The Cardiovascular Effects of a New Inhalation Anesthetic, Forane, in Human Volunteers at Constant Arterial Carbon Dioxide Tension*

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The cardiovascular effects of Forane, a new inhalation anesthetic, were examined in seven unmedicated volunteers under conditions of constant arterial carbon dioxide tension and body temperature. Comparison of results during anesthesia with awake values demonstrated maintenance of myocardial function but progressive vasodilatation as anesthesia deepened. No significant changes in the cardiac output, ballistocardiogram I-J wave amplitude, ejection time, mean rate of ventricular ejection, or pre-ejection period occurred with onset or deepening of anesthesia. Arterial pressure decreased, as did total peripheral resistance. Increased muscle and skin blood flow and forearm venous compliance suggested that the loss of resistance was due in part to dilatation of vessels in the skin and muscles. Cardiac output was maintained by an increased heart rate which compensated for the decreased stroke volume. Comparisons of results during the first and fifth hours of anesthesia demonstrated only minor changes with increased duration of anesthesia. These included further increases in forearm blood flow and an increase in base excess. (Key words: Forane; Circulation; Circulatory effects of anesthesia; Myocardial function.)

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Received from the Department of Anesthesia, University of California, San Francisco, California, and the Department of Anesthesiology (Dr. Shakespeare), Stanford University School of Medicine, Palo Alto, California 94305. Accepted for publication March 10, 1971. Supported in part by USPHS grants 5T1 GM 0063-12 and 1 P01 CM 15561-02 and by Ohio Medical Products, Division of Air Reduction Company, Inc. Presented in part at the annual meeting of the American Society of Anesthesiologists, New York, October 1970.

IN THE LABORATORY we have compared some properties of a new inhalation anesthetic, Forane (Compound 469) (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) with those of halothane. The studies demonstrated several advantages of the new compound: 1) no sensitization of the myocardium to exogenously-administered epinephrine in dogs [1]; 2) no hepatic metabolism in miniature swine [2]; 3) lower blood–gas partition coefficient,[3] leading to more rapid emergence from anesthesia. In most other respects no advantage could be demonstrated for either agent, since both are cardiorespiratory depressants in dogs without hepatic or renal toxicity, stable in the presence of soda lime, and not flammable. The only disadvantage of Forane was a slightly more pungent odor. These studies led us to an evaluation of the cardiovascular, respiratory, toxicologic and neuromuscular properties of Forane in man. This paper reports the cardiovascular effects of Forane at constant arterial carbon dioxide tension (Pa_{CO_2}).

Methods

Informed consent was obtained from seven healthy male volunteers whose average age was 23 ± 1 years (standard error). The procedures for obtaining consent and the study protocol were approved by the Committee on Human Experimentation of the University of California, San Francisco. Physical examination, chest x-ray, complete blood count, and urinalysis disclosed no abnormalities in any subject.

The methods of study have been described.[4] In awake subjects we measured arterial, right atrial, and peripheral venous pressures (strain

TABLE 1. Data from the Awake (Control) Period

	Number of Subjects	Mean ± SE
Age (years)	7	23 ± 1
Height (cm)	7	171 ± 5
Weight (kg)	7	67 ± 3
Cardiac output (l/min)	7	5.2 ± 0.5
Mean right atrial pressure (torr)	7	5.0 ± 0.6
Mean arterial pressure (torr)	7	95 ± 3
Total peripheral resistance (ohms)	7	1,386 ± 117
Heart rate (beats/min)	7	70 ± 5
Stroke volume (ml)	7	78 ± 5
Left ventricular minute work (kg meters/min)	7	6.68 ± 0.62
Left ventricular stroke work (kg meters)	7	0.099 ± 0.006
Ejection time* + 1.6 × heart rate (msec)	6	404 ± 2
Mean rate of ventricular ejection (ml/sec)	6	297 ± 7
Pre-ejection period (msec)		118 ± 4.3
Forearm (muscle) blood flow (ml/100 ml/min)	7	2.5 ± 0.3
Forearm venous compliance (ml/torr)	7	0.079 ± 0.02/100
Finger (skin) blood flow (ml/100 ml/min)	7	17.7 ± 5.4

* Duration of ventricular ejection corrected for heart rate by the formula of Weissler.[12]

gauges) from catheters placed with the subject under local anesthesia. These catheters also enabled us to measure arterial and right atrial blood gases (P_{O_2}, P_{CO_2}, and *p*H with electrodes), cardiac output and blood volume (both by the dye-dilution technique, Waters densitometer) and hematocrit (microhematocrit technique). We recorded the electrocardiogram. Finger and forearm blood flows were transduced with Whitney strain gauges. The ballistocardiogram was recorded from an ultra-low-frequency air-bearing ballistocardiogram bed weighing 3 kg. The bed was undamped, with a natural frequency of 0.18 Hz. Acceleration was transduced in the head–foot (y) axis with a variable capacitance accelerometer. We measured cardiac cycle intervals from the electrocardiogram in conjunction with the arterial pressure wave and heart sounds. We measured end-tidal P_{CO_2} (infrared analysis). Skin and oral (awake) or esophageal (anesthetized) temperatures were recorded.

After placement of all sensors, subjects breathed 100 per cent oxygen via a mouthpiece from a circle anesthetic system. A nose clip prevented ventilation via the nose. We controlled breathing in the awake and anesthetized subjects with a Ventimeter/Ventilator to maintain Pa_{CO_2} at or slightly below the resting awake values. All measurements described above were repeated until stable cardiac output readings were obtained. Since initial cardiac outputs in the awake state were greater than those obtained subsequently, we assumed that the two lowest consecutive cardiac outputs were representative of the awake state.

Anesthesia was induced with Forane in oxygen by mask. The trachea was intubated without muscle relaxants and the endotracheal tube cuff was inflated. The alveolar anesthetic concentration was adjusted to 1.2 per cent and maintained for a minimum of ten minutes. This concentration was chosen as representative of a light level of anesthesia, at or below the predicted [5] minimum alveolar concentration (MAC) of Forane. Initial trials demonstrated that the subjects remained anesthetized and tolerated tracheal and esophageal appliances at this concentration. All measurements made with the subject awake were then repeated. The alveolar Forane was increased in turn to

TABLE 2. Results of Measurements during the First (Set 1)

	Time from Induction (Min)	Alveolar Forane (Per Cent)	Cardiac Output	Mean Right Atrial Pressure†	Mean Arterial Pressure	Total Peripheral Resistance	Heart Rate	Stroke Volume
Set 1— first hour of anesthesia	36 ± 3	1.20 ± 0.01	101 ± 6	− 0.03 ± 0.7	73‡ ± 3	76‡ ± 6	120 ± 8	85‡ ± 2.1
	57 ± 4	1.83 ± 0.01	94 ± 5	0.7 ± 0.8	63‡ ± 3	68‡ ± 6	118‡ ± 6	80‡ ± 3
	78 ± 4	2.42 ± 0.02	± 89 ± 7	1.47‡ ± 0.6	46‡ ± 2	49‡ ± 4	120 ± 8	75 ± 4
Set 2— fifth hour of anesthesia	28 4 ± 8	1.21 ± 0.01	101 ± 7	0.01 ± 0.6	71‡ ± 3	73‡ ± 6	119 ± 9‡	87‡ + 5
	303 ± 7	184 ± 0.02	102 ± 9	0.01 ± 0.3	60‡ ± 30	62‡ ± 7	125‡ ± 8	82‡ ± 5
	320 ± 8	2.43 ± 0.03	112 ± 8	0.3 ± 0.5	53‡ ± 5	45‡ ± 4	136‡ ± 5	80‡ ± 5

* The number of subjects was seven except where "n = x."
† All results expressed as per cent of control except mean right atrial pressure, which is torr change from control.

1.8 per cent and 2.4 per cent and measurements were repeated ten minutes after attaining each concentration. Alveolar Forane was reduced to 1.2 or 1.8 per cent and maintained there for three hours. Measurements were made each half hour during this period. The original sequence of 1.2, 1.8, and 2.4 per cent Forane was then repeated.

Forane concentrations were measured by infrared analysis of end-tidal samples. End-tidal samples at the time of cardiovascular measurements were also analyzed for Forane by gas chromatography (flame detector). These methods gave results that agreed within 10 per cent.

Statistical comparisons were made using paired t tests, with each subject serving as his own control. Values were accepted as significant when $P < 0.05$. The data are presented as mean ± standard error.

Results

Table 1 lists control values. Results of measurements made during the first hour and the fifth (final) hour of anesthesia are given in table 2 and figure 1.

With induction of anesthesia, arterial pressure decreased in response to decreased total peripheral resistance without change in cardiac output or right atrial pressure. As the anesthetic concentration increased, cardiac output did not change significantly. However, the range of values was broad. Arterial pressure decreased significantly as anesthetic concentration increased; this was accounted for by the fall in total peripheral resistance. A small but significant increase in right atrial pressure occurred only at 2.4 per cent Forane during the first hour.

The cardiac output was maintained because

and Fifth (Set 2) Hours of Anesthesia*

Left Ventricular Minute Work	Left Ventricular Stroke Work	Ejection Time	Mean Rate of Ventricular Ejection	I-J Wave of Beg Amplitude	Pre-ejection Period	Forearm (Muscle) Blood Flow	Finger (Skin) Blood Flow	Forearm Venous Compliance
74‡ ± 5	65‡ ± 5	95 ± 2 n = 6	101 ± 2 n = 6	92 ± 10 n = 5	95.8 ±8.9 n = 5	199‡ ± 34	752 ± 331 n = 6	154 ± 28
60‡ ± 4	55‡ ± 9	97.8 ± 2.6 n = 5	104 ± 1.2 n = 5	95 ± 18 n = 5	92.2 ± 9.2 n = 6	218‡ ± 45	623 ± 295 n = 6	156 ± 26
44‡ ± 4	46‡ ± 8	99 ± 2 n = 6	103 ± 2 n = 6	83 ± 8 n = 5	96.3 ± 6.7 n = 5	227‡ ± 52	300 ± 113 n = 6	169 ± 33
73‡ ± 5	62‡ ± 4	93.2 ± 0.8 n = 5	99.8 ± 2.4	91 ± 17 n = 5	92.5 ± 25.5 n = 5	304‡ ± 46	304‡ ± 70	119 ± 25
65‡ ± 5	53‡ ± 4	97 ± 2 n = 6	103 ± 2 n = 6	95 ± 21 n = 5	86.1 ± 13.1 n = 6	334‡ ± 69	271 ± 85	130 ± 28
61‡ ± 6	44‡ ± 6	99 ± 1 n = 6	106 ± 3 n = 6	107 ± 21 n = 7	86.4 ± 10.2 n = 6	424‡ ± 94 n = 6	427 ± 149 n = 6	129 ± 21

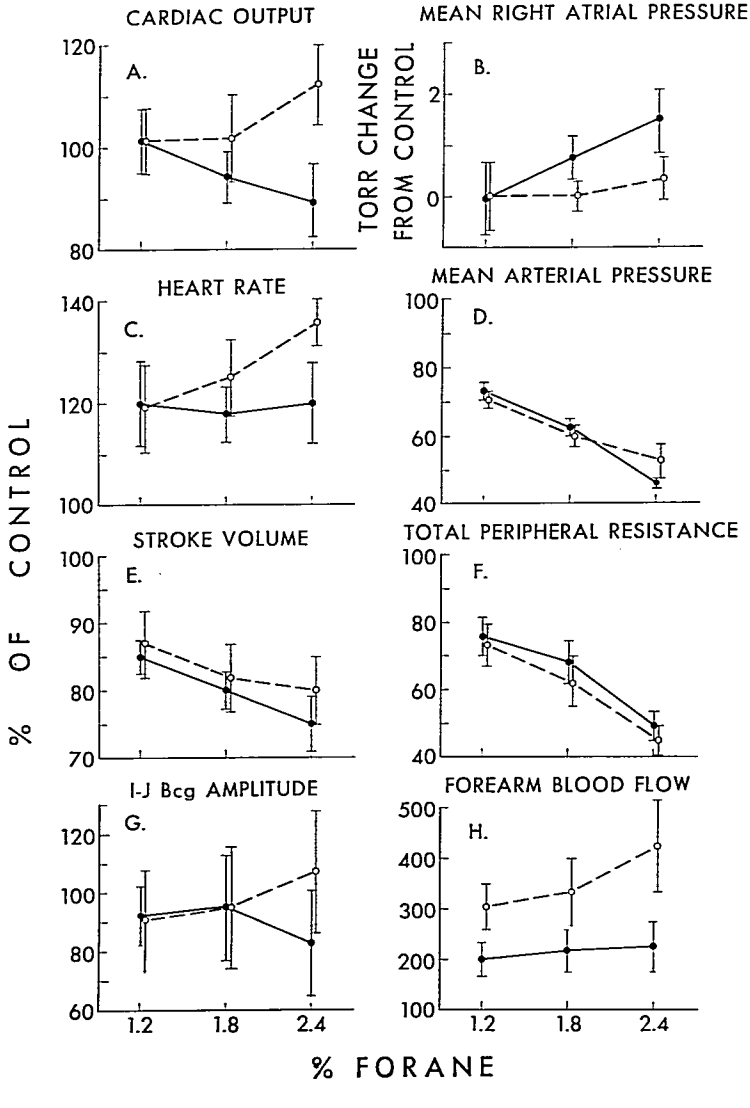
‡ Difference from control significant at 0.05 level.

heart rate increased and compensated for decreased stroke volume. Stroke volume was less than control at each anesthetic level. A further significant decrease in stroke volume occurred at 2.4 per cent Forane in the first hour. Heart rate was significantly above control at 1.8 and 2.4 per cent Forane. Other indices of cardiac effects, the I-J wave amplitude of the ballistocardiogram, mean rate of ventricular ejection, ejection time, and pre-ejection period did not change significantly. Left ventricular minute and stroke work were less than control throughout anesthesia. The decrease of left ventricular minute work was dose-related during the first hour of anesthesia, but during the fifth hour this relationship was not so clear.

Both muscle and skin vasodilatation occurred. The range of values was large. Nevertheless, significant muscle flow increases occurred at 1.2 and 1.8 per cent Forane. Skin blood flow increased but variation in values precluded significance. Skin temperature (table 3) during anesthesia was consistently above control values, as would be expected with increased skin blood flow.

A small but significant decrease of base excess occurred with the onset of anesthesia (table 3). This change was reversed as anesthesia continued. Oxygen consumption decreased during anesthesia but the decrease was significantly less than control only at 2.4 per cent Forane during the first hour and at 1.8 per cent Forane during the fifth hour. The increased cardiac output/oxygen consumption ratio reflected the unchanged cardiac output with decreased oxygen consumption.

Review of the electrocardiograms from all volunteers revealed no arrhythmias during anesthesia in four subjects. In two subjects, single but repeated atrial or ventricular premature contractions occurred with coughing dur-



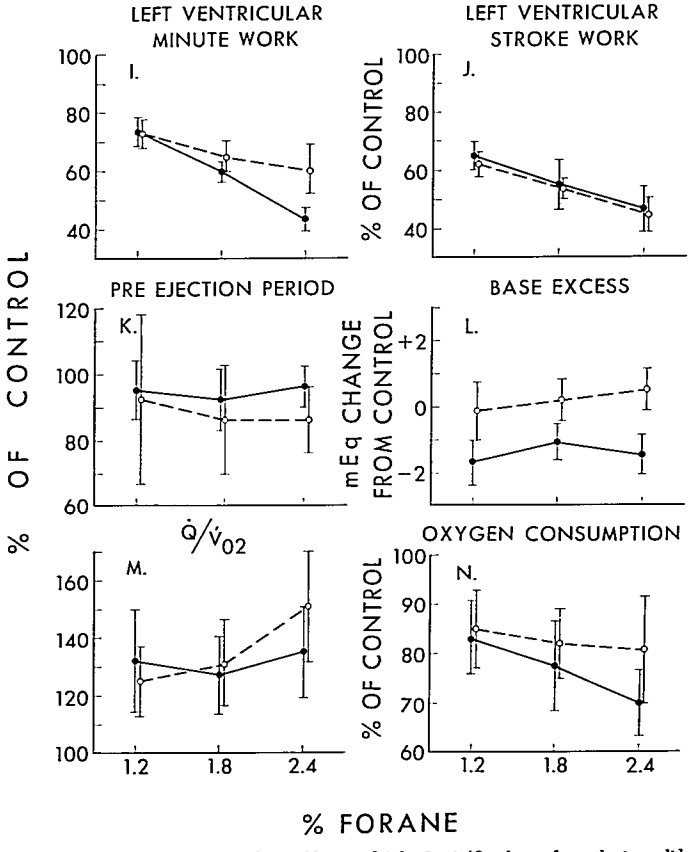


FIG. 1 (left and above). Data from tables 2 and 3 for Set 1 (first hour of anesthesia—solid line) and Set 2 (fifth hour of anesthesia—dashed line). All horizontal axes represent per cent alveolar Forane. All vertical axes represent percentages of control values except those for mean right atrial pressure (torr change from control) and base excess (mEq change from control).

ing endotracheal intubation. In one subject a single premature ventricular contraction was also seen at 2.4 per cent alveolar Forane during the first hour. One volunteer developed junctional rhythm early during induction of anesthesia, but sinus rhythm returned after 25 beats. During the first hour of anesthesia in this subject, single but repeated premature ventricular and atrial contractions occurred at 1.2 and 1.8 per cent Forane but not at 2.4 per

TABLE 3. Temperatures, Blood Gas Values, Oxygen Consumption and Cardiac Output/Oxygen Consumption (Mean ± SE) at times of Measurement of Other Variables*

	Alveolar Forane (Per Cent)	Oral or Esophageal Temperature (C)	Skin Temperature (C)	P_{aO_2} (torr)	P_{aCO_2} (torr)	pH$_a$	Base Excess (mEq/l)†	Oxygen Consumption (ml/min)	Cardiac Output/ Oxygen Consumption Ratio
Control	0	36.8 ± 0.1	31.0 ± 1.5	± 53‡ ± 7	38.0 ± 0.8	7.40 ± 0.01	− 1.11 ±.82	210 ± 16	25.4 ± 0.82
Set 1—first hour of anesthesia	1.20 ± 0.01	36.5 ± 0.11	32.1 ± 1.7	503 ± 25	35.4 ± 1.6	7.39 ± 0.02	− 1.64‡ ± 0.67	171 ± 18	31.9 ± 3.5
	1.83 ± 0.01	36.5 ± 0.09	32.2 ± 1.7	526 ± 18	37.1 ± 1.6	7.39 ± 0.02	− 1.11 ± 0.55	153 ± 18	31.2 ± 3.1
	2.42 ± 0.02	36.4 ± 0.09	33.5 ± 1.2	508 ± 25	36.5 ± 1.4	7.39 ± 0.02	− 1.46 ± 0.62	143‡ ± 13	33.0 ± 3.7
Set 2—fifth hour of anesthesia	1.21 ± 0.01	36.7 ± 0.10	33.9 ± 1.3	552 ± 7	37.7 ± 0.8	7.40 ± 0.01	− 0.11 ± 0.85	182 ± 26	31.3 ± 3.1
	1.84 ± 0.02	36.7 ± 0.10	33.5 ± 1.3	525 ± 26	38.4 ± 1.7	7.40 ± 0.01	0.18 ± 0.64	174‡ ± 24	32.3 ± 3.1
	2.43 ± 0.03	36.7 ± 0.09	33.4 ± 1.5	523 ± 15	38.3 ± 1.4	7.40 ± 0.02	− 0.54 ± 0.67	169 ± 34	36.7 ± 4.8

* Number of subjects was seven.
† All values absolute numbers except base excess, which is change from control in mEq/l.
‡ Difference from control is significant at 0.05 level.

cent Forane. These recurred briefly on recovery from anesthesia when the alveolar Forane was 1.4 per cent.

A small decrease in hematocrit occurred without change in blood volume (table 4). These results probably reflect blood loss from sampling (approximately 200 ml) and replacement with electrolyte solution.

There were only minor differences between results obtained during the first and fifth hours of anesthesia. Muscle blood flow was significantly greater at 1.2 and 1.8 per cent Forane during the fifth hour than during the first hour. Base excess was significantly increased during the fifth hour at 2.4 per cent Forane over the value at this concentration during the first hour.

Discussion

RESULTS DURING THE FIRST HOUR OF ANESTHESIA

Forane has unique cardiovascular effects compared with four other anesthetics we have evaluated in similar studies, halothane,[4] diethyl ether,[6] cyclopropane,[7] and fluroxene.[8] Comparisons with halothane are particularly pertinent since halothane is the potent inhalation anesthetic most widely used. Such comparisons are qualitative only, since quantitative comparisons await determination of the potency of Forane in man. We are determining MAC * in current clinical studies to provide a standard for comparison. In contrast to its response to halothane, cardiac output is sustained as Forane concentration increases. Cardiac output is maintained by an increase in heart rate which offsets the decrease in stroke volume. With halothane, heart rate was unchanged and the decrease in cardiac output paralleled a decrease in stroke volume. Forane caused a dose-related decrease in peripheral resistance which did not occur with halothane. Forane caused a greater decrease in peripheral resistance than any of the other four agents we have studied. Much of the change in pe-

* Studies in progress indicate a MAC of slightly under 1.3 per cent in man; in dogs it is 1.46 ± 0.25 (SD).

ripheral resistance may have occurred in muscle and skin where, proportionately, the decrease in resistance was much greater than the reduction in total resistance. Another unique finding was the lack of change of right atrial pressure with Forane at the two lighter levels of anesthesia and the smallness of the change at the deep level of anesthesia. In contrast, all four other anesthetics increased right atrial pressure at all concentrations. The I-J wave amplitude of the ballistocardiogram was maintained at control values at all levels of Forane anesthesia, in contrast to a significant decrease with halothane. Two other indices of the ability of the heart to contract related to I-J wave amplitude, mean rate of ventricular ejection and pre-ejection period, were maintained at control levels during Forane anesthesia. These measures decrease during halothane anesthesia. Like halothane, Forane decreased left ventricular work and left ventricular stroke work, but the decrease was not as great with Forane because cardiac output was maintained.

In its ability to double muscle blood flow at all anesthetic levels Forane contrasts with all four agents previously studied. The average increase in skin blood flow was also greater with Forane than with the other anesthetics.

As with halothane, oxygen consumption fell with Forane. With each agent consumption was significantly below control values at the deep level of anesthesia only. In contrast to its response to halothane, the cardiac output was maintained at a time when the oxygen consumption was decreasing, resulting in an increase in the ratio of cardiac output to oxygen consumption. Increases in cardiac output–oxygen consumption occurred in six of the seven subjects. An indication that delivery of oxygen to tissues was adequate during Forane anesthesia was the minimal change in base excess.

Results during the Last Hour of Anesthesia

In contrast to halothane,[4] diethyl ether,[6] and fluroxene,[8] Forane produces remarkably little change in circulatory effects with increasing duration of anesthesia. The only significant changes in early vs. late effects were an increase in forearm blood flow and increase in base excess. The usual manifestations of increasing duration of anesthesia are those of cardiovascular stimulation. Thus, halothane, ether, and fluroxene are associated with temporally-related increases in cardiac output, stroke volume, heart rate, oxygen consumption, and cardiac output/oxygen consumption ratio, and decreases in total peripheral resistance and mean right atrial pressure. These changes were conspicuously absent during prolonged Forane anesthesia. Another anesthetic associated with relatively little change in cardiovascular dynamics with duration of administration is cyclopropane.[7] Why this difference between agents? One property common to agents which are associated with temporally-related cardiovascular stimulation is *in-vivo* metabolism. Agents which produce stimulation have been shown to be metabolized. Halsey *et al.*[2] have been unable to demonstrate *in-vivo* hepatic metabolism of Forane or cyclopropane in miniature swine. It may be that metabolites of halothane, ether, and fluroxene are responsible for this phenomenon.

Of what advantage is the lack of temporally-related cardiovascular stimulation? It means that as Forane anesthesia proceeds changes in cardiovascular responses do not reflect changes of anesthetic effects, but rather alterations in stress or response to stress, for instance, blood loss. With halothane, diethyl ether, or fluroxene, the right atrial pressure may fall 4–8 cm H_2O from the first to fifth hours of anesthesia. In the same time the heart rate increases 10 to 30 per cent. These might be misinterpreted as evidence of decreased blood volume or changing level of anesthesia with halothane, diethyl ether, or fluroxene. Such misinterpretation would be less likely with Forane. Another advantage is the provision by Forane of stable cardiovascular conditions for experiments in animals.

Table 4. Hematocrit and Blood Volume Values

	Hematocrit (Per Cent)	Blood Volume (Liters)
Control (awake)	42.7 ± 0.7	6.63 ± 0.4
After Set 1 measurements	41.9 ± 0.5	6.65 ± 0.4
Prior to Set 2 measurements	40.0 ± 0.7	6.26 ± 0.5

The pattern of circulatory effects of Forane suggests beta-adrenergic stimulating properties. Increased heart rate and dilatation of muscle vessels are compatible with beta stimulation.[9] Most anesthetics are direct myocardial depressants, as indicated by their effect on the isolated heart.[10] We expected Forane would have a similar effect. Despite this, we found maintenance of cardiac output and contractility (as indicated by I-J wave, pre-ejection period or rate of ventricular ejection) even at deep levels of anesthesia, with little or no elevation of right atrial pressure. In part, these may be reflex responses to lowered mean arterial pressure and concomitant increased venous compliance but, in part, the responses may also reflect beta-stimulating properties of Forane.

Concomitant administration of Forane and nitrous oxide, an agent with weak alpha-adrenergic stimulating properties,[11] would be expected to attenuate the decrease in total peripheral resistance seen with Forane alone. Current studies of volunteers in which the cardiovascular effects of the Forane–nitrous oxide combination are being measured indicate that this is true. Higher arterial pressure is maintained because the decrease in peripheral resistance is less with the combination than with Forane alone at equipotent anesthetic levels. In initial clinical studies we have also found notable increases in arterial pressure with surgical incision. Whether the response is due primarily to the influence of attendant sympathetic stimulation on peripheral resistance or to cardiac output, or to both, is not known.

The technical assistance of Mrs. Anne White and Miss Dianne M. K. Impelman is gratefully acknowledged. The gas chromatograph analyses were performed by Mr. Richard Shargel.

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Drugs

METHOXYFLURANE TOXICITY Inorganic fluoride and nonvolatile organic fluoride were measured in a patient who had nephrotoxic effects thought to be due to methoxyflurane anesthesia. Concentrations of both fluorides were markedly elevated compared with concentrations in two patients who received methoxyflurane but did not develop nephrotoxic changes. Indirect evidence suggests that the inorganic fluoride concentration was sufficient to account for the nephrotoxic effects. The prolonged elevation of inorganic fluoride observed can be explained on the basis of the breakdown of the nonvolatile organic fluoride to inorganic fluoride and the poor renal clearance of both types. (*Taves, D. R., and others: Toxicity Following Methoxyflurane Anesthesia. II. Fluoride Concentrations in Nephrotoxicity, J.A.M.A. 214: 91 (Oct.) 1970.*)