and halothane levels were measured by sampling gas obtained from a nasopharyngeal catheter (CAPNOMAC®, Datex, United Kingdom). At the end of surgery, anesthesia was discontinued, and the patient was transferred to a custom-built MR compatible transport trolley and moved to the MRS suite. When the patient was awake, with satisfactory airway reflexes, she was positioned in the magnet, and the MRS study began. The patient received 40% oxygen via a face mask from the end of surgery until the point at which she was removed from the magnet bore. The magnet bore was ventilated by an efficient exhaust system. Pulse oximetry, ECG and noninvasive blood pressure monitoring continued during transport, recovery, and spectroscopy, and the patient's management was supervised by two experienced anesthetists. Conductive monitoring leads (e.g., ECG, pulse oximetry) will tend to carry interference from external sources that produce radiofrequency (RF) signals, which are close to the spectral frequency being studied. All monitoring leads were therefore routed through low-pass filters in order to avoid introducing RF interference into the scanning area. The tubing used for noninvasive blood pressure monitoring was extended to

MRM 30:680–684 (1993)

From The NMR Unit (D.K.M., C.J.P., I.J.C., J.S., J.D.B., G.A.C.) and The Department of Anaesthetics (G.G.L., J.G.W.), Hammersmith Hospital, Du Cane Road, London W12 0HS.

Address correspondence to: David K. Menon, NMR Unit, Hammersmith Hospital, Ducane Road, London W12 0HS, United Kingdom.

Received May 20, 1992; revised July 13, 1993; accepted August 12, 1993.

This work was supported by Picker International and the Medical Research Council of the United Kingdom.

0740-3194/93 $3.00

a length of 12 m, and modified by replacing metal connectors with nylon ones. All patients gave written informed consent, and approval for MRS studies in patients requiring intensive monitoring was obtained from the Medical Research Ethics Committee of the Hammersmith Hospital and Royal Postgraduate Medical School.

Fluorine-19 MRS was performed on a prototype Picker system operating at 1.6 Tesla. The transmitter coil was a saddle with an internal diameter of 50 cm. The homogeneity of the transmitter coil was demonstrated on phantoms that showed <5% variation in the B_1 field produced in a volume the size of the head. A single turn surface coil (6 cm in diameter), orthogonal to the plane of the transmit coil was positioned over the right temporal region and used as a receiver. A vial containing 1 ml of 0.7 *M* sodium fluoride (NaF) was taped to the receiver coil and served as a standard for chemical shift estimation (the resonance from NaF being assumed to resonate at 0 ppm). Both transmitter and receiver coils were double tuned for protons (68 MHz) and fluorine (64 MHz). The proton signal from tissue water was used to optimize the magnetic field homogeneity and to obtain a low resolution image as an aid to spectral localization. Typical linewidths for the water resonance were 40 to 50 Hz. Unlocalized ^{19}F MR spectra were acquired from the whole sensitive volume of the coil with repetition times (*TR*) of 0.5, 1, and 5 s (256, 128, and 64 averages, respectively), using a 200-μs trapezoidal 90° pulse, previously calibrated on a phantom of neat halothane. Five hundred twelve data points were acquired with a sweep width of 10 kHz. Spectra were zero-filled to 1024 points and subjected to 10 to 15 Hz line broadening prior to Fourier transformation. The spin-lattice relaxation time constant (T_1) was estimated using standard formulae (12). In four patients further spectra were acquired using a two-dimensional chemical shift imaging (2-D CSI; with spatial encoding in a single dimension) sequence (13), thus localizing the signal to a series of eight parasagittal planes with a nominal width of 3 cm; either 32 or 64 averages were acquired at each phase-encoding step with a repetition time of 1 s (total acquisition time for each sequence was between 4 and 8 min). The data acquisition delay produced by the phase encoding pulses and their associated eddy currents was 2.1 ms. Other data collection and processing parameters were similar to those used for the unlocalized spectra. Following this, up to four successive whole volume spectra were acquired with *TR* 1 s (128 averages). Although formal measurements of the spin-spin relaxation time constant (T_2) were not obtained, measurements of T_2^* were made from the linewidths of individual peaks. The line broadening applied prior to Fourier transformation was corrected in the measurement of T_2^*. These estimates of T_2^* make no allowance for inhomogeneous line broadening and must hence be interpreted with caution.

In a separate experiment we acquired spectra from halothane in water, olive oil, and methanol in order to assess the effect of the environment on the chemical shift of halothane. Twelve microliters of halothane were dissolved in 60 ml of each of the above solvents. We also dissolved a similar concentration of halothane in an emulsion of lecithin in water (prepared by sonicating 5 g of lecithin in 60 ml of distilled water). Transmit and receive coils were set up as described in the *in vivo* experiments, with a NaF capillary as chemical shift reference. The B_1 field was calibrated using a 50 ml sample of neat halothane, the ^{19}F signal from which was also used to optimize the magnetic field homogeniety. Spectra were then acquired from the container of neat halothane with a 90° pulse and a repetition time of 1 s, accumulating 128 averages with 1024 data points and a sweep width of 10 kHz. The vial of neat halothane was then successively replaced by halothane in each of the above solvents. Because all of the samples were in similar spherical vials, and because the setup was undisturbed during changeover, field homogeniety was preserved from one sample to the next. Spectra from all of the phantom experiments were Fourier transformed without line broadening after zero filling the data to 2048 points. Chemical shifts of halothane (relative to NaF) were measured in each of the spectra.

RESULTS

The inspired concentration of halothane and the duration of anesthesia in this preliminary study was dictated by the duration and course of surgery. The mean duration of anesthesia was 30 min (range 25–45 min) and the end-tidal concentration of halothane at the completion of surgery varied between 1.2 and 1.6%. The delay between the end of anesthesia and acquisition of the first fluorine

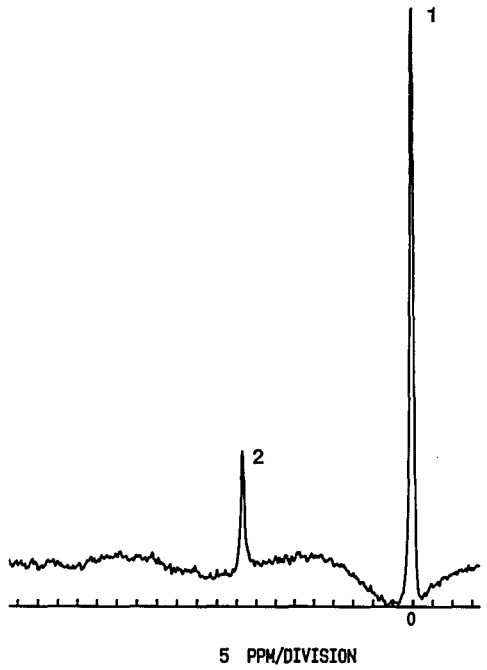

FIG. 1. Spectrum acquired from the whole sensitive volume of the surface receiver coil with *TR* 1 s and 90° pulse angle (128 averages). The large resonance on the right (1) arises from NaF, which is used as a chemical shift reference. A single resonance is seen at +43 ppm (2). The baseline roll arises from a combination of a short dwell time (100 μs) and the dead-time of the receiver system.

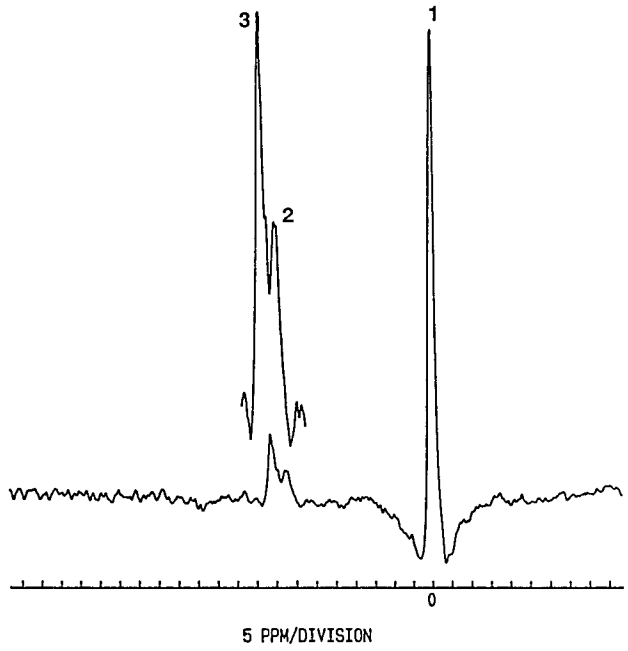

FIG. 2. Spectrum acquired from the whole sensitive volume of the surface receive coil with *TR* 5 s and 90° pulse angle (64 averages). The large resonance on the right (1) arises from NaF, which is used as a chemical shift reference. The two resonances at +38 (2) and +41 ppm (3) are clearly seen in the inset where the peaks have been enlarged.

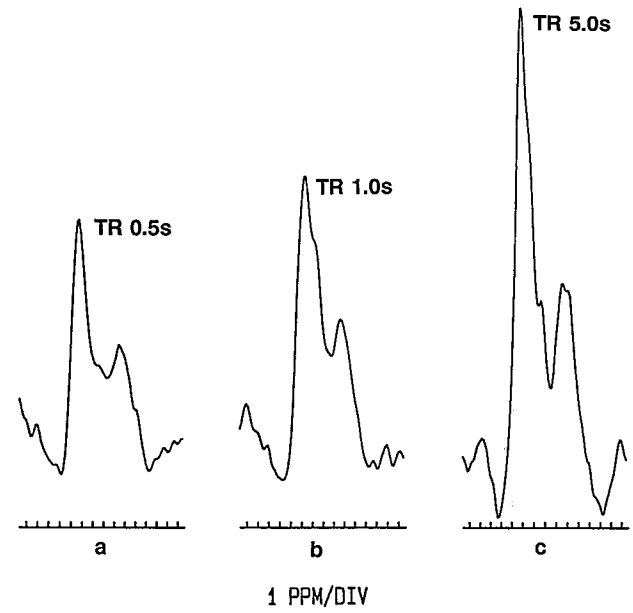

FIG. 3. Spectra acquired from the whole sensitive volume of the coil acquired with repetition times (*TR*) of (a) 0.5 s (256 averages), (b) 1 s (128 averages), and (c) 5 s (64 averages). The observed increase in intensity with the longer *TR* values suggests T_1 values of 0.5–1 s for both resonances with a slightly longer T_1 for the resonance at +41 ppm.

spectrum varied from 35 to 80 min. Expired halothane concentrations were below detection limits of the CAPNOMAC® (0.05%) in all patients when ^{19}F MRS was initiated.

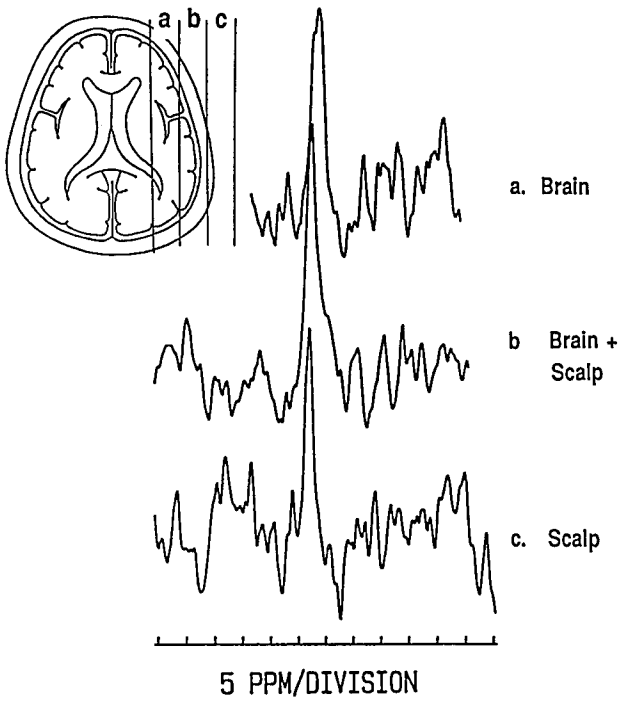

FIG. 4. Spectra from three contiguous planes of the head acquired during the course of a 2-D CSI sequence. The location of the planes is shown on a line diagram of a transverse image of the head. Note that the resonances from the superficial and deep slices have different chemical shifts (+38 and +41 ppm) and different linewidths.

Unlocalized Spectra

Spectra from seven of the eight patients showed a single resonance (Fig. 1). The signal-to-noise ratio (SNR) was typically 20 after 128 data collections, *TR* 1 s. The chemical shift of this resonance varied from patient to patient with a mean (±SD) of +43.3 (±1.8) ppm. The T_2^* of this resonance varied from 3.5 to 10 ms (mean (±SD) 6 (±2.6) ms). In two of these patients, spectra were collected with *TR* values of 0.5, 1, and 5 s. These spectra suggested a T_1 value of between 0.5 and 1 s.

In the remaining patient there were two resonances, with one peak at +38 ppm and the second at +41ppm (Fig. 2). Comparison of spectra acquired with *TR* 0.5, 1, and 5 s (Fig. 3) suggested that both resonances had a T_1 value between 0.5 and 1 s, with the resonance at +41 ppm exhibiting a slightly longer T_1.

Localized Spectra

Localized spectra were obtained in four patients. In three of these patients, a solitary peak was seen in the whole volume spectrum. In all of these the 2-D CSI sequence showed a signal in slices containing mostly brain, making it unlikely that the signal arose predominantly from scalp fat.

In a fourth patient, two overlapping peaks were seen in the unlocalized spectrum, resonating at +38 and +41 ppm. The 2-D CSI sequence showed that the former arose from deeper slices containing chiefly white matter, while the latter arose from superficial slices that contained both

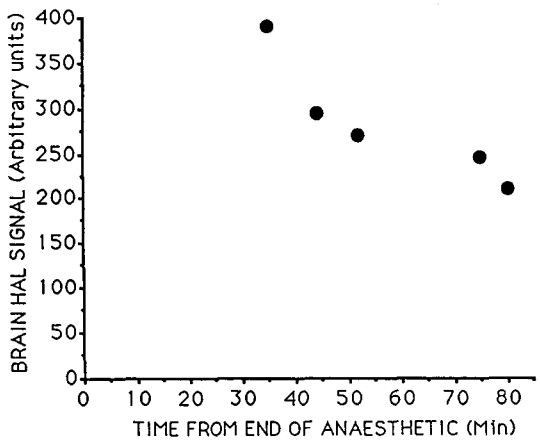

FIG. 5. Graph showing decay of signal intensity (arbitrary units) of halothane resonance with time seen in a patient where a single resonance was noted and was localized to the brain using a 2-D CSI sequence. Signal intensities are from whole volume spectra acquired with *TR* 1 s, 90° pulse and 128 averages, and are represented by solid circles.

scalp and gray matter (Fig. 4). The deeper resonance (at +38 ppm) was broader than the more superficial resonance (at +41 ppm), suggesting that the latter had a longer T_2. Values of T_2^* (calculated from the linewidths) were 4 and 30 ms for the deep and superficial resonances, respectively.

We acquired five spectra with similar data collection parameters in one patient (who exhibited a single resonance at +44.8 ppm) over a 65-min period and were able to plot a time course of halothane signal intensities (Fig. 5).

Phantom Studies

Good quality spectra were obtained from all the samples with SNR varying from 5 (for the water phantom) to >50 for the neat halothane. The chemical shifts of halothane in different environments are listed below:

Halothane (neat): +41.5 ppm
Halothane (water): +43.1 ppm
Halothane (olive oil): +42.9 ppm
Halothane (methanol): +41.5 ppm
Halothane (lecithin/water): +43.2 ppm

DISCUSSION

The results of the present study are consistent with data from previous animal experiments on several counts. The chemical shifts of the single halothane resonance observed in the majority of our patients are similar to those obtained by Litt *et al.* (6), who found that halothane in the rat brain had a chemical shift of approximately +42 ppm relative to potassium fluoride. The variability of the chemical shift may arise from differences in local field strength between the reference sample and cerebral tissue; however, some of this variability may have resulted from variations in local pH and ionic concentrations. The values for T_1 of halothane are also consistent with published results from animal experiments (6, 14) (~1.0 s and 0.7 ± 0.2 s). The T_2^* of the single resonance is similar to values of T_2 obtained in animals in some experiments. For example, Evers *et al.* (4) found that halothane in the *ex vivo* rat brain possessed two distinct T_2 values of 3.6 ± 0.6 ms and 43 ± 8 ms, while James *et al.* (14) quote a T_2 value ranging between 3.5 and 65 ms *in vivo*. It is thus unclear from the previous literature whether the variation in T_2 values represents a single continuous range or a truly bimodal distribution. T_2^* values for the single halothane resonance in our experiments ranged from 4 to 10 ms suggesting T_2 values that were greater than these numbers. This would be consistent with the data from James *et al.* (14). However, in the single patient where two resonances were seen, the T_2^* values for the two peaks were 4 and 30 ms. Although this would fit with the bimodal distribution described by Evers *et al.* (4), it must be remembered that we were measuring T_2^* rather than T_2.

The data that we have for decay of halothane levels with time are limited. The unlocalized spectra were acquired from the whole sensitive volume of the coil, which has a nonuniform profile over a volume of about 450 ml. The poor volume localization and variation in sensitivity across the field of view make it difficult to obtain any estimate of cerebral halothane concentrations, and hence do not permit direct comparisons with previous pharmacokinetic data. It does seem clear, however, that halothane is detectable in the brain using ^{19}F MRS up to 90 min after a relatively short anesthetic. Previous animal studies that have addressed this issue are in conflict; although some studies have shown that halothane is detectable in mouse/rat brain up to 6.5 h after a relatively prolonged anesthetic with halothane (5), other authors have reported that halothane retention in the brain is much less prolonged (6), and there is evidence to suggest that some of the more persistent signal may have arisen from trifluoroacetate (15). The use of ^{19}F MRS to obtain precise pharmacokinetic data will require better volume localization.

The significance of resonances with two separate chemical shifts is uncertain. The water resonance that was used for shimming prior to acquisition of ^{19}F MR spectra showed no splitting, but the patient may have subsequently moved, and hence caused degradation in field homogeneity. We cannot exclude this as a cause of the appearance that we observed, because we were unable to demonstrate similar findings in other patients, and, because of the limited examination time, phase maps were not obtained in this patient study. Other possibilities exist. It has been suggested that halothane vapor in the ambient air may give rise to a second resonance (6). This possibility seems unlikely because we used an efficient ventilation system and because the second resonance was clearly present even when halothane was undetectable in expired gas. One possibility is that both these resonances arise from halothane itself, in two different physicochemical environments, as suggested by Evers *et al.* (4). Alternatively, one of the resonances may be due to a metabolite of halothane, perhaps trifluoroacetate (15). However, previous reports have indicated that, in animal brain at least, the separation between the

halothane and trifluoroacetate resonances is less than 1 ppm (14).

Previous *ex vivo* studies (16) and our phantom data do suggest that the chemical shift of halothane may vary with environment to an extent that may account for the two separate resonances. We also used lecithin as solvent because previous studies have suggested that this compound may be more representative of the site of action of general anesthetics in the brain (17), and because the triglycerides in olive oil may actually be a better model for adipose tissue in the scalp. The minimal difference in the chemical shift of halothane in water and olive oil suggests that the lipophilicity or hydrophilicity of the solvent is not the only factor that is responsible for variation in chemical shift. It has been hypothesized that the presence of both polar and nonpolar groupings characterizes lecithin and increases its resemblance to neural membranes *in vivo* (17), but only small changes in chemical shift were seen in this environment. Whatever the reason for the cause of the two discrete resonances, we are as yet unable to provide a clear explanation for their apparent spatial separation in the 2-D CSI experiment.

In conclusion, this study demonstrates the feasibility of clinical ^{19}F MR spectroscopic studies of fluorinated volatile anesthetic agents. The data obtained are consistent with results of previous animal experiments, and confirm the need for short *TE* sequences or CSI with short acquisition delays when using ^{19}F MRS to study fluorinated anesthetic agents. The apparent spatial localization of the two resonances from halothane to superficial and deep planes in the 2-D CSI study deserves further investigation. The use of ^{19}F MRS to measure early pharmacokinetics of fluorinated volatile agents in patients is likely to be limited by the delay inherent in transporting an unconscious postoperative patient to an MR unit with safety. These considerations may dictate the necessity of volunteer studies if the full potential of the technique is to be realized.

REFERENCES

1. N. Yasuda, S. H. Lockhart, E. I. Eger, R. B. Weiskopf, B. H. Johnson, B. A. Freire, Fassoulaki A. *Anesthesiology* **74,** 489 (1991).
2. N. R. Bolo, K. M. Brennan, R. M. Jones, T. F. Budinger, *Ann. N. Y. Acad. Sci. (USA)* **508,** 451 (1987).
3. W. Wolf, M. S. Silver, M. J. Albright, H. Weber, U. Reichardt, R. Sauer, *Ann. N. Y. Acad. Sci.(USA)* **508,** 491 (1987).
4. A. S. Evers, B. A. Berkowitz, D. A. d'Avignon, *Nature* **328,** 157 (1987); Correction A. S. Evers, B. A. Berkowitz, D. A. d'Avignon, *Nature* **341,** 766 (1989).
5. A. M. Wyrwicz, C. B. Conboy, *Magn. Reson. Med.* **9,** 219 (1989).
6. L. Litt, R. Gonzalez-Mendez, T. L. James, D. I. Sessler, P. Mills, W. Chew, M. Moseley, B. Pereira, J. W. Severinghaus, W. K. Hamilton, *Anesthesiology* **67,** 161 (1987).
7. P. Mills, D. I. Sessler, M. Moseley, W. Chew, B. Pereira, T. L. James, L. Litt, *Anesthesiology* **67,** 169 (1987).
8. S. H. Lockhart, Y. Cohen, N. Yasuda, B. Freire, S. Taheri, L. Litt, E. I. Eger II, *Anesthesiology* **74,** 575 (1991).
9. L. Litt, S. Lockhart, Y. Cohen, N. Yasuda, F. Kim, B. Friere, M. Laster, N. Peterson, S. Taheri, L-H. Chang, D. I. Sessler, M. Moseley, E. I. Eger II, T. L. James, *Ann. N. Y. Acad. Sci. (USA)* **625,** 707 (1991).
10. A. S. Evers, B. W. Dubois, *Ann. N. Y. Acad. Sci. (USA)* **625,** 725 (1991).
11. A. M. Wyrwicz, *Ann. N. Y. Acad. Sci. (USA)* **625,** 733 (1991).
12. G. C. Levy, I. R. Peat, *J. Magn. Reson.* **18,** 500 (1975).
13. D. R. Bailes, D. J. Bryant, G. M. Bydder, H. A. Case, A. G. Collins, I. J. Cox, P. R. Evans, R. R. Harman, A. S. Hall, S. Khenia, P. McArthur, A. Oliver, M. R. Rose, B. D. Ross, I. R. Young, *J. Magn. Reson.* **74,** 158 (1987).
14. T. L. James, L-H. Chang, W. Chew, R. Gonzalez-Mendez, L. Litt, P. Mills, M. Moseley, B. Pereira, D. I. Sessler, P. R. Weinstein, *Ann. N. Y. Acad. Sci. (USA)* **508,** 64 (1987).
15. A. M. Wyrwicz, C. B. Conboy, B. G. Nicols, K. R. Ryback, P. Eisele, *Biochim. Biophys. Acta* **929,** 271 (1987).
16. A. M. Wyrwicz, Y-E. Li, J. C. Schofield, C. T. Burt, *FEBS Lett.* **162,** 334 (1983).
17. S. Taheri, M. J. Halsey, J. Liu, E. I. Eger II, D. D. Koblin, M. J. Laster, *Anesth. Analg.* **72,** 627 (1991).