

Halothane Biotransformation in Obese and Nonobese Patients

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Serum levels of inorganic fluoride, trifluoroacetic acid, and bromide ion were measured at various time intervals following two hours of halothane anesthesia in 17 morbidly obese and eight nonobese patients. Ionic fluoride, a marker of reductive halothane metabolism, increased in the obese but not the nonobese patients. This is of concern since reductive halothane metabolism is associated with hepatotoxicity in animals. In addition, serum bromide levels were higher after 48 h in the obese patients compared to the nonobese patients (mean \pm SE, $1,311 \pm 114$ vs. 787 ± 115 μ M, $P < 0.01$). Sedative levels of bromide were not attained in any patient. Peak trifluoroacetic acid levels were similar in the two patient groups. Sex, age, medication intake, and smoking history had no influence on the halothane metabolite levels found in this study. (Key words: Anesthetics, volatile: halothane. Biotransformation (Drug): flurometabolites. Complications: obesity. Toxicity: metabolites. Ions: bromide, fluoride.)

PREVIOUS INVESTIGATIONS have documented increased biotransformation of volatile anesthetic agents in obese compared to nonobese patients.^{1,2} This is disconcerting since volatile anesthetic metabolism may result in toxicity. Specific organ injury by volatile anesthetics can be initiated by reactive intermediate binding to tissue macromolecules or from noxious end products created by drug metabolism.³

The purpose of this study was to measure metabolites of halothane following similar anesthetic exposure in obese and nonobese patients. A controlled study measuring these variables has not been reported previously. Serum fluoride (F), trifluoroacetic acid (TFA), and bromide (Br) were measured since these metabolites are markers of reductive, oxidative, and total halothane biotransformation, respectively⁴ (fig. 1). Reductive halothane metabolism has been associated with hepatotoxicity in animals, while excessive Br ion may cause sedation.

Methods

Seventeen morbidly obese and eight nonobese patients were studied. Each obese patient was scheduled for gastric stapling. Each nonobese patient was scheduled for elective intra-abdominal surgery (total abdominal hysterectomy, $n = 6$; splenectomy, $n = 1$; and colon resection, $n = 1$). Approval for this study was obtained from

the Human Subject Committee at the University of Arizona Health Sciences Center and prior consent was obtained from each patient. All patients were in good health with no evidence of hepatic or renal dysfunction. Pre-medication consisted of diazepam (10–15 mg) and Maa-lox® (30 ml) orally, as well as intramuscular glycopyrolate (0.2–0.3 mg). Intravenous gallamine (20 mg) was administered and each patient was oxygenated (3–5 min) prior to induction of anesthesia. Anesthesia was induced with thiopental (250–750 mg) followed by succinylcholine (80–160 mg), cricoid pressure, and placement of a cuffed endotracheal tube. Anesthesia was maintained for two hours with halothane in 60 per cent nitrous oxide and oxygen. Inspired halothane concentrations ranged from 0.9 to 3 per cent to maintain end-expired concentrations from 0.44 to 1.57 per cent. If necessary, halothane was discontinued after 2 h and anesthesia was maintained with fentanyl (50–100 μ g) and 60 per cent nitrous oxide with oxygen to limit halothane exposure to 2 h or less. Pancuronium bromide was utilized for muscle relaxation and ventilation was controlled mechanically to maintain carbon dioxide tension at 40 ± 5 mmHg as determined by serial arterial blood-gas measurements. In addition, intraoperative arterial oxygen tension was maintained greater than 80 mmHg in each patient. Halothane exposure in MAC hours was calculated from serial end-tidal halothane concentrations, corrected to atmospheric pressure at sea level. The latter were measured with a Varian 1400® gas chromatograph, utilizing gas-tight syringes, a 10 per cent SE 30 column, and thermoconductivity detection. Injector port, column, and detector temperatures were 150, 80, and 180° C, respectively. The carrier gas was helium at a flow rate of 100 ml/min. A calibration curve was prepared using known halothane gas standards.

Arterial and/or venous blood samples were obtained prior to halothane exposure and at 1, 2, 3, 4, 24, 48, and 72 h following initiation of anesthesia. An additional blood sample was obtained one to two weeks following surgery. An Orion fluoride ion specific electrode was used to determine serum inorganic F concentrations. Serum Br and TFA concentrations were determined by the gas chromatographic method of Maiorino *et al.*⁵

Statistical analysis employed the Student's *t* test for intergroup comparisons, while Pearson correlation coefficients were utilized for analysis of factors potentially affecting halothane biotransformation. In addition, the influence of weight on metabolite levels was evaluated by linear regression analysis. Statistical significance was defined as $P < 0.05$.

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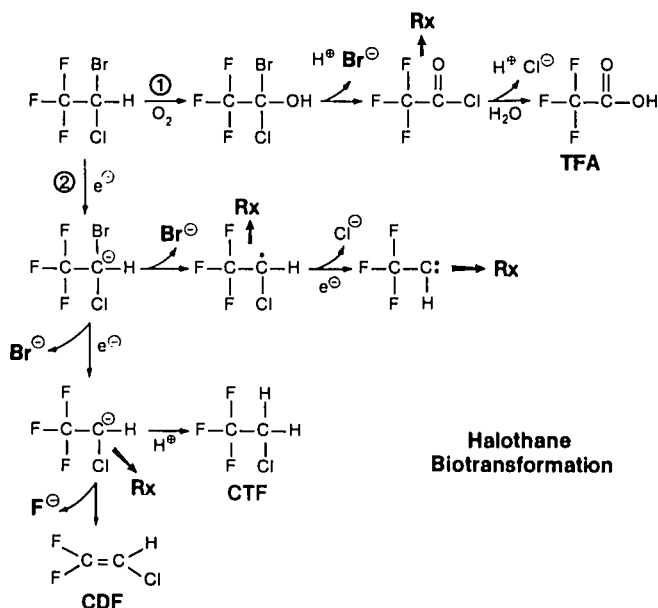


FIG. 1. Proposed scheme of halothane biotransformation. Oxidative and reductive metabolism are depicted by pathways 1 and 2, respectively. Trifluoroacetic acid (TFA) is produced by oxidative biotransformation, while ionic fluoride (F) results from the reductive pathway. Bromide ion (Br) is produced by both routes of halothane metabolism. Chlorodifluoroethylene (CDF) and chlorotrifluoroethane (CTF) are reductive volatile metabolites.

Results

Age, height, sex distribution, medication intake, MAC hour exposure, duration of anesthesia, and smoking history, were similar in obese and nonobese patients (table 1). However, weight, body mass index,[§] and body surface area differed between the two groups of patients.

Serum inorganic F increased significantly from control in the obese patients but not in nonobese counterparts (fig. 2). In addition, mean values of individual maximum F concentrations differed significantly in the obese patients compared to the nonobese patients (table 2).

Serum concentrations of Br and TFA increased significantly from control in both obese and nonobese patients (figs. 3 and 4). In addition, the obese patients had significantly higher levels of Br and TFA compared to the nonobese patients, after 48 and 72 h, respectively. The mean values of individual maximum TFA concentrations did not differ between the two patient groups (table 2), and correspondingly no correlation was found between peak TFA levels and weight. The mean value for maximum Br concentration was higher in the obese patients (table 2). In addition, a positive linear correlation was found between weight and peak serum Br levels ($r = 0.55$, $P < 0.01$). Lastly, no correlation was

[§] BMI = $\text{Wt (kg)}/\text{ht}^2(\text{m})$.

TABLE 1. Patient Characteristics (Means \pm SEM)

	Obese	Nonobese
Number	17	8
Age (years)	41 \pm 2	41 \pm 3
Sex (F/M)	13/4	6/2
Ht (cm)	166 \pm 2	163 \pm 2
Wt (kg)	125 \pm 5*	59 \pm 5
BMI (kg/m ²)	45 \pm 1*	22 \pm 2
BSA (m ²)	2.26 \pm 0.06	1.62 \pm 0.07
MAC hours	1.60 \pm 0.12	1.65 \pm 0.16
Duration of anesthesia (min)	112 \pm 15	118 \pm 7
Smoker (yes/no)	4/13	2/6
Medications (yes/no)	5/12	2/6

* Significantly different from nonobese, $P < 0.001$.

found between age, sex, medication, or smoking history and levels of F, TFA, and Br at the intervals measured.

Discussion

This study found elevated serum inorganic F and Br, and similar serum TFA concentrations in obese compared to nonobese patients following equivalent halothane exposure. Logically, the differing metabolite levels found in the two groups of patients results from differences in metabolite production, distribution, or elimination. The latter possibility is unlikely since altered drug clearance has never been demonstrated in morbidly obese patients.⁶ Likewise, for all drugs studied, morbidly obese patients have an increase in volume of drug distribution which would tend to lower, rather than raise serum drug concentrations.⁶ Thus, higher F and Br levels in obese compared to nonobese patients is likely due to enhanced metabolite production in the obese patients.

Our finding of elevated ionic F in morbidly obese patients after halothane anesthesia confirms the report by Young *et al.*¹ These investigators found higher peak F

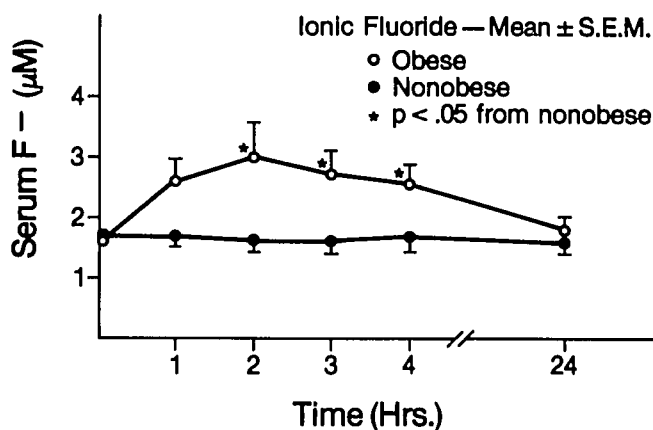


FIG. 2. Ionic fluoride levels in 17 obese and eight nonobese patients during and following halothane anesthesia.

TABLE 2. Peak Halothane Metabolite Levels
(Means \pm SEM)

	Obese	Nonobese
Fluoride (μM)	3.2 \pm 0.6* (1.2-10.1)	1.9 \pm 0.2 (1.1-2.6)
Bromide (μM)	1311 \pm 114† (572-2,346)	787 \pm 115 (202-1,151)
TFA (μM)	613 \pm 66 (187-1,023)	501 \pm 94 (244-1,066)

Range of values are in parenthesis. Significantly different from non-obese, $P < 0.05^*$ and $P < 0.01^\dagger$.

levels (10.4 μM) than those found in our study, but anesthetic exposure was longer (average three hours). Similar increases in inorganic F ion during and following halothane exposure have not been reported in nonobese subjects despite extensive investigation.⁷⁻¹⁰ However, elevation of chlorodifluoroethylene (CDF) and chlorotrifluoroethane (CTF), both end products of reductive halothane metabolism (fig. 1), have been reported by Sharp *et al.*¹¹ in nonobese patients. Gourlay *et al.*¹² also reported elevation of these metabolites in four patients, two of which were obese. Levels of these two metabolites appeared to be higher in the obese patients.

These results are bothersome since reductive halothane metabolism is associated with hepatotoxicity in animals.¹³ In the experimental model of halothane hepatitis levels of inorganic F ion, CDF, and CTF are elevated above control values and correlate well with the degree of hepatic injury.¹⁴

Because of these findings, elevated inorganic F ion, as well as the CDF and CTF metabolites, suggest a potential for halothane hepatotoxicity in morbid obesity. In this regard a large scale epidemiologic investigation

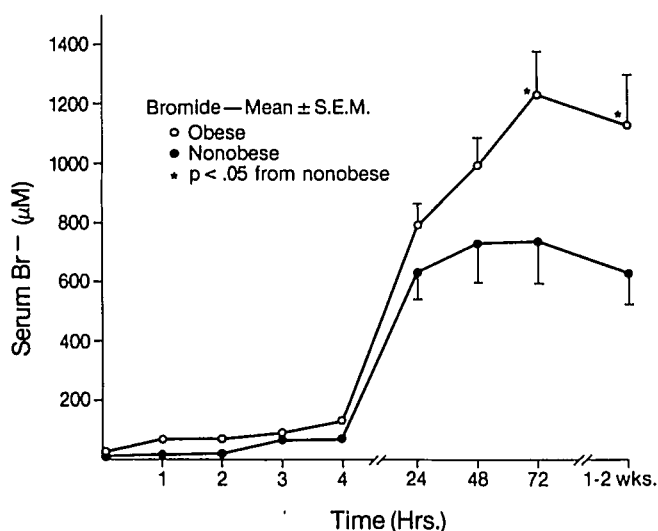


FIG. 3. Serum bromide levels in 17 obese and eight nonobese patients following two hours of halothane exposure.

found that 38 per cent of patients with evidence of unexplained postoperative jaundice following halothane anesthesia were obese.¹⁵ However, it must be stressed that the level of reductive halothane metabolism found in this study and that of Young *et al.* was not associated with clinically evident hepatotoxicity.

Reductive metabolism is favored in an hypoxic hepatic environment and likely, this is the reason obese patients have a propensity for reductive halothane metabolism. Oxygen delivery to the hepatocyte probably is impaired in obesity because of fatty infiltration of the liver, a finding present in over 80 per cent of these patients.¹⁶ Furthermore, halothane decreases liver blood flow,¹⁷⁻¹⁹ and hypoxemia is frequently present in obesity because of altered respiratory physiology.¹⁶ Thus, the combination of decreased hepatic and respiratory reserve, coupled with possible anesthesia-associated respiratory compromise and hepatic blood flow reduction, may render the morbidly obese patient at risk for reductive halothane biotransformation.

Previous investigators^{7,10,20-22} have reported elevation of Br ion in nonobese patients following halothane anesthesia. In this study Br was increased in all patients, but was significantly higher in the obese compared to the nonobese patients following similar halothane exposure (fig. 3). In fact, maximum levels in our obese patients were approximately two times that of our nonobese patients.

The main theoretical concern about Br ion in the postoperative period is sedation, which occurs with levels in the range of 6-12 mM.²⁰ These levels were not attained by either the obese or nonobese patients in this study (table 2). This finding is similar to other investigations in nonobese patients. However, peak Br levels following halothane anesthesia depend on duration of expo-

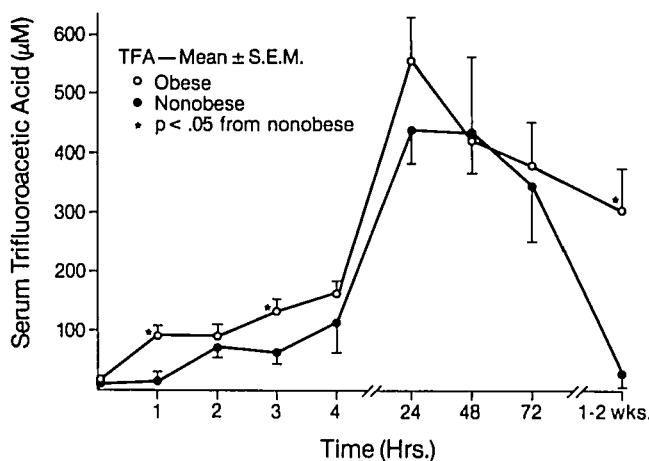


FIG. 4. Trifluoroacetic acid levels in eight nonobese and 17 obese patients following equivalent halothane exposure.

sure.²⁰⁻²² Because of this, and also because bromide levels were two times higher in our obese patients, sedative levels of Br might be attained in some obese patients with prolonged halothane exposure. Further investigation is required to document this speculation.

The fact that peak Br levels occur at least three days after halothane exposure suggests that halothane is released slowly from fat tissue stores and subsequently metabolized.²³ Since obese patients have excess adipose tissue mass available for halothane storage, it is not surprising that they have increased Br levels compared to nonobese patients. Thus, this study demonstrated that weight, like duration of halothane exposure, correlated with Br levels following halothane anesthesia.

Levels of TFA, an end product of oxidative halothane metabolism, were similar in obese and nonobese patients. This finding is surprising, since F and Br levels were higher in our obese group of patients. The reason for this result is unknown.

As stated previously, TFA is formed by oxidative halothane biotransformation, while Br is formed by both oxidative and reductive metabolism (fig. 1). In animals, levels of TFA and Br following halothane exposure are very similar.⁵ Presumably, this results because one molecule of Br is released as each molecule of TFA is formed in the oxidative pathway of halothane metabolism (fig. 1). Thus, higher bromide levels than TFA levels in both obese and nonobese patients suggests that a significant amount of reductive halothane metabolism occurred in the postoperative period. Clearly, other factors could also explain this finding. The concern about reductive halothane biotransformation has been outlined previously.

Finally, this study found that age, sex, medications, or smoking habits had no influence on halothane metabolite levels in either the obese or nonobese patients. This finding is consistent with previous investigations which have indicated that these factors influence volatile anesthetic metabolism, little, if at all.^{20,21,24}

In summary, this study demonstrated that qualitative and quantitative differences in halothane biotransformation occur in morbidly obese compared to nonobese patients despite similar drug exposure. Serum inorganic F, a marker of reductive halothane metabolism, increased in obese but not nonobese patients. This is worrisome since reductive halothane biotransformation is associated with hepatotoxicity in animals. In addition, Br levels following halothane anesthesia were two times higher in obese compared to nonobese patients. Possibly with prolonged halothane exposure, sedative levels of Br ion could be attained in severely obese patients. Lastly, age, sex, medications, and smoking habits did not influence the levels of halothane metabolites.

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