Anesthesiology
55:559–576, 1981

REVIEWS

BRYAN E. MARSHALL, M.D., Editor

Isoflurane: A Review

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ISOFLURANE was the 469th compound made by Dr. Ross Terrell and his associates in their search for a better inhaled anesthetic.[1] Because isoflurane was more difficult to synthesize and purify, its discovery in 1965 followed that of its isomer, enflurane (compound 347). Initial work in animals led to human studies which indicated that isoflurane might possess superior attributes. Further studies in animals and volunteers, and clinical testing in 3,000 patients, confirmed these initial impressions.

Introduction of isoflurane was scheduled for 1975. However, results from a preliminary study by Corbett[2] suggested that isoflurane might be a hepatocarcinogen. As a consequence, approval of isoflurane was withheld by the Food and Drug Administration pending replication of Corbett's study. Corbett himself participated in the subsequent investigation, which did not confirm his preliminary results.[3] Isoflurane is now approved for clinical use by the Food and Drug Administration.

Structure and Physical Properties

Isoflurane is a methyl ethyl ether having many physical properties similar to those of its isomer, enflurane (table 1).[4] Halogenation with five fluorines and one chlorine renders isoflurane nonflammable over all clinically useful concentrations.[5] The vapor pressure of isoflurane more closely resembles that of halothane than that of enflurane. In fact, a halothane tec-type vaporizer (*e.g.*, a Fluomatic®) will deliver close to the indicated concentration when filled with isoflurane.[6] Similarly, an isoflurane vaporizer (*e.g.*, a Fortec®) will deliver the indicated concentration when filled with halothane. However, interchanging vaporizers in this way risks misidentifying their contents.

Potency

In 100 per cent oxygen, isoflurane has a MAC of 1.15 per cent (table 1).[7] As with other inhaled anesthetics, the dose-response curves which define MAC at various ages are steep. Thus, nearly all patients move in response to incision at 80–90 per cent of MAC, while few move at 120–130 per cent of MAC.

The MAC for isoflurane lies midway between that for halothane (0.75 per cent)[8] and that for enflurane (1.68 per cent).[9] The potency of all three anesthetics permits the concomitant administration of nearly 100 per cent oxygen. The addition of 70 per cent nitrous oxide decreases isoflurane MAC by 0.7 per cent (*i.e.*, each 10 per cent nitrous oxide equals 0.1 per cent isoflurane).[7] An additive effect is also seen for other anesthetics (table 1).

Various factors may decrease MAC. Nitrous oxide[7] and other depressant drugs such as morphine,† alcohol,[10] and lidocaine[11] each lower MAC. In adults, aging produces a parallel decrease in MAC for both isoflurane and halothane (fig. 1).[7,12] Isoflurane MAC has not been measured in patients younger than 20 years of age. If the parallel relationship between isoflurane and halothane in adults extends to the young patient, then isoflurane MAC at four years of age would be 1.4 per cent and at six months, 1.6 per cent.[13] Each decrease in body temperature of one °C decreases MAC by about 5 per cent.[13] Pregnancy may reduce MAC by 40 per cent.[14] Two occurrences may increase isoflurane MAC: chronic ingestion of alcohol, implying that the alcoholic patient may be resistant to the anesthetic effect of isoflurane; and the concomitant administration of the convulsant vapor flurothyl.[15] The latter may explain why enflurane is less potent than its isomer, isoflurane. The convulsant properties of enflurane[16] may antagonize its anesthetic effect; isoflurane does not induce seizure activity,[17] and hence does not antagonize its anesthetic effect.

Pharmacokinetics of Isoflurane

The blood/gas partition coefficient of isoflurane (1.4) is less than that of other potent inhaled anesthetics used today (table 1).[18] Only nitrous oxide has a lower solubility. The low blood solubility of isoflurane permits its alveolar concentration to rise rapidly towards the inspired concentration (fig. 2).[18] This rate is higher than

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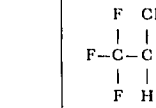
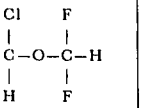
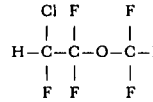
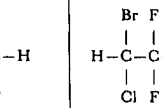
† France CJ, Saidman LJ, Wahrenbrock EA: The effect of morphine on isoflurane requirements in man. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1974, pp 49–50.

TABLE 1. Some Properties of Currently Available Inhaled Anesthetics

	Isoflurane	Enflurane	Halothane	Methoxyflurane	Nitrous Oxide
					 44
Molecular weight (g)	184.5	184.5	197.4	165.4	——
Specific gravity (25° C)	1.50	1.52	1.86	1.41	——
Boiling point (° C)	48.5	56.5	50.2	104.7	——
Vapor pressure at 20° C (torr)	240	172	244	22.8	——
Minimum inflammable concentration in 70 per cent N_2O, 30 per cent O_2 (per cent)	7.0	5.8	4.8	> vapor pressure	——
MAC in O_2*	1.15	1.68	0.75	0.16	110
MAC in 70 per cent N_2O*	0.50	0.57	0.29	0.07	——
Blood/gas partition coefficient (37° C)	1.4	1.9	2.3	12	0.47
Conductive rubber/gas partition coefficient (at room temperature)	62	74	120	630	1.2
Preservative	None	None	Thymol	Butylated hydroxytoluene	None
Stability in soda lime	Stable	Stable	Breaks down	Breaks down	Stable
Per cent of uptake recovered as metabolites	0.17	2.4	20	50	> 0

* In 30- to 55-year-old patients; per cent of 1 atm.

that of other potent agents; only nitrous oxide rises more rapidly.[18,19]

The speed with which the alveolar concentration of isoflurane approaches the inspired concentration suggests that induction should be more rapid than with the more soluble halothane. In fact, the reverse tends to be the case. As with enflurane, the mild pungency of isoflurane limits the rate at which the inspired concentration can be increased without provoking breath-holding or coughing.[20,21] This limitation may be largely circumvented by administering premedication or nitrous oxide and/or by using an intravenous agent for induction.[20,21]

The alveolar concentration of isoflurane rises to 50 per cent of that inspired in the first 5–10 min of anesthesia (fig. 2). That is, induction requires an inspired concentration which is twice as large as that needed in the alveoli. Induction commonly requires an alveolar concentration that is approximately 50 per cent larger than MAC (50 per cent more to accelerate brain equilibration). Thus, 1.1 per cent isoflurane with 70 per cent nitrous oxide, or 1.7 per cent without nitrous oxide, may be needed for induction and would require inspired concentrations of 2.2 and 3.4 per cent, respectively. Slightly higher delivered concentrations might be required to wash out the anesthetic circuit, to counterbalance the depletion of isoflurane in rebreathed gases, and to account for loss of anesthetic to rubber, plastic, or soda lime.[22] The relatively low solubility of isoflurane in rubber or plastic minimizes uptake by these substances (table 1).

Once induction is complete, the inspired concentration must be lowered to compensate for the decreased uptake consequent to the progressive equilibration of isoflurane with the tissues of the body. By 30 min, the alveolar concentration equals 70 per cent of the inspired concentration (fig. 2). That is, the inspired concentration is only 1.4 times greater than the alveolar concentration. The ratio, of course, becomes still smaller with time. To maintain an alveolar concentration that is 30 per cent above MAC requires an inspired concentration of 1.3–1.4 per cent isoflurane in the presence of 70 per cent nitrous oxide, and 2.0–2.1 per cent without nitrous oxide. These figures are approximations which must be adjusted to suit the needs of the patient. Age and hypothermia decrease the figures, as does a tendency to hypotension. If patient management requires hypotension or profound muscle relaxation, this may indicate delivery of higher concentrations.

The closeness of the alveolar and inspired concentrations for isoflurane suggests that the inspired concentration more accurately reflects the partial pressure of anesthetic in tissue than is the case with more soluble agents. That is, the effective anesthetic partial pressure may be controlled with slightly greater precision with

isoflurane than with enflurane or halothane. Similarly, the effective partial pressure may be changed with slightly greater control in the case of isoflurane.

The lower solubility of isoflurane also enhances its elimination. As with induction, the differences between isoflurane and enflurane or halothane appear to be small but consistent: recovery is slightly more rapid with isoflurane.[4] The duration of anesthesia affects the rate of recovery.[4,18] In a study of 896 patients, those anesthetized with isoflurane for less than one hour opened their eyes on command 7.3 min after discontinuation of anesthesia. This time increased to 11.2 (± 1.0) min for patients anesthetized for two to three hours. However, a longer period of anesthesia did not cause a further increase: patients anesthetized for five to six hours opened their eyes in 11.4 ± 3.8 min (Isoflurane New Drug Application, pp. 626–627).

The rapid elimination of isoflurane has several implications. Mental function soon returns to normal[23]; and circulatory, respiratory, and neuromuscular depression are quickly reversed. The swift return of mental function also suggests that there may be little postoperative analgesia. Finally, rapid elimination of a drug decreases its potential for liver or kidney toxicity: if the anesthetic has left the body it cannot be biodegraded to noxious metabolites.

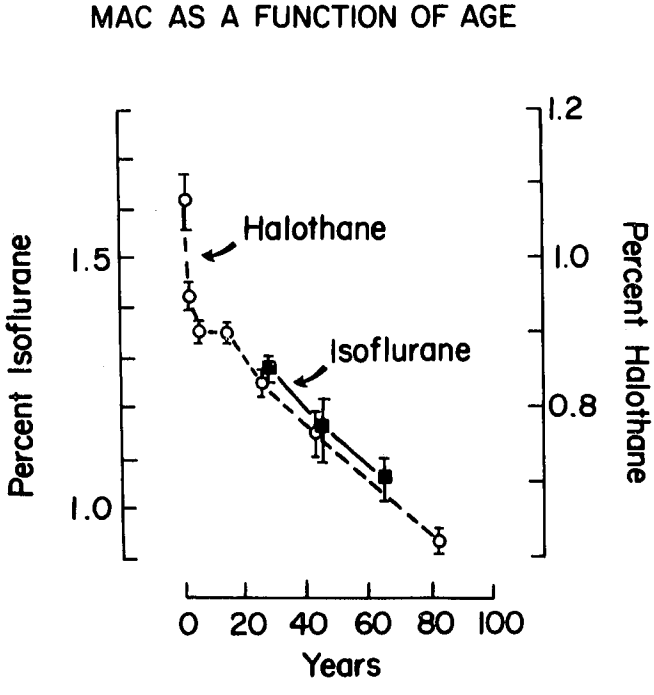


FIG. 1. MAC for isoflurane[7] and halothane[12] in adult patients and MAC for halothane in children[12] are plotted together using the same zero starting point (zero suppressed). For adults, the decrease in MAC with aging is parallel for the two anesthetics. Data for isoflurane MAC in infants and children are not available. (Reproduced with permission from Stevens *et al.*[7])

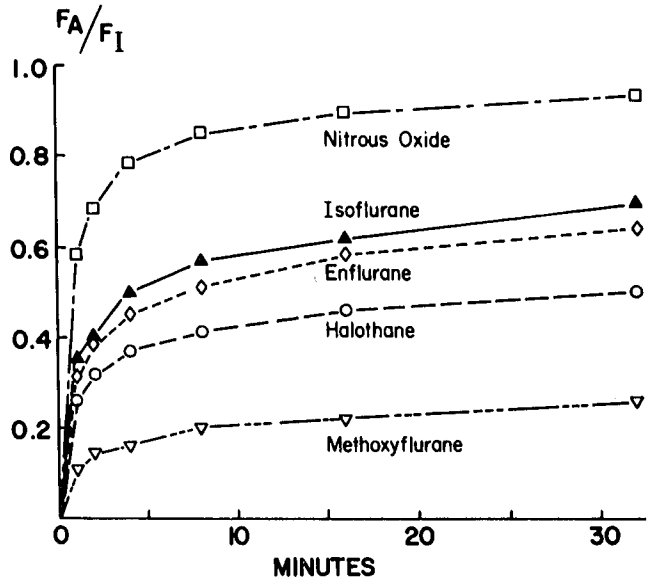


FIG. 2. Volunteers were given subanesthetic concentrations of isoflurane[18] or a mixture of nitrous oxide, enflurane, halothane, and methoxyflurane.[19] End-tidal (F_A) and inspired (F_I) concentrations were measured. The graph of the ratio of F_A/F_I indicates the rate at which the alveolar concentration approached the concentration being breathed. (Reproduced with permission from Eger.[4])

RESPIRATORY EFFECTS

All inhaled anesthetics, including isoflurane, depress ventilation. The degree of depression produced by a given anesthetic dose (*i.e.*, MAC fraction) may differ with the variable measured. As with other inhaled anesthetics,[24,25] the ventilatory response to hypoxia is markedly decreased in humans at 0.1 MAC isoflurane and virtually disappears at 1 MAC (Knill R: Personal communication). As anesthetic dose is increased, the ventilatory response to imposed increases in Pa_{CO_2} progressively decreases, linearly approaching zero at about 2 MAC (fig. 3).[25,26] Depression of the response to hypoxia and to increased Pa_{CO_2} means that anesthetized patients are less apt to compensate for stresses imposed on the respiratory system (*e.g.*, airway obstruction, malfunction of the carbon dioxide absorption system, and partial paralysis from administration of muscle relaxants). Accordingly, the potential for hypoxemia and respiratory acidosis increases.

The effect of anesthetic dose to increase Pa_{CO_2} in spontaneously breathing volunteers (not undergoing surgery) differs among anesthetics. One to 1.5 MAC nitrous oxide given in a pressure chamber‡ does not increase Pa_{CO_2},

‡ Winter PM, Hornbein T, Smith G, et al: Hyperbaric nitrous oxide anesthesia in man: Determination of anesthetic potency (MAC) and cardiorespiratory effects. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1972, pp 103–104.

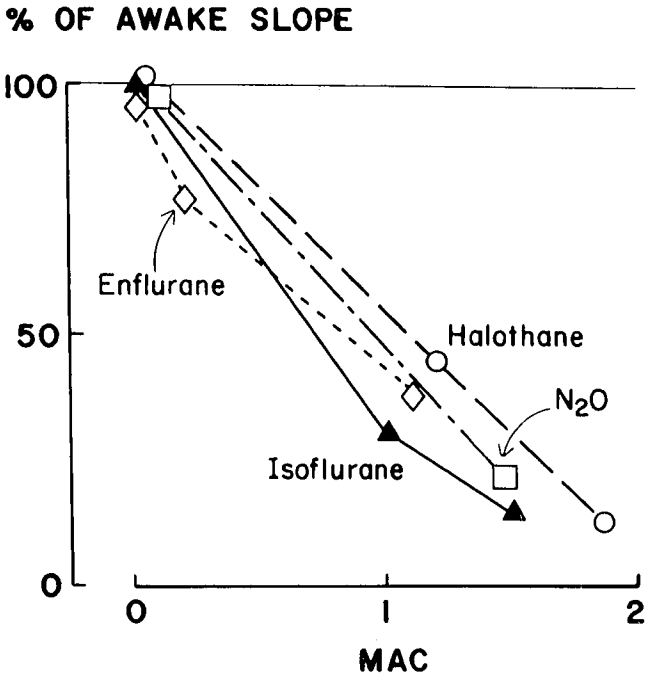


FIG. 3. Volunteers anesthetized with enflurane,[25] halothane,[26] isoflurane,[26] or nitrous oxide‡ in oxygen (1.5 atm nitrous oxide was given in a pressure chamber) were tested for their ventilatory response to imposed increases in Pa_{CO_2}. The responses progressively decreased as alveolar anesthetic concentration increased, approaching zero response at about 2 MAC. (Reproduced with permission from Eger.[4])

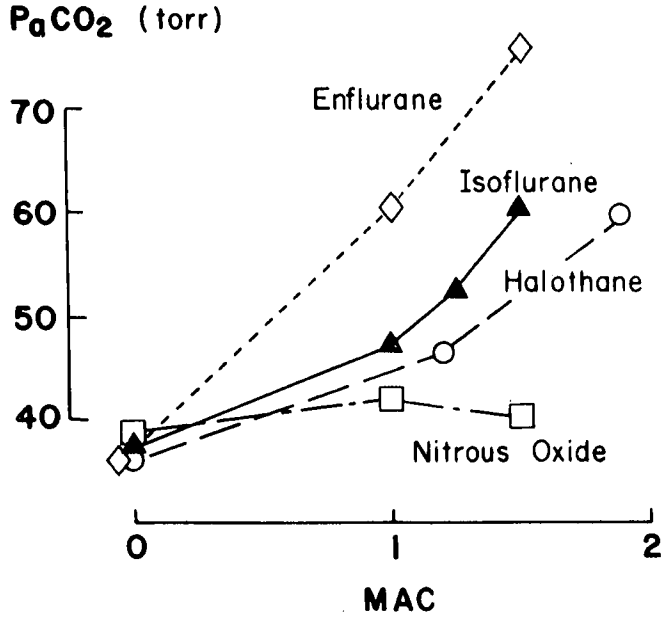


FIG. 4. Pa_{CO_2} was measured in volunteers given enflurane, halothane, isoflurane, or nitrous oxide in oxygen. Nitrous oxide did not increase Pa_{CO_2}. For the remaining agents, the greatest increase at any MAC level was seen with enflurane. Isoflurane was slightly more depressant than halothane.[25,26]‡ (Reproduced with permission from Eger.[4])

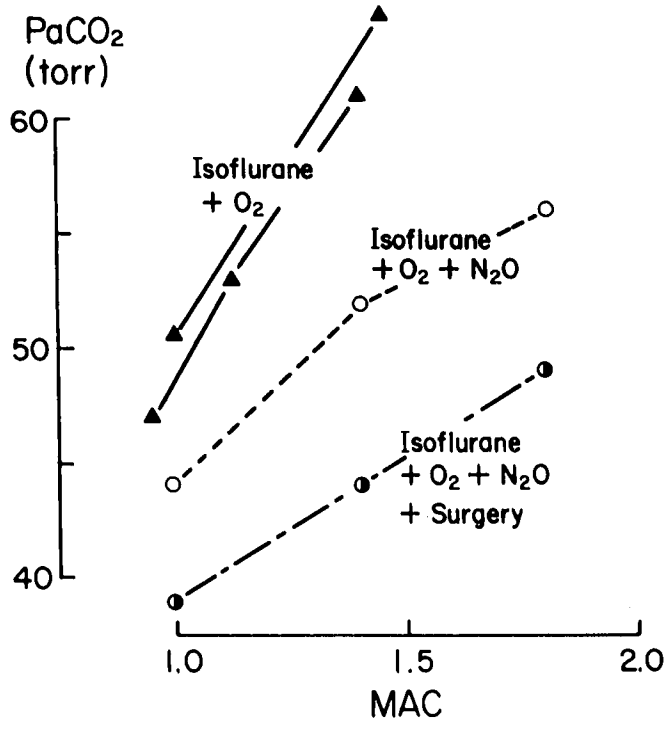


FIG. 5. Pa_{CO_2} values were obtained from two studies of young, unstimulated volunteers anesthetized with isoflurane in oxygen.[26-27] Pa_{CO_2} values also were obtained before and 20 min after the start of surgery in middle-aged patients anesthetized with isoflurane in 70 per cent nitrous oxide.[28] MAC levels were corrected for age and the contribution of nitrous oxide. Substitution of nitrous oxide for an equal MAC fraction of isoflurane decreases Pa_{CO_2}. Also, the stimulus of surgery causes a further decrease: at 1 to 1.8 MAC, the average Pa_{CO_2} is below 50 torr.[28]

while enflurane profoundly depresses ventilation, as indicated by a rise in Pa_{CO_2} to 60–70 torr (fig. 4). Note that this does not mean that nitrous oxide is not a respiratory depressant (fig. 3). Isoflurane and halothane lie between these extremes, isoflurane being perhaps slightly more depressant.

The absence of an effect of nitrous oxide on Pa_{CO_2} implies that substitution of nitrous oxide for an equal MAC fraction of a potent agent (*i.e.*, the total MAC administered would not change) would decrease the respiratory acidosis produced by the potent agent. Data from studies in volunteers and unstimulated patients support this hypothesis (fig. 5).[26-28] Patients given 1.5 MAC isoflurane plus nitrous oxide have a Pa_{CO_2} that is 10 torr less than the Pa_{CO_2} of volunteers given 1.5 MAC isoflurane in oxygen. Morphine medication prior to anesthesia with isoflurane and nitrous oxide does not increase Pa_{CO_2} if the MAC contribution of the morphine is taken into account.[29]

The stimulation of ongoing surgery further reduces Pa_{CO_2} in patients anesthetized with isoflurane (fig. 5).[28,29] At 1.5 MAC, the average Pa_{CO_2} is less than 50 torr.

However, the Pa_{CO_2} is higher than might be predicted from the increase in ventilation associated with the stimulus of surgery. The increased ventilation does not cause a commensurate decrease in Pa_{CO_2} because CO_2 production also increases.[29] These effects of surgery probably apply to all anesthetics.

Although the use of nitrous oxide and the stimulation provided by surgery ameliorate much of the respiratory acidosis induced by isoflurane, Pa_{CO_2} may still increase, particularly at deeper levels of anesthesia. Controlling ventilation may be required to achieve normocapnia or hypocapnia. As with other anesthetics, assisted ventilation does not effectively lower Pa_{CO_2}. The apneic threshold (the minimum Pa_{CO_2} which initiates ventilation) is only approximately 3.4 torr lower than the Pa_{CO_2} produced by spontaneous ventilation.[30] That is, assisted ventilation cannot lower Pa_{CO_2} more than 3.4 torr and normally would be less effective than that.

Respiratory mechanics were studied by Rehder *et al.*[31] in five volunteers. After control (awake) measurements were obtained, the subjects were anesthetized with isoflurane and paralyzed with an infusion or succinylcholine; their tracheas were topically anesthetized with lidocaine prior to endotracheal intubation. Control measurements were repeated at 1 and 2 per cent isoflurane. Functional residual capacity and lung compliance decreased from awake levels at 1 per cent but not at 2 per cent. Both levels of anesthesia increased pulmonary resistance. Other approaches to general anesthesia produce comparable effects.[32]

Circulatory Effects

Like other anesthetics, isoflurane depresses the contractility of the isolated heart. Isoflurane produces a dose-related decrease in the maximum velocity of shortening, in the mean maximal developed force, and in other indices of contractility in papillary muscle of the cat.[33] At MAC, the decreases are comparable to those seen with halothane or methoxyflurane but are greater than those seen with diethyl ether or enflurane. Papillary muscle from cats with congestive heart failure is more sensitive to the depressant effects of isoflurane and other anesthetics.[33] These *in vitro* findings may differ from results obtained in intact animals, volunteers, or patients. One to 2 MAC isoflurane does not depress the preejection period, the mean rate of ventricular ejection, or ejection time in healthy young normocapnic volunteers. Also, these concentrations do not decrease the IJ wave of the acceleration ballistocardiogram, a sensitive measure of myocardial function (fig. 6).[34] In contrast, halothane[35] and enflurane[36] depress the ballistocardiogram IJ wave in a dose-related fashion.

Right atrial pressure is unaffected by 0.9 to 1.4 MAC

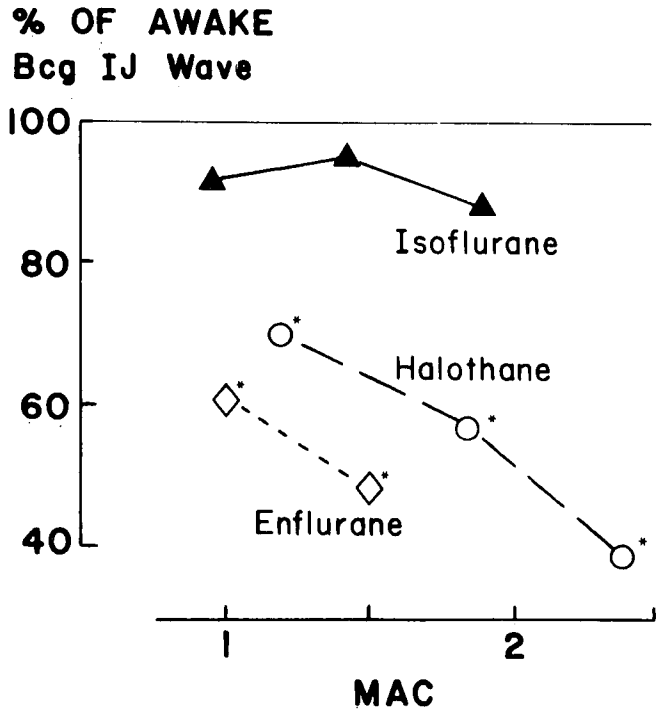


FIG. 6. The acceleration imparted to the body by ejection of blood from the heart was assessed in young normocapnic volunteers by measuring the ballistocardiogram (Bcg) IJ wave. Enflurane[36] and halothane[35] decreased the Bcg IJ wave in a dose-related fashion (asterisks indicate a significant difference from awake values), while isoflurane[34] had no effect. (Reproduced with permission from Eger.[4])

isoflurane and rises but slightly at 1.9 MAC (fig. 7). This also may indicate minimal myocardial depression in the 1–2 MAC range since isoflurane does not appreciably alter afterload (pulmonary artery pressure and resistance to blood flow).[37] Halothane[35] and enflurane[36] increase right atrial pressure, as does nitrous oxide. However, the increase with nitrous oxide reflects (at least in part) an increase in pulmonary artery resistance to blood flow.[38]

The stability of right atrial pressure with isoflurane not only suggests minimal myocardial depression but also indicates that the heart remains efficient. With halothane or enflurane, the increase in right atrial pressure may distend the right ventricle and thereby increase myocardial wall tension. This will tend to increase myocardial work and oxygen consumption associated with a given cardiac output and afterload. In dogs, isoflurane decreases myocardial oxygen consumption and coronary vascular resistance, does not alter coronary blood flow, and increases coronary venous oxygen saturation.[39] Halothane and enflurane decrease coronary blood flow and myocardial consumption and do not alter coronary vascular resistance or venous oxygen saturation.[39]

In normocapnic volunteers, 0.9 to 1.9 MAC isoflurane and 1 to 1.5 MAC nitrous oxide do not change cardiac

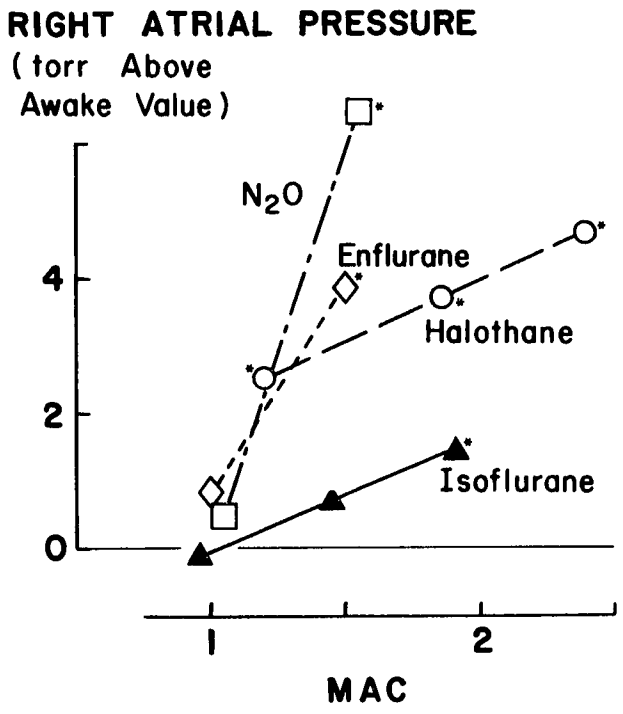


FIG. 7. In normocapnic volunteers, 0.9 to 1.4 MAC isoflurane[34] did not increase right atrial pressure, while 1.9 MAC did (asterisks indicate a significant difference from awake values). Enflurane[36] and nitrous oxide‡ produced a significant increase at 1.5 (but not 1.0) MAC, as did 1.2 to 2.4 MAC halothane.[35] Nitrous oxide was given in a pressure chamber at 1.1 and 1.6 atm (total pressure in both cases, 1.9 atm). (Reproduced with permission from Eger.[4])

output (fig. 8).[34] Enflurane and halothane produce a dose-related decrease in output secondary to a decrease in stroke volume.[35,36] Isoflurane (but not nitrous oxide) also decreases stroke volume. Heart rate increases and cardiac output remains at awake levels.[34] Heart rate also increases with nitrous oxide. On the average, lesser increases (or no increase) in rate are seen in patients undergoing surgery under isoflurane anesthesia.[37,40-42] The smaller increase (from awake values) in patients may result from a higher awake rate (*i.e.*, a higher "control" rate), greater age, or administration of narcotics. Although an increase in heart rate normally is well-tolerated, it represents a negative attribute of isoflurane. An increase in rate increases myocardial work and decreases the duration of diastole. The shorter diastolic time decreases the period available for myocardial perfusion. Although a potential exists for increased myocardial oxygen consumption and decreased oxygenation, isoflurane anesthesia (in dogs) *decreases* consumption and increases oxygen content in coronary sinus blood.[39]

The absence of an effect of isoflurane on indices of myocardial function (*e.g.*, the ballistocardiogram IJ wave) or cardiac output, and the minimal effect on right atrial pressure suggest a greater margin of cardiovascular safety with isoflurane than with enflurane or halothane. Indeed, normocapnic volunteers may not tolerate anesthesia with 2 MAC enflurane, as evidenced by an alarming decrease in cardiac output and blood pressure.[36] Volunteers anesthetized with isoflurane and halothane, however, are able to tolerate similar concentrations.[34,35]

A wider margin of cardiovascular safety with isoflurane also is suggested by results of a study in rats.[43] The myocardial concentration of anesthetic which produces circulatory collapse may be divided by the concentration required for anesthesia (MAC) to obtain a "cardiac anesthetic index." A larger ratio indicates a larger margin of safety. The ratio for isoflurane (5.7) is significantly larger than that for enflurane (3.3) or halothane (3.0). These results in rats and humans should not be interpreted as meaning that isoflurane cannot depress the heart: cardiovascular collapse will occur in rats and other animals[44] at sufficiently high concentrations of isoflurane.

While clinically used concentrations of isoflurane may not depress the heart, they nonetheless cause a dose-related decrease in blood pressure (fig. 9).[34] Substitution of nitrous oxide for an equivalent MAC fraction of isoflurane partially ameliorates this decrease[45] in pressure in volunteers or unstimulated patients. The stimulus provided by ongoing surgery additionally increases pressure towards normal awake levels.[4] Of course, even dur-

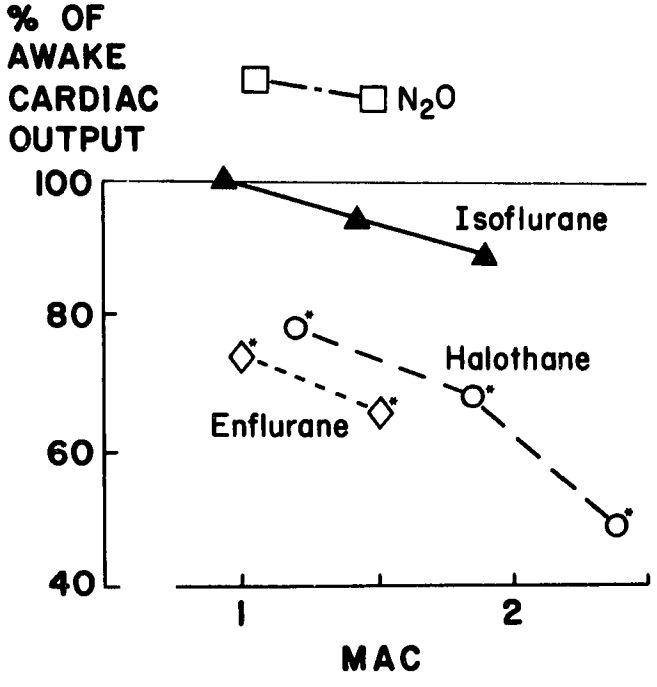


FIG. 8. Normocapnic volunteers given enflurane or halothane have a dose-related decrease in cardiac output (asterisks indicate a significant difference from awake values.[35,36] The same MAC levels of isoflurane or nitrous oxide do not alter cardiac output.[34]‡ (Reproduced with permission from Eger.[4])

ing surgery deep levels of anesthesia can produce profound hypotension. The relationship between pressure and anesthetic concentration suggests that pressure may be used as a guide to the depth of anesthesia.

The decrease in systemic arterial pressure may be of concern in patients with arteriosclerosis/atherosclerosis in whom perfusion to some vital organ may be limited. That is, the lowering of pressure may decrease perfusion and compromise local tissue oxygenation because compensatory vasodilation is limited or impossible. In fact, this does not appear to be a common problem during isoflurane anesthesia, in part because pressure is readily sustained by several factors (decreasing the dose of anesthetic, substitution of nitrous oxide, surgical stimulation), and in part because like other potent inhaled anesthetics, isoflurane decreases oxygen consumption in all tissues, including the heart. Overall, evidence does not suggest significant tissue hypoperfusion. Central venous oxygen saturation increases and base excess changes not at all or decreases only slightly (1 to 2 mEq/l).[20,34] Serum lactic acid either does not increase§ or increases only slightly by an amount comparable to that obtained with other general anesthetics.[46]

Isoflurane decreases systemic arterial pressure by reducing total peripheral resistance. In contrast, halothane and enflurane primarily decrease pressure by reducing cardiac output. Isoflurane decreases or does not alter resistance in gut and kidney,[47,¶] heart,[39,47,§,¶] brain,[48,49] skin,[34] and muscle[34,37] (at least one reference for each tissue suggests a decrease). The large decrease in resistance to blood flow through muscle more than compensates for the associated decrease in perfusion pressure; muscle blood flow may increase two- to three-fold in unstimulated volunteers. This increase may account in part for the capacity of isoflurane to enhance the action of muscle relaxants, particularly succinylcholine (see below).

The tendency of isoflurane to decrease resistance may be used to diagnose hypovolemia. In the hypovolemic patient, vasoconstriction often can sustain systemic blood pressure at normal levels. Isoflurane anesthesia may reveal hypovolemia by producing vasodilation and a greater hypotension than expected for a given depth of anesthesia.

As noted above, substitution of nitrous oxide for an equal MAC fraction of isoflurane increases systemic blood pressure (and left-ventricular work). Since this substitution does not affect cardiac output, nitrous oxide must increase total peripheral resistance. Indeed, these are the only changes induced by nitrous oxide; in normocapnic volunteers, myocardial function, heart rate, and stroke volume are unaffected.[45]

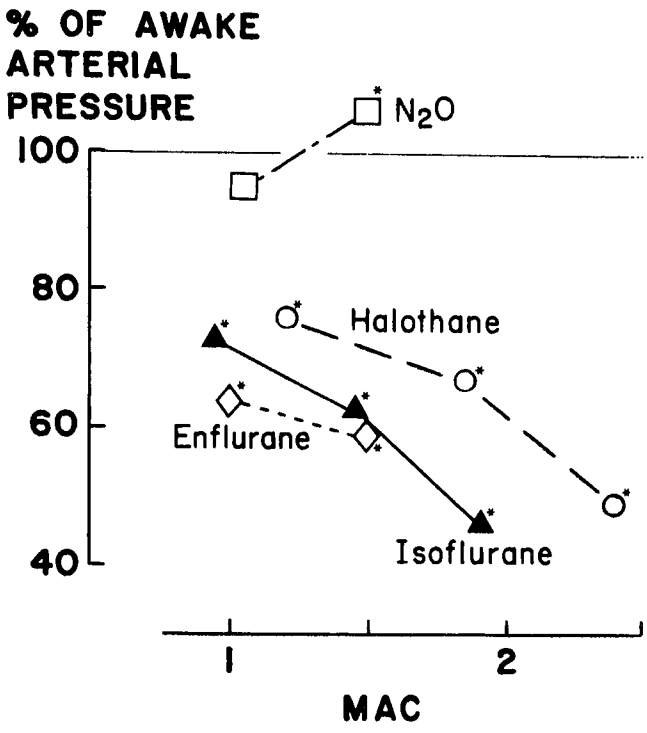


FIG. 9. In normocapnic volunteers, isoflurane, enflurane, and halothane decrease mean arterial blood pressure in a dose-related fashion.[34-36] Nitrous oxide does not decrease pressure and, in fact, causes a slight increase at 1.5 MAC.‡ Asterisks indicate a significant difference from awake values. (Reproduced with permission from Eger.[4])

Isoflurane anesthesia does not affect heart rhythm.[4,20,21,50,51] The incidence of atrial, nodal, or ventricular arrhythmias is not increased over preoperative values by isoflurane. In contrast, halothane increases the incidence of ventricular arrhythmias four-fold (Isoflurane New Drug Application, p. 512).

During isoflurane anesthesia, submucosal injection of epinephrine increases pulse rate and blood pressure but rarely causes ventricular extrasystoles.[52] The dose of epinephrine which produces ventricular extrasystoles in 50 per cent of patients anesthetized with 1.25 MAC isoflurane (*i.e.*, the ED_{50}) is 6.7 μg/kg (fig. 10). In a 70-kg patient, this equals 470 μg or 47 ml of a 1:100,000 solution. A much smaller dose of epinephrine (2.1 μg/kg) produces ventricular extrasystoles in 50 per cent of patients given 1.25 MAC halothane. Although the ED_{50} for 1.25 MAC enflurane is larger than the ED_{50} for isoflurane, the dose-response relationship for enflurane is flatter than that for isoflurane (fig. 10). Thus, for some patients anesthetized with enflurane, the dose of epi-

§ Merin RG: Myocardial metabolic effects of isoflurane. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1976, pp 573–574.

¶ Wang H, Kao CK: The effects of enflurane and isoflurane on hemodynamics and regional blood flow in the dog. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1976, pp 581–582.

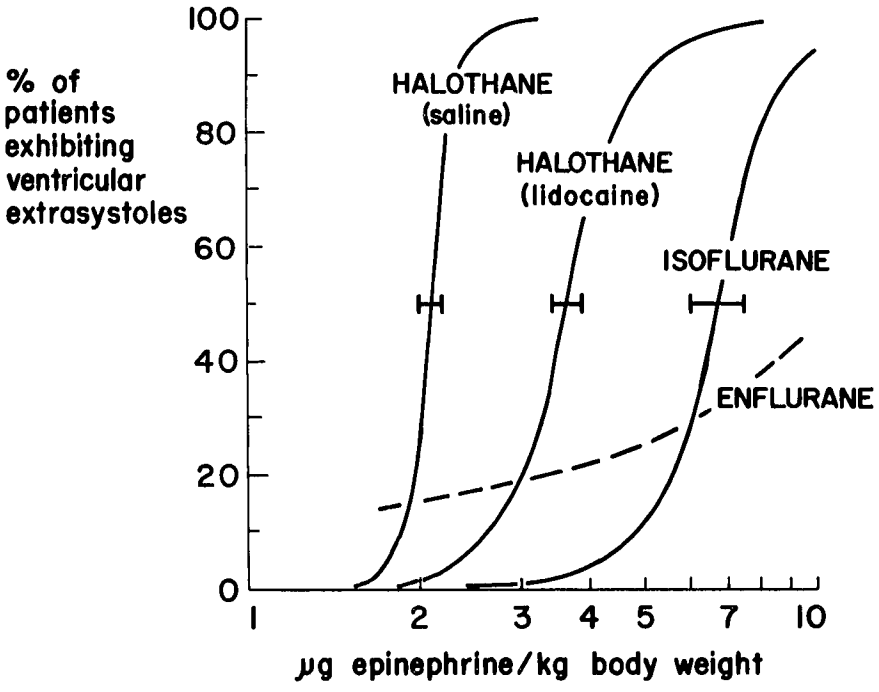


FIG. 10. Patients were given 1.25 MAC enflurane, halothane, or isoflurane in oxygen. The electrocardiogram was monitored while epinephrine was injected submucosally for hemostatic purposes. The total dose of injected epinephrine and the development of ventricular extrasystoles (defined as three or more premature ventricular contractions) were noted. These data are used to obtain the graphs and the dose of epinephrine producing ventricular extrasystoles in 50 per cent of patients (the ED_{50}). For halothane, the ED_{50} was 2.1 μg/kg when the medium for epinephrine injection was saline, and rose to 3.7 μg/kg when the medium was 0.5 per cent lidocaine. For isoflurane, the ED_{50} was 6.7 μg/kg (epinephrine in saline). The curve for enflurane is flatter than that for halothane or isoflurane: a few patients given enflurane developed extrasystoles at relatively low doses of epinephrine. (Reproduced with permission from Johnston *et al.*[52])

nephrine producing extrasystoles is lower than with isoflurane anesthesia.[52,53] Data from animal studies also suggest that isoflurane does not increase epinephrine-induced arrhythmogenicity.[54,55] For all anesthetics, stability of rhythm is more likely if lidocaine accompanies the injection of epinephrine.[52,53]

Rhythm stability probably is maintained during isoflurane anesthesia because isoflurane does not slow conduction through His-Purkinje fibers.[56] In contrast, halothane does slow conduction and thereby may permit reentry of impulses.[57]

As indicated, there does not appear to be an adverse cardiovascular interaction between isoflurane and epinephrine. Other interactions similarly appear to be innocuous or, relative to other anesthetics, may favor isoflurane. Animal studies suggest that vasopressors are less likely to produce arrhythmias during isoflurane as opposed to halothane anesthesia.[55] Isoflurane decreases arrhythmic activity induced by ouabain.[58] In dogs, beta-sympathetic blockade with propranolol does not adversely affect the cardiovascular effect of 2 MAC isoflurane,[59] but may produce untoward depression with 2 MAC enflurane[60] or halothane.[59]

Several studies suggest that isoflurane has little or no effect on pulmonary hemodynamics. Older (average age 63 years) healthy normocapnic patients were given a basal anesthetic of nitrous oxide and etomidate. The addition of 0.75 or 1.5 per cent isoflurane did not change pulmonary arterial blood pressure, wedge pressure, or vascular resistance.[37] Similarly, isoflurane did not affect or only slightly decreased pulmonary arterial blood pressure in animals;[39,61,62] pulmonary vascular resistance did not change[62] or slightly increased,[61] and wedge pressure did not change.[59,63]

One circulatory effect of isoflurane remains controversial. Mathers *et al.*[64] and Benumof and Wahrenbrock[65] reported that isoflurane and/or nitrous oxide inhibit the pulmonary vasoconstrictive response to hypoxia in dogs, while halothane and enflurane do not. In contrast, other investigators have found that halothane in humans,[66] dogs,[67,68] and cats,[67,68] and enflurane in rats[69] inhibit this response. It may be that all inhaled anesthetics diminish the response. The relative capacity of isoflurane to impair this reflex remains to be determined. Regardless, it appears that isoflurane in normal patients or volunteers does not compromise oxygenation of arterial blood. Although the effect in patients with respiratory disease has not been studied systematically, such patients have been anesthetized with isoflurane without incident.

In summary, isoflurane possesses both favorable and unfavorable cardiovascular effects. It sustains myocardial contractility and does not sensitize the heart to the arrhythmogenic effects of epinephrine or other vasopressors. Central venous pressure is unchanged or minimally increased. The cardiovascular margin of safety is greater than that found with other potent inhaled anesthetics. Safety does not appear to be impaired by beta-sympathetic blockade. Isoflurane lowers blood pressure by decreasing resistance to blood flow in nearly all tissues. The decrease in resistance is particularly large in muscle. Heart rate is increased. Left-ventricular work and myo-

cardial oxygen consumption are decreased. Although isoflurane does not appreciably affect pulmonary arterial blood pressure, wedge pressure, or resistance to blood flow, the pulmonary vasoconstrictive response to hypoxia may be depressed.

These circulatory effects suggest that isoflurane may be useful in patients with limited cardiovascular reserve. The sustained contractility without an increase in right atrial pressure and the decrease in afterload may benefit the patient with coronary artery disease who requires surgery. On the other hand, in such a patient the increase in pulse rate may increase myocardial oxygen consumption and induce ischemia. As with other potent inhaled agents, isoflurane anesthesia may be given with nearly 100 per cent oxygen. Although 100 per cent oxygen can also be administered with high-dose narcotic anesthesia, this approach lacks the flexibility available with potent inhaled agents. The increase in muscle blood flow associated with isoflurane may hasten the overall rewarming process following cardiopulmonary bypass. The effect on total peripheral resistance may augment the effect of vasodilators such as sodium nitroprusside and thereby may decrease their potential for adverse side effects (*e.g.*, cyanide toxicity). On the other hand, the decrease in resistance may be hazardous in patients with aortic or mitral stenosis in which outflow resistance of the stenotic valve fixes cardiac output.

Effects on the Brain

Isoflurane causes a dose-related depression of the central nervous system. A particularly substantial change occurs between 0.25 and 0.5 MAC; 0.25 MAC produces amnesia.[70] In dogs, cerebral oxygen consumption decreases sharply at about 0.4 MAC.[71] At this concentration, the electroencephalogram voltage amplitude from the posterior portion of the brain becomes less than the amplitude from the anterior portion.[72,73] This shift to anterior dominance might reflect the passage from consciousness to unconsciousness.[72,73]

As the alveolar isoflurane concentration increases towards 1 MAC, electroencephalographic frequency and voltage also increase (fig. 11).[17,20,21,74] At concentrations above MAC, voltage continues to increase but frequency decreases. At deeper levels of anesthesia, voltage and frequency decrease. Burst suppression occurs at 1.5 MAC, and an isoelectric pattern appears at 2 MAC.[17,20]

Unlike its isomer enflurane,[16] isoflurane does not produce convulsive activity. Higher anesthetic concentrations, hypocapnia, or auditory stimulation do not induce

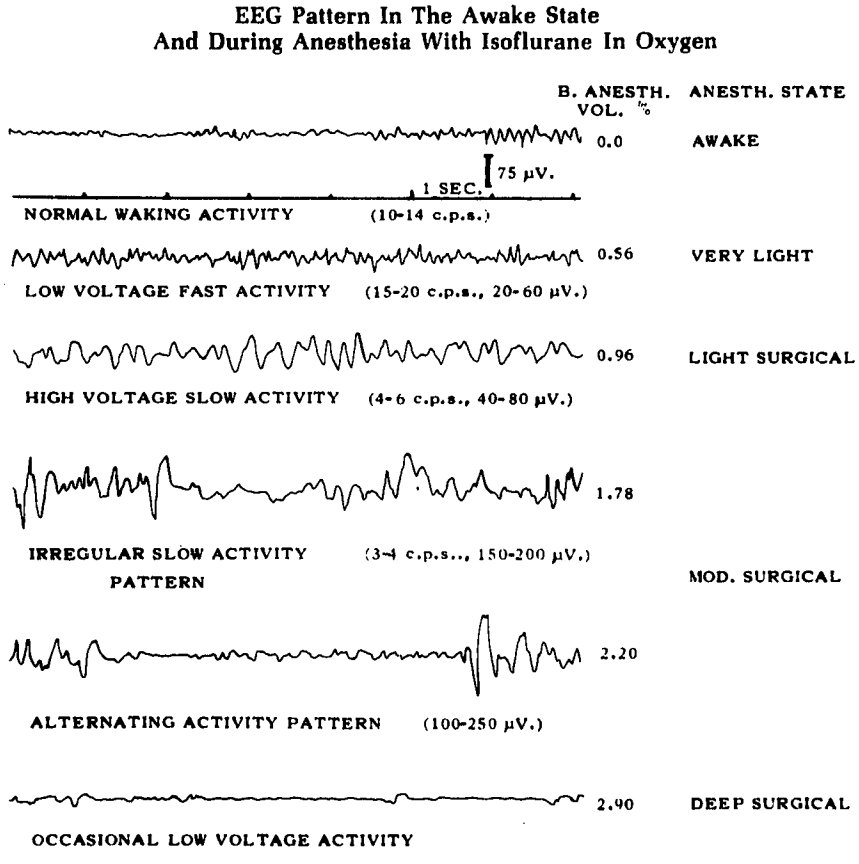


FIG. 11. Isoflurane in oxygen produces a consistent sequence of electroencephalographic changes as anesthesia deepens. Concentrations below MAC increase voltage and frequency. Above MAC, voltage may increase further while frequency decreases. At deeper levels of anesthesia (blood concentrations of 2.20 volumes per cent), burst suppression ("alternating activity pattern") occurs and proceeds to an isoelectric pattern at 2.90 volumes per cent. Blood levels may be converted to MAC equivalents by multiplying by 0.6; thus, the 0.69 and 1.78 blood values ("B. anesth. vol. %") bracket MAC. (Reproduced with permission from Homi *et al.*[20])

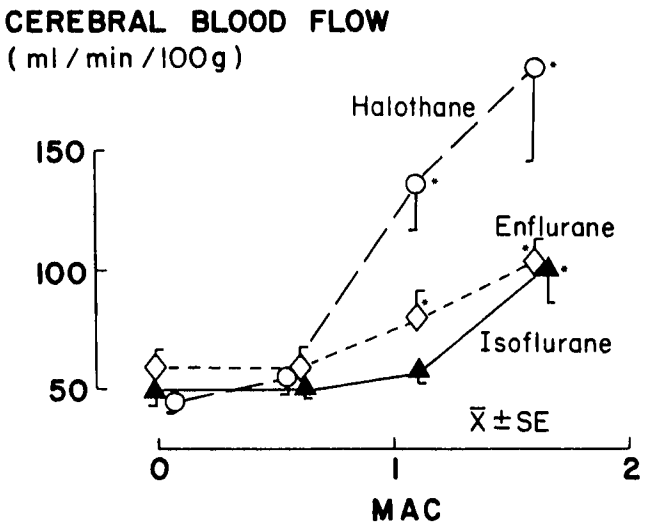


FIG. 12. Cerebral blood flow was measured in awake volunteers. Anesthesia then was induced with various anesthetics plus nitrous oxide. After induction, the volunteers were paralyzed, nitrous oxide was eliminated and ventilation controlled to maintain normocapnia. A normal systemic blood pressure was sustained by infusion of phenylephrine. Cerebral blood flow was unaltered at 0.6 MAC. At 1.1 MAC, no change occurred with isoflurane; however, an increase was seen with enflurane and, to a greater extent, with halothane. At 1.6 MAC, all anesthetics increased flow: enflurane and isoflurane doubled flow, while halothane tripled it.** Asterisks in figure indicate significant differences from control values. (Reproduced with permission from Eger.[4])

seizures during isoflurane anesthesia.[17,21,74,75] Enflurane may provoke seizure activity by exaggerating sensory-evoked responses.[72] Isoflurane markedly depresses such responses.[72,74]

No persistent decrements in intellectual function were found in volunteers subjected to prolonged isoflurane or halothane anesthesia.[23] Small decrements were seen two but not four days after anesthesia. A similar study comparing halothane and enflurane failed to reveal any decrement in function.[76] However, in both studies, volunteers given halothane had more untoward (but transient) symptoms (nausea, confusion) than volunteers anesthetized with isoflurane or enflurane.

Although isoflurane does not increase cerebral blood flow in normocapnic, normotensive volunteers at 0.6 to 1.1 MAC, it doubles flow at 1.6 MAC (fig. 12).** In contrast, enflurane and halothane increase flow at 1.1 MAC. At 1.6 MAC, halothane may triple flow. The more limited increase in flow at a given MAC of isoflurane *vs.* halothane may be a consequence of the smaller increase in vascular cyclic AMP relative to ATP with isoflurane.[77] Both agents decrease cerebral metabolism,[78] and this should tend to decrease cerebral blood flow by increasing brain P_{O_2} and decreasing brain P_{CO_2}.

The smaller change in cerebral blood flow produced by isoflurane implies a smaller change in intracranial pressure. A lesser increase (or no increase) would be important in patients with preexisting elevations of intracranial pressure (*e.g.*, secondary to a tumor or vascular lesion). Animal and human evidence indicate a more benign effect of isoflurane. In normocapnic dogs, isoflurane increases intracranial pressure by 25 per cent, while similar levels of enflurane or halothane produce 100 per cent increases.†† In patients, the increase in intracranial pressure that may occur with anesthesia is reversed more readily by hypocapnia when isoflurane rather than halothane is used.[79]

However, enflurane, halothane, and isoflurane do not prevent the cerebral edema or increase in intracranial pressure that follows a traumatic injury to the brain.[80]

The preceding survey suggests that isoflurane may be of value in patients requiring intracranial surgery. Hypocapnia may prevent or abolish any increase in intracranial pressure. This is accomplished less easily with halothane or enflurane (with the latter agent, hypocapnia may induce convulsive activity at deeper levels of anesthesia). Blood pressure may be readily controlled without decreasing myocardial function or total body perfusion. Like other potent inhaled agents, isoflurane can be given with close to 100 per cent oxygen. The more rapid elimination of isoflurane makes possible an earlier postoperative evaluation of neurological function: wakefulness should return in 5 to 30 min, the length of recovery depending in part on the duration and level of anesthesia. Finally, the results of volunteer studies suggest that isoflurane may produce less nausea than halothane, an effect that might be of particular benefit in a patient following intracranial surgery.

NEUROMUSCULAR EFFECTS

Like other modern inhaled anesthetics, isoflurane can produce adequate relaxation for any surgical procedure.[20,21,50,51] Depression of neuromuscular transmission and/or contractility is evidenced by a decreased ability to sustain a tetanic response to ulnar nerve stimulation, especially at higher frequencies of stimulation.[81] Increasing the alveolar concentration of isoflurane further decreases the capacity to sustain a response to tetanic stimulation. At a given MAC level, the depression of the tetanic response is greater with isoflurane than with halothane.[81]

** Murphy FL Jr, Kennell EM, Johnstone RE, et al: The effects of enflurane, isoflurane, and halothane on cerebral blood flow and metabolism in man. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1974, pp 61–62.

†† Schettini A, Mahig J: Comparative intracranial dynamic responses in dogs to three halogenated anesthetics. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1973, pp 123–124.

As indicated, isoflurane can produce adequate muscle relaxation for any operative procedure. However, the concentration needed may be higher than desirable. To achieve adequate relaxation without imposition of higher anesthetic concentrations may require the use of muscle relaxants. Like other potent inhaled anesthetics, isoflurane enhances the action of nondepolarizing muscle relaxants.[20,21,51,82,83] This enhancement is identical to that produced by enflurane (fig. 13). Both enflurane and isoflurane are two to three times more effective than halothane, which, in turn, is almost twice as effective as nitrous oxide (a "balanced" approach).[34]

Increasing the concentration of isoflurane decreases the requirement for muscle relaxant (fig. 14).[83] The effect of higher concentrations is considerable. In the normal patient given 2 MAC isoflurane, 1.6 mg/m^2 (*i.e.*, about 3 mg) of *d*-tubocurarine decreases twitch height by 50 per cent (fig. 14), and 3 mg/m^2 may produce a depression of 90 per cent or greater. Similar results have been obtained with pancuronium.[83] An increase in anesthetic concentration increases the potentiation produced by both isoflurane and halothane, but at any given MAC level, the potentiation is appreciably greater with isoflurane.

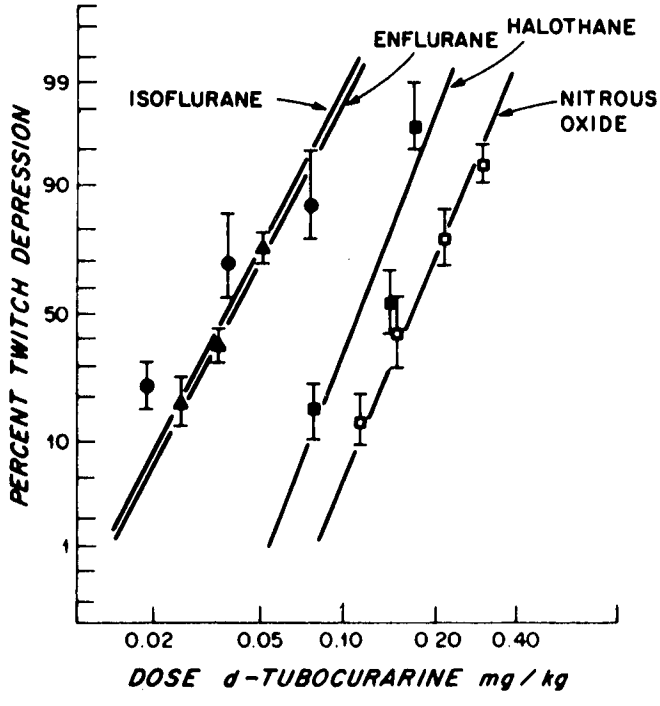


FIG. 13. Anesthesia was produced in normal normocapnic patients with a balanced technique ("nitrous oxide 'curve' ") or with 1.25 MAC enflurane, halothane, or isoflurane. Following establishment of anesthesia, various doses of *d*-tubocurarine were given, and the maximum depression of thenar twitch height (ulnar nerve stimulation) was observed. Halothane potentiated the effect of *d*-tubocurarine more than the balanced technique with nitrous oxide (*i.e.*, the graph for halothane is shifted to the left). Isoflurane and enflurane, in turn, produced a greater potentiation (by a factor of 2 or 3) than did halothane. (Reproduced with permission from Ali and Savarese.[84])

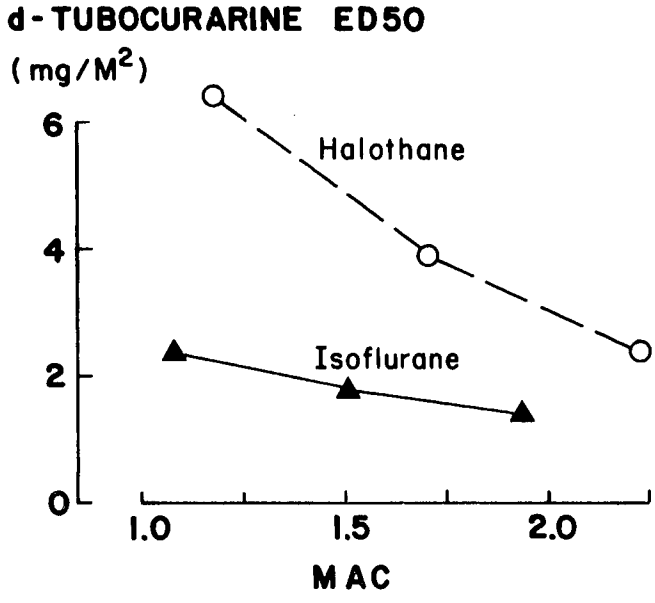


FIG. 14. Patients were anesthetized with a constant alveolar concentration of isoflurane or halothane.[83] Various doses of *d*-tubocurarine (one dose per patient) then were given, and the maximum depression of the thenar twitch response to ulnar nerve stimulation was observed. The resulting dose-response curves were used to determine the dose of *d*-tubocurarine required to depress the twitch by 50 per cent (the ED_{50}). An increase in either halothane or isoflurane decreased the ED_{50}. However, at any given level, the ED_{50} was two to three times higher with halothane. (Reproduced with permission from Eger.[4])

In vivo, isoflurane enhances the action of succinylcholine more than does enflurane or halothane,[82,85] perhaps as a result of the augmentation of muscle blood flow produced by isoflurane. A more rapid delivery of succinylcholine to the myoneural junction would decrease the time available for plasma pseudocholinesterase to degrade the succinylcholine.

The enhancement of relaxant effect by isoflurane may be of value for several reasons. The decreased requirement for relaxants may reduce the incidence or degree of cardiovascular side effects (*e.g.*, histamine release and hypotension with *d*-tubocurarine). The need for relaxant antagonists, which can have adverse cardiovascular effects, may also decrease.[86,87] Most important, the elimination of isoflurane following anesthesia should reduce much of the relaxant effect,[88,89] which in turn decreases the danger of residual postoperative paralysis and inadequate ventilation.

The relaxation and potentiation of effect of muscle relaxants provided by isoflurane may be of particular value in patients with a limited neuromuscular reserve (*e.g.*, those with myasthenia gravis or simply debilitation), or in those with impairment of the systems that eliminate (kidney) or metabolize (liver) relaxants. In

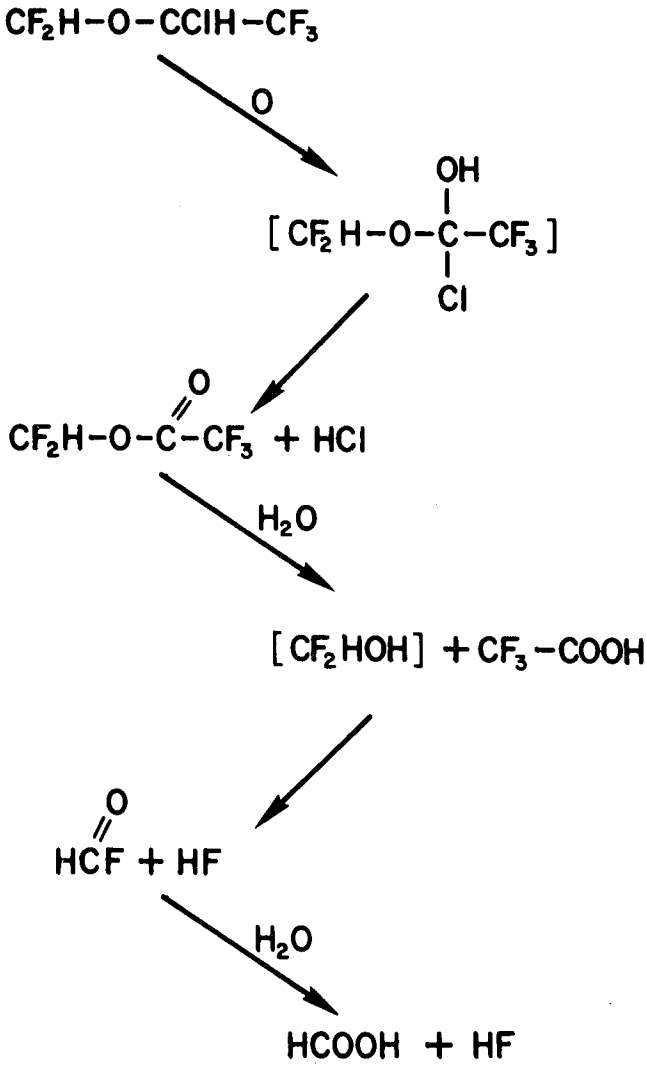


FIG. 15. This probable oxidative pathway of isoflurane metabolism was suggested by RA Van Dyke and RC Terrell (personal communication). The general scheme was predicted (particularly the preferential oxidative attack on the ethyl alpha carbon-hydrogen bond) by G. Loew.[105] (Reproduced with permission from Eger.[4])

these patients, the danger of residual postoperative paralysis is particularly great. The reduced dose of relaxant required in the presence of isoflurane and the rapid postanesthetic elimination of isoflurane should diminish this danger.

Stability, Metabolism, and Toxicity

Isoflurane and enflurane do not oxidize spontaneously and are not broken down by sunlight (ultraviolet light) or soda lime (table 1). In contrast, halothane and methoxyflurane spontaneously oxidize and are broken down by ultraviolet light and soda lime. The addition of a preservative prevents spontaneous oxidation with halothane (thymol) and methoxyflurane (butylated hydroxytoluene). Vaporization of the anesthetic concentrates the preservative, and the residual preservative may "gum up" the moving parts of tec-type vaporizers (*e.g.*, the turnstiles). Breakdown of halothane by ultraviolet light[90] or soda lime[91,92] may form very small amounts of toxic products. This breakdown may make the use of low-flow or closed systems less desirable, since such systems increase the rebreathing of breakdown products.[92] This limitation does not apply to isoflurane or enflurane. Thus, the physical stability of isoflurane appears to be a significant asset.

The physical stability of isoflurane is reflected in its resistance to biodegradation (table 1). The earliest studies of isoflurane metabolism failed to reveal significant biodegradation.[93-95] Subsequent studies using more sensitive techniques did show that isoflurane was broken down.[96-100] However, less than 0.2 per cent of the isoflurane taken up could be recovered as urinary metabolites.[100] This estimate of metabolism is one-tenth that for enflurane[101] and one-hundredth that for halothane[102] or methoxyflurane.[103]

Inorganic fluoride and trifluoroacetic acid have been identified as end products of isoflurane metabolism.[104] These products probably are produced by a sequence which begins with insertion of an active oxygen atom into the bond connecting hydrogen to the ethyl alpha carbon (fig. 15).[105] Both direct and indirect evidence suggest that this is the primary site of oxidative metabolism: the hydrogen bond to the methyl carbon is exceedingly resistant to attack;[106] and if chlorine replaces the hydrogen connected to the ethyl alpha carbon, no measurable metabolism occurs.[107] The sequence that follows the initial oxidation at the ethyl alpha carbon is predicted but has not been verified except for the end products of fluoride ion and trifluoroacetic acid.

The importance of anesthetic metabolism lies in the association between metabolism and liver and kidney toxicity.[108] The near absence of isoflurane metabolism suggests that isoflurane is not nephrotoxic or hepatotoxic. Data from animal and human studies support this predicted lack of toxicity. Mice, rats, or guinea pigs subjected to 35 days of continuous exposure to subanesthetic (up to 0.1 MAC) concentrations of isoflurane, enflurane, nitrous oxide, or diethyl ether do not develop degenerative liver lesions; exposure to 0.01 MAC halothane does produce such lesions.[109,110] Pretreatment of rats with phenobarbital (to induce liver enzymes) and two hours of subsequent 1 MAC isoflurane or enflurane anesthesia with subsequent hypoxia does not produce hepatic necrosis, whereas 1 MAC halothane anesthesia with subsequent hypoxia does produce necrosis.[111] Similarly, in rats pretreated with phenobarbital, an upper abdominal operation (sham procedure) under halothane anesthesia

produces hepatic necrosis,[112] while the same operation under isoflurane (or enflurane) anesthesia does not.[112]

Prolonged and/or repeated isoflurane anesthesia does not produce hepatorenal injury in animals.[113-115] Isoflurane plus hypoxia and hypercapnia does not cause hepatic necrosis, while similar treatment with chloroform does produce necrosis.[4] The production of reactive metabolites from chloroform metabolism decreases liver glutathione. No measurable glutathione depletion occurs in mice given isoflurane.[116] Finally, administration of 80 per cent nitrous oxide for 30 min results in a 67 per cent inactivation of liver methionine synthetase in mice; no inactivation results from four hours of isoflurane, enflurane, halothane, or xenon anesthesia at similar MAC levels.[117]

The above studies indicate that some anesthetics can produce injury when given in the presence of various severe stresses but that isoflurane does not. Further support for the absence of a hepatotoxic effect of isoflurane comes from studies in volunteers given 9 MAC-hours of isoflurane.[118] Bromsulphalein (BSP) retention usually is unaltered (fig. 16), and serum liver enzymes do not increase. In contrast, BSP retention increases one and sometimes seven days after anesthesia in volunteers given 12 MAC-hours of halothane.[118] Volunteers given 10 MAC-hours of enflurane show an increase in SGOT and LDH one but not five days after anesthesia.[119] In patients, BSP retention increases two days following isoflurane anesthesia; however, this increase is slight, and is less than that found with halothane anesthesia.[4] Postoperative increases in enzyme and bilirubin levels after isoflurane anesthesia are not different from those following nitrous oxide-narcotic anesthesia, and are similar to, or less than, those occurring after halothane anesthesia.[4,51] The Isoflurane New Drug Application (p 86) reported that increasing the duration of isoflurane anesthesia in patients did not increase postoperative serum liver enzymes. If preoperative levels were elevated, they tended to decrease after either isoflurane or halothane anesthesia. Repeated anesthesia with isoflurane in 58 patients was not associated with subsequent liver injury.

Although serum inorganic fluoride increases after isoflurane anesthesia, this increase (2–4 μM/l) is one-tenth that occurring after enflurane and is far too small to influence renal function.[98,120] Enzyme induction with phenobarbital,[99,121,122] phenytoin,[122] or isoniazid[123] increases *in vitro* but not *in vivo*[99] metabolism of isoflurane. Enzyme induction may increase *in vitro* inorganic fluoride production four-fold; however, even if this increase were reflected *in vivo*, serum fluoride levels would not approach threshold levels for nephrotoxicity.[124]

Isoflurane,[99] enflurane,[120] halothane,[99,125] and nitrous oxide plus intravenous agents[126] depress renal blood flow, glomerular filtration rate, and urinary flow *during* anesthesia. However, as would be predicted from the limited increase in serum inorganic fluoride, isoflurane is not associated with postanesthetic renal injury. Prolonged or repeated or chronic (days) subanesthetic exposures to isoflurane do not produce demonstrable renal injury or dysfunction in animals.[96,109,115] Volunteers given prolonged and profound isoflurane anesthesia do not have increases in BUN or creatinine.[118] Patients given isoflurane do not demonstrate postoperative renal impairment. Electrolytes remain normal and BUN decreases, perhaps because of diminished protein intake. Creatinine is unchanged and creatinine clearance may even increase after isoflurane (or halothane) anesthesia.[4] Three to four MAC-hours of isoflurane, enflurane, or halothane anesthesia do not impair the postoperative capacity of the kidney to concentrate urine: in all cases the postoperative response to the subcutaneous injection of vasopressin (vasopressin challenge test) remains normal.[98,120]

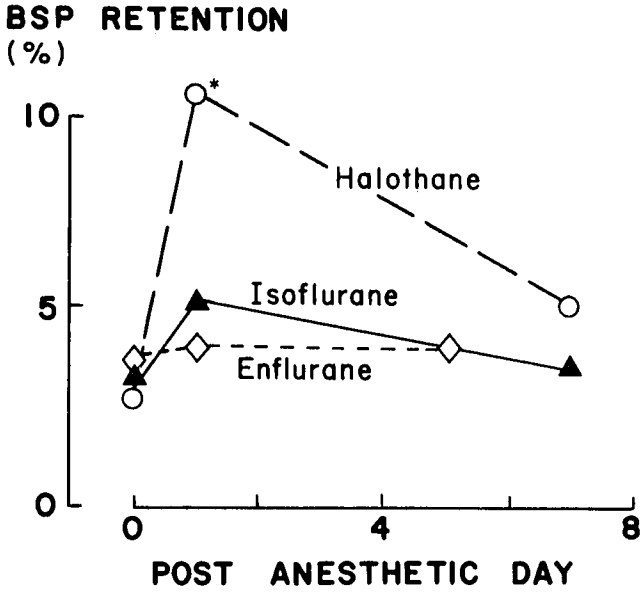


FIG. 16. Bromsulphalein retention increased to abnormal levels one day after 11.7 MAC-hours of halothane in volunteers (asterisk indicates significant difference from control values).[118] No such change was seen after 8.8 MAC-hours of isoflurane[118] or 9.6 MAC-hours of enflurane.[119] (Reproduced with permission from Eger.[4])

Studies of Mutagenicity, Teratogenicity, and Carcinogenicity

As indicated, the introduction of isoflurane was delayed by the suggestion that isoflurane might produce liver tumors.[2] Reevaluation of the initial study disclosed several reasons why the initial results were not confirmed in a second study that used larger numbers of the same strain of mice and a wider range of isoflurane concentrations.[3] The initial study was flawed by 1) contamination of animals with a potential carcinogen (poly-

brominated biphenyls); 2) use of non-peer control animals; 3) failure to treat control animals and experimental animals identically (*i.e.*, control animals were not put in the exposure chambers and were not exposed to 100 per cent oxygen); and 4) failure to use a "blind" approach when examining gross or microscopic specimens. These flaws were eliminated in the second study.

Additional tests indicate that isoflurane is not a carcinogen. Several studies suggest that isoflurane is not a mutagen. The most widely accepted test of mutagenicity, which was devised by Dr. Bruce Ames, measures the capacity of a putative mutagen-carcinogen to cause a mutation in the bacteria Salmonella typhimurium. The Ames test also examines the mutagenicity of metabolites of the putative carcinogen by including induced liver microsomes in the test mixture.[127] The Ames test indicates mutagenicity for 90 per cent of chemicals known to be carcinogens and gives "false positive" results for roughly 10 per cent of chemicals that are not carcinogenic.[128] The dose required to produce mutagenicity is proportional to that required to induce cancer in animals.[129] The Ames test indicates that isoflurane, enflurane, methoxyflurane, and nitrous oxide are not mutagens.[130,131] Although halothane gives a negative result, supposed metabolites of halothane give a positive result.[132,133] Vinyl-containing anesthetics such as fluroxene give positive results.[130] Exchanges between sister chromatids (the sister chromatid exchange test) in ovary cells of Chinese hamsters increase following exposure to a mutagen-carcinogen. The sister chromatid exchange test also indicates that vinyl-containing anesthetics are mutagens.[134] Negative results are obtained with isoflurane, enflurane, halothane, methoxyflurane, and nitrous oxide.[134]

Mice exposed to 1 MAC enflurane, chloroform, or trichloroethylene display a small but significant increase in sperm abnormalities.[135] In contrast, no effect on sperm is seen after exposure to isoflurane. Unpublished data by Coate (report to Ohio Medical Products, July 13, 1979) reveal no dominant lethal effect of isoflurane. Coate exposed male Sprague-Dawley rats to 0.15 or 0.6 per cent isoflurane for two hours a day for 14 days. These animals were mated with untreated female rats at weekly intervals over the ensuing nine weeks; no consistent differences from control matings with unexposed males were found in the number of dead implants or implantation efficiency. Similarly, female rats given 0.15 or 0.6 per cent isoflurane for two hours a day for 14 days were then mated with unexposed males. Although rats given 0.6 per cent isoflurane did not gain as much weight as unexposed animals, pregnancy rates, reproductive indices, pup weights, implantation efficiencies, incidence of dead implants, and number of days to insemination were not affected by the exposure to isoflurane.

Coate also studied the teratogenicity of isoflurane in CD-1 mice and Sprague-Dawley rats. The mice received 0.075 or 0.3 per cent isoflurane and the rats received 0.1 or 0.4 per cent for two hours a day on days 6 through 15 of gestation. The incidence of visceral or skeletal abnormalities did not differ from that found in untreated controls. Whether higher concentrations given for longer periods on selected days of gestation might prove teratogenic remains to be determined, but these initial findings do not indicate that isoflurane is a significant teratogen. If subsequent studies confirm these results, isoflurane would differ from nitrous oxide[136,137] and from halothane,[138] which are teratogens. If a difference exists, it may result from 1) the effect of nitrous oxide to impair DNA synthesis by inactivating methionine synthetase,[117] and/or 2) the biodegradation of halothane to reactive metabolites. Isoflurane does not inactivate methionine synthetase,[117] and the minute metabolism of isoflurane would suggest the absence of significant production of reactive metabolites.

In summary, isoflurane appears not to be a mutagen, teratogen, or carcinogen.

Miscellaneous

No case of malignant hyperthermia during or after isoflurane anesthesia has been reported. However, the clinical experience with isoflurane is far too small to suggest that this could not happen. Isoflurane can produce malignant hyperthermia in Poland China swine.‡‡ Isoflurane augments caffeine-induced contracture of muscle from frogs[139] and from patients thought to be susceptible to malignant hyperpyrexia.[140] These results also suggest that isoflurane and enflurane have roughly the same capacity, which is less than that of halothane, to produce malignant hyperpyrexia.

Isoflurane anesthesia decreases or does not change intraocular pressure in children.[141] The effect in adults and the effect of deeper levels of anesthesia have not been studied.

Isoflurane, enflurane, and halothane relax uterine muscle in a dose-related fashion.[142] Because it increases bleeding, isoflurane anesthesia is not recommended for therapeutic suction abortion.[143] Isoflurane has not been studied sufficiently to establish its safety for delivery. Preliminary results of administering 0.3 to 0.7 per cent isoflurane to women in the second stage of labor suggest that this range of concentrations produces analgesia equivalent to that achieved with 40 per cent nitrous ox-

‡‡ Murphy FL Jr, Nelson TE, Strobel GE, et al: A comparison of halothane, isoflurane, enflurane, and fluroxene in triggering malignant hyperthermia in susceptible swine. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1973, pp 181–182.

ide.§§ However, analgesia develops faster with nitrous oxide. Isoflurane 0.3–0.7 per cent and 40 per cent nitrous oxide do not differ in their effect on blood loss and fetal well-being (as determined by Apgar scores, fetal blood gases). As opposed to the innocuousness of these findings for analgesia in humans, results from animal studies indicate that *deep* levels of anesthesia (2 MAC) with either isoflurane or halothane produce unwanted changes in fetal well-being (acidosis, decreased oxygenation).[144]

A Summary and Comparison

Although isoflurane is not the ideal anesthetic, in many ways it is superior to other potent inhaled anesthetics. It is physically stable. Its low blood solubility (which is lower than that of other potent inhaled anesthetics) facilitates control of anesthetic depth and speeds recovery from anesthesia. The usual absence of myocardial depression when isoflurane is administered in the 1–2 MAC range sets it apart from enflurane or halothane, which both cause depression. Similarly, arrhythmias secondary to epinephrine injection are least likely to occur during isoflurane anesthesia. Isoflurane and enflurane potentiate the effect of muscle relaxants and do so more than halothane. This action reduces the likelihood of postoperative relaxant hangover. Neither halothane nor isoflurane has enflurane's capacity to produce seizure activity. Cerebral blood flow and intracranial pressure may be less increased by isoflurane than by halothane or enflurane anesthesia; control of intracranial pressure probably is more readily accomplished during isoflurane anesthesia. Of great significance is the fact that isoflurane biodegradation is one-tenth that of enflurane and one-hundredth that of halothane. Therefore, hepatotoxicity and nephrotoxicity are absent or extremely rare.

Some of the limitations of isoflurane are shared by enflurane and/or halothane. Although all three anesthetics decrease blood pressure, only enflurane and isoflurane increase heart rate in unstimulated humans. Enflurane and isoflurane are mildly pungent while halothane is not. This pungency limits the rate of induction. All three depress ventilation; enflurane is clearly most depressant and halothane probably least depressant. All may produce malignant hyperthermia. All cause uterine relaxation and at anesthetic levels probably increase uterine bleeding at delivery.

Isoflurane has two disadvantages relative to enflurane and halothane. It is more expensive and the clinical experience with it is far less. Thus, some presently unknown noxious effect may be revealed by future use.

We also may compare isoflurane with the nitrous-narcotic (balanced) approach to anesthesia. This approach is often chosen over enflurane or halothane because of the minimal myocardial depression that balanced anesthesia produces, and because organ toxicity is probably nonexistent. These reasons carry less force *vis-à-vis* isoflurane: isoflurane has little myocardial depressant effects over the usual range of anesthesia in normal patients (1–2 MAC), and the near absence of isoflurane biodegradation correlates with the inability to demonstrate hepatotoxicity or nephrotoxicity following isoflurane anesthesia.

Some differences in cardiovascular or other effects may still cause anesthetists to choose the balanced approach to anesthesia. Pulse rate does not increase and blood pressure remains normal or increases. Intracranial pressure is decreased when the balanced approach is used (unless hypercapnia is permitted). Uterine bleeding is not increased during therapeutic suction abortion or delivery, and malignant hyperthermia is unlikely even in patients susceptible to this condition.

Conversely, isoflurane has several advantages over the balanced approach. Although both anesthetic techniques depress respiration, isoflurane does not produce a "stiff chest" or recurrent postoperative depression of breathing. Blood pressure may be controlled and the work of the heart decreased with isoflurane. Awareness is less likely during isoflurane anesthesia. Recovery is rapid and may be less frequently accompanied by nausea or recurrent somnolence. Management of postoperative pain is not made difficult by the need to administer narcotic antagonists. As with other potent inhaled agents, isoflurane itself can produce adequate relaxation; the balanced approach requires the use of muscle relaxants. Isoflurane potentiates the effect of all muscle relaxants to a far greater extent than does the balanced approach. Potent general anesthetics do not cause constriction of gut muscle or the sphincter of Oddi. Finally, the ease of anesthetic management with isoflurane-oxygen anesthesia nearly equals that with isoflurane-nitrous oxide-oxygen anesthesia; conversely, the absence of nitrous oxide may compromise the ease of use and safety of the balanced technique. For these reasons, isoflurane is likely to play a major role in the future delivery of anesthetic care.

§§ Hicks JS, Shnider SM, Cohen H: Isoflurane (Forane) analgesia in obstetrics. Abstracts of Scientific Papers, annual meeting of the American Society of Anesthesiologists, 1975, pp 99–100.

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