# Ventricular Arrhythmias Induced in Monkeys by the Inhalation of Aerosol Propellants

GEORGE J. TAYLOR IV, WILLARD S. HARRIS, and MORTON D. BOGDONOFF

*From the Department of Medicine, Section of Cardiology, University of Illinois Hospital and College of Medicine, Chicago, Illinois 60612*

ABSTRACT After inhaling fluoroalkane gases, which are used as aerosol propellants, some people have died suddenly and unexpectedly. Seeking an explanation, we had 14 monkeys inhale these gases. All developed ventricular premature beats, bigeminy, or tachycardia, which began at an average of 39 (SE ±4.2) sec. Fluoroalkanes were present in blood, but arterial hypoxemia or hypercapnia was absent, and arterial pressure was reduced only slightly. In contrast, without fluoroalkanes, 3 min of asphyxia or anoxia caused arrhythmias in only one monkey whose arterial oxygen tension had fallen to 16 mm Hg. The ventricular arrhythmias caused in well oxygenated monkeys by fluoroalkane gases may either be mediated through beta adrenergic receptors, since propranolol abolished these arrhythmias, or result from a nonadrenergic, direct, toxic effect of these gases on the heart. These results suggest that some deaths after propellant inhalation may be caused by ventricular tachycardia or fibrillation.

## INTRODUCTION

The fluoroalkane gases used as aerosol propellants may cause sudden death (1). Healthy youths inhaling such gases in order to "turn on" may, within minutes, die unexpectedly (2). The abruptness of death and the lack of explanatory findings at postmortem examination suggest that a cardiac arrhythmia might be responsible. In discharging sympathomimetic amines, pressurized bronchodilator nebulizers also release fluoroalkane gases as propellants. In 1968 Speizer, Doll, and Heaf (3) and Speizer, Doll, Heaf, and Strang (4) reported that since 1960, when these pressurized bronchodilator aerosols had been introduced into England and Wales, the incidence of sudden and unexpected death among patients with asthma had steadily risen in these two countries. Speizer et al. (4) found "no clear indication" of the cause for this rising asthma mortality but stated that "the increase in the use of pressurized aerosol bronchodilators correlates closely with the increase in asthma mortality in Britain." In 1969 Inman and Adelstein (5) reported additional statistics, which they felt were consistent with a link between the increased deaths in asthma and the excessive use of pressurized nebulizers, and, in their summary, concluded "that the excess deaths [in England and Wales], estimated to have numbered more than 3500 in the period 1961–67, were likely to have been the result of over use of pressurized aerosols and that the subsequent decline in mortality has resulted from a greater awareness by doctors and patients of the dangers of over use." Recently, fluoroalkane gas propellants were found to sensitize the hearts of mice to the early appearance during asphyxia of T-wave depression and lethal sinus bradycardia and atrioventricular block (1). It was postulated that in other species these propellants might also cause ventricular tachyarrhythmias (1). To test this hypothesis in primates, we investigated the effects of fluoroalkane gas propellants without asphyxia in monkeys.

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## METHODS

Nine male and five female adult monkeys from a breeding colony were studied. The ages ranged from 3 to 5 yr and the weights from 2.8 to 12.5 kg. Seven were *Macaca mulatta,* five were *M. fascicularis,* and two were *M. arctoides.*

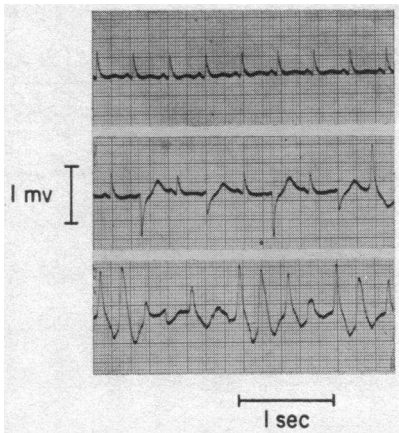


FIGURE 1 The effects of breathing a mixture of 30% Freon 12 (dichlorodifluoromethane)-9% Freon 114 (dichlorotetrafluoroethane)-61% oxygen for 30 sec on the electrocardiogram (lead II) of a 6.4 kg male monkey (*Macaca mulatta*) anesthetized with sodium thiamylal. All three recordings were obtained while the animal breathed room air. The top tracing, taken immediately before the fluoroalkane-$O_2$ inhalation, shows regular sinus rhythm. Ventricular premature beats first appeared at 30 sec of fluoroalkane-$O_2$ inhalation, which was then immediately stopped. The middle panel, recorded 9 sec after the end of fluoroalkane-$O_2$ inhalation, shows ventricular premature beats (2nd, 4th, 6th, 8th, and 9th QRS complexes) and bigeminy. The bottom panel, recorded 18 sec after the end of fluoroalkane-$O_2$ inhalation, shows ventricular tachycardia. Bag breathing with 100% $O_2$ was then begun, and the ventricular premature beats gradually decreased in frequency, disappearing 48 sec after they had started.

11 were studied anesthetized, 2 after 2.5% sodium thiamylal (0.5–1.5 ml) i.v., and 9 after 1 mg/kg phencyclidine hydrochloride (1-[1-phenylcyclohexyl]piperidine hydrochloride (Parke, Davis & Co., Detroit, Mich.) i.m. Phencyclidine, which is used widely to immobilize and anesthetize infrahuman primates, does not produce arrhythmias or other adverse cardiovascular effects in the dose employed and has no known role in endogenous catecholamine metabolism or distribution (6–8). Three other monkeys were studied awake but restrained; one was then anesthetized with phencyclidine and restudied. The 12 anesthetized animals breathed through a cuffed endotracheal tube. An indwelling needle was placed in the femoral artery of two animals. In five others, a polyethylene catheter (I.D. 0.9 mm, length 18 cm) was inserted by cutdown into the femoral artery, advanced into the abdominal aorta, and connected to a Statham P23Db strain gauge transducer two-thirds the transthoracic distance from the back. Aortic pressures in these five and electrocardiograms (lead II) in all monkeys were recorded at 25 mm/sec paper speed. Mean pressures were obtained by electronic integration. From seven phencyclidine-anesthetized animals 1.5-ml samples of arterial blood were drawn into heparinized, greased, glass syringes, which were immediately placed in iced water. Within 1.5 hr $P_{O_2}$, $P_{CO_2}$, and pH of these samples were analyzed with an Instrumentation Laboratory Inc. (Watertown, Mass.) model 313 blood gas and pH analyzer. In three monkeys the fluoroalkane gases in 1 ml samples of arterial blood were immediately extracted in 1 ml chloroform and, after storage overnight at 10°C, were analyzed by gas chromatography with a Research Specialties Co. apparatus (Richmond, Calif.) equipped with a flame ionization detector. The column (6 ft × ¼ inches) was packed with 25% SE 30 on 70–80 mesh Anakrom AB (HCL Scientific, Inc., Rockford, Ill.). Flow rate of the carrier gas, helium, was 70 ml/min. Column temperature was 65°C and detector temperature was 100°C.

From a flaccid, 3.5 liter bag, gases were breathed spontaneously through a face mask by awake monkeys and an endotracheal tube by anesthetized monkeys. A 60% Freon 12 (dichlorodifluoromethane)–40% Freon 114 (dichlorotetrafluoroethane) mixture (E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.) was mixed in the bag with either compressed air (one awake and two anesthetized monkeys) or 100% $O_2$ (two awake and nine anesthetized monkeys). Contents of the bag proximal to its orifice, sampled with a 25 µl Hamilton 702 syringe (Hamilton Co., Whittier, Calif.), were found by gas chromatography to contain 30 ±2.0% Freon 12 and 9 ±0.5% Freon 114 by volume. In addition, as a comparison intervention, compressed air was given to three, asphyxia to four, and 100% $N_2$ to seven monkeys. Asphyxia was induced with either the bag deflated or the endotracheal tube occluded.

The monkeys were studied supine at 10:00 a.m. after an overnight fast. After receiving a 3 min comparison intervention and then recovering by breathing room air for 15 or 30 min, all monkeys breathed the fluoroalkane-containing mixture. When the first ventricular premature beat appeared, fluoroalkane administration was immediately stopped. After breathing room air for 30 min, the three awake monkeys were reexposed to the fluoroalkane mixture. After 30 min recovery breathing room air, two awake and nine anesthetized monkeys received a 2 min i.v. infusion of 0.07 mg/kg propranolol hydrochloride. Since we found that isoproterenol hydrochloride, infused intravenously at 1.25, 2.5, and 5 µg/min, raised heart rate in the monkey 14, 56, and 64 beats/min before, but only 4, 10, and 44 beats/min after, 0.07 mg/kg propranolol hydrochloride i.v., this dose of propranolol seems potent, but not excessive, for blocking beta adrenergic receptors in the monkey. Starting 15 min after propranolol, the same studies that had been done before propranolol were repeated except that the fluoroalkane mixture was given for 2 min or until an arrhythmia or convulsion appeared. Statistical analysis was performed with Student's *t* test (9).

## RESULTS

Except for one monkey, who had ventricular premature beats at 105 sec of nitrogen inhalation, when his arterial blood $P_{O_2}$ was 16 mm Hg, 3 min of asphyxia, 100% $N_2$ or compressed air caused no arrhythmias. In contrast, all 14 monkeys breathing fluoroalkane propellant gas developed ventricular premature beats, which appeared within (mean ±SE) 39 ±4.2 (range 20–72) sec (Fig. 1). The frequency of ventricular premature beats during the first 3 sec after their onset was 40 ±7 (range 8–90)/min. Although propellant inhalation stopped immediately, and the animals breathed well, the ventricular extrasystoles became more frequent in 11 of the 14 monkeys, reaching a peak rate (measured for 3-sec intervals) in these 11 animals of 90 ±11 (range 25–120)/min, which occurred 10–30 sec after the arrhythmia began. Three

TABLE I

*Effects of Nitrogen and of Fluoroalkane-Oxygen on $P_{O_2}$, $P_{CO_2}$, and pH of Arterial Blood*

| Monkey | Control | | | Nitrogen inhalation | | | Fluoroalkane-oxygen inhalation | | |
|---|---|---|---|---|---|---|---|---|---|
| | $P_{O_2}$ | $P_{CO_2}$ | pH | $P_{O_2}$ | $P_{CO_2}$ | pH | $P_{O_2}$ | $P_{CO_2}$ | pH |
| | *mm Hg* | *mm Hg* | | *mm Hg* | *mm Hg* | | *mm Hg* | *mm Hg* | |
| 1 | 95 | 23 | 7.36 | 35 | 30 | 7.28 | 101 | 15 | 7.28 |
| 2 | 95 | 20 | 7.42 | 40 | 20 | 7.39 | 115 | 20 | 7.32 |
| 3 | 96 | 26 | 7.42 | 29 | 22 | 7.50 | 140 | 25 | 7.43 |
| 4 | 130 | 27 | 7.36 | 16 | 25 | 7.39 | 136 | 25 | 7.46 |
| 5 | 97 | 42 | 7.44 | 29 | 38 | 7.30 | 116 | 24 | 7.42 |
| 6 | 98 | 24 | 7.40 | 25 | 26 | 7.45 | 110 | 25 | 7.45 |
| 7 | 130 | 23 | 7.44 | 39 | 23 | 7.45 | 132 | 25 | 7.40 |
| Mean | 106 | 26 | 7.41 | 30* | 26 | 7.39 | 121 | 23 | 7.39 |
| SE | ±6.2 | ±2.7 | ±0.01 | ±3.2 | ±2.3 | ±0.03 | ±5.5 | ±1.5 | ±0.03 |

* Significantly different from the control ($P < 0.001$) and fluoroalkane-oxygen ($P < 0.001$) values.

monkeys developed bigeminy without ventricular tachycardia; four others developed ventricular tachycardia (three or more consecutive extrasystoles). The seven animals with bigeminy or ventricular tachycardia (Fig. 1) were bag breathed with 100% $O_2$ until the arrhythmia disappeared. The other seven breathed room air on their own; their ventricular extrasystoles persisted 0.5–3 min. Three monkeys were exposed twice to propellant before propranolol. The first time, they developed ventricular extrasystoles at 30, 42, and 35 sec of propellant inhalation, with initial (first 3 sec) frequencies of 18, 40, and 60 extrasystoles per min and peak frequencies of 120, 80, and 110 extrasystoles per min. The second time, ventricular extrasystoles appeared at 25, 36, and 20 sec of propellant inhalation, with initial and peak frequencies of 20, 30, and 60/min and 40, 110, and 120/min.

In the two monkeys anesthetized with sodium thiamylal, the time of onset and the initial and peak frequencies of ventricular premature beats in one, who developed ventricular tachycardia, were 30 sec, 18/min, and 120/min and in the other were 35 sec, 40/min and 40/min. The time of onset and the initial and peak frequencies in the three awake monkeys, one of whom developed bigeminy, averaged 30 sec, 36/min, and 46/min, and in the 10 phencyclidine-anesthetized monkeys, five of whom developed ventricular tachycardia or bigeminy, averaged 44 ±5.2 (range 20–65) sec, 41 ±8 (range 9–80)/min, and 75 ±14 (range 9–120)/min. Thus, the presence, absence, or kind of anesthesia did not appear to affect either the time of onset or the frequency of ventricular arrhythmias associated with propellant inhalation.

After propranolol, none of the interventions was associated with ventricular premature beats. Of 11 monkeys, 6 tolerated 2 min of fluoroalkane inhalation without arrhythmia or convulsion, 1 had an atrioventricular nodal rhythm at 105 sec, and 4 convulsed without arrhythmia at 60, 90, 100, and 110 sec.

Fluoroalkane-induced ventricular arrhythmias were not associated with hypoxemia or hypercarbia (Table I), or with myocardial ischemia secondary to marked arterial hypotension. Nitrogen inhalation lowered arterial blood $P_{O_2}$ to an average of 30 mm Hg, without causing arrhythmias except in one animal. In contrast, while causing ventricular extrasystoles in all animals, fluoroalkane-oxygen inhalation failed to lower arterial $P_{O_2}$ or raise $P_{CO_2}$. Control levels of arterial systolic, diastolic, and mean pressure in five monkeys averaged 141 ±3, 89 ±4, and 107 ±4 mm Hg before and 128 ±6, 86 ±2, and 99 ±2 mm Hg after propranolol. Immediately before the onset of ventricular arrhythmias, fluoroalkane-oxygen inhalation caused systolic, diastolic and mean pressures to fall 21 ±4 ($P < 0.01$), 7 ±6 (NS), and 12 ±4 ($P < 0.05$) mm Hg, respectively. After propranolol, fluoroalkane-oxygen inhalation for 2 min lowered these 9 ±6 (NS), 10 ±2 ($P < 0.01$), and 10 ±3 ($P < 0.05$) mm Hg.

The control heart rate (mean ±SE) of the 12 anesthetized monkeys was 158 ±8 beats/min, whereas that of the three awake monkeys was 180, 200, and 220 beats/min. Asphyxia in four animals, 100% $N_2$ in seven, and compressed air in three raised heart rate an average of 19 ±5, 9 ±9, and 2 ±2 beats/min, respectively. Before ventricular arrhythmias appeared, fluoroalkanes raised heart rate 20 and 35 beats/min in two awake monkeys, had no effect in the third, and raised it 19 ±5 beats/min ($P < 0.005$) in 12 anesthetized animals. Propranolol slowed the heart rate of 11 animals 40 ±4.2 beats/min ($P < 0.001$). After propranolol, fluoroalkanes slowed heart rate 6 ±4 beats/min, an insignificant amount.

During the control period, no fluoroalkane gas was detected in arterial blood of three monkeys tested, but

when ventricular premature beats appeared at 35, 42, and 45 sec of propellant-oxygen inhalation, Freon 12 and 114 concentrations in arterial blood were 5.5 and 1.8 mg/100 ml in the first, 6.3 and 2.3 mg/100 ml in the second, and 6.5 and 2.2 mg/100 ml in the third monkey.

## DISCUSSION

The inhalation of fluoroalkane propellant gas by nonhypoxic, nonhypercarbic monkeys, either awake or anesthetized, quickly induces ventricular premature beats, bigeminy, and tachycardia. At this time fluoroalkane gas is present in blood, and arterial pressure has fallen only slightly. Because part of the antiarrhythmic effect of propranolol may be nonspecific, the abolition of these tachyarrhythmias by propranolol is consonant with, but fails to prove, their mediation through beta adrenergic receptors (10). The present results do not exclude a direct action of the fluoroalkane gases on the receptors. More likely, however, these gases act indirectly, perhaps causing a discharge of catecholamines or sensitizing ventricular myocardium to the arrhythmogenic effects of catecholamines.

Many hydrocarbons sensitize hearts, through unknown mechanisms, to the production of ventricular arrhythmias by injected epinephrine (11). Cardiac adrenergic activity in monkeys at rest may be unusually high. Beta adrenergic receptor blockade by propranolol slowed the average simian heart rate 40 beats/min, compared with only 6 beats/min slowing produced in 37 awake normal men by nearly twice the dose per kilogram (12). Although epinephrine was not injected, fluoroalkane gases absorbed into the blood may have sensitized the simian myocardium to the arrhythmic effects of endogenous catecholamines. With the data at hand, however, it must be clearly emphasized that the ventricular arrhythmias induced by inhalation of fluoroalkane propellants could be attributed, equally well, to a direct toxic effect of these gases on the heart.

The present results suggest that ventricular tachycardia and fibrillation may be causes of the sudden and unexpected deaths in youths who "turn on" by inhaling aerosol propellants and, perhaps, in some people with asthma who use pressurized bronchodilator nebulizers excessively. However, since the arrhythmic effects of fluoroalkanes may differ among and within species, caution must be exercised in interpreting these results obtained in monkeys as necessarily predicting the effects of these agents in man. Without causing ventricular premature beats, fluoroalkanes sensitize the hearts of mice (1) and, in preliminary studies, of rats and dogs to the early appearance of lethal bradyarrhythmias during asphyxia. Some human propellant sniffers may be asphyxiated by the bag used to deliver gas, displacement of oxygen from inspired air, or medullary respiratory depression. When fluoroalkane gas is present, such asphyxia might cause a fatal bradyarrhythmia, with or without ventricular premature beats and subsequent fibrillation.

The concentration of fluoroalkane gas administered to the monkeys is probably equal to, or less than, that inhaled by youths who "turn on" by breathing either from a plastic bag filled with aerosol gas or from the gas stream directed through a cardboard tube. Since the concentration given the monkeys far exceeds that a person might inhale during ordinary use of a nebulizer, the present results do not indicate that such use is hazardous. On the other hand, since the amount of propellant absorbed into the blood from hairspray, cosmetic, and household aerosols is unknown, the possibility has not been excluded that propellant inhalation might be toxic to the hearts of people who use aerosols excessively, such as hairdressers, housewives, and persons with asthma. Five commonly used brands that we have tested release 38 (deodorant), 80 (hairspray), 180 (deodorant), 218 (cooking pan lubricant), and 231 (makeup finish) ml of gas/sec. Medihaler-Iso (Riker Laboratories, Northridge, Calif.) (13), a bronchodilator nebulizer containing 350–400 doses, delivers with each discharge 12.5 ml of gas and 75 $\mu$g isoproterenol sulfate. Another, the Isuprel Mistometer (Winthrop Laboratories, New York) (13), contains about 300 doses and releases with each discharge 5.8 ml of gas and 125 $\mu$g isoproterenol hydrochloride. The ventricular arrhythmic effects of the fluoroalkane gas and catecholamine, which are absorbed simultaneously, may be additive or synergistic. In addition, it seems possible that certain conditions, such as hypoxemia or ischemic heart disease, might enhance cardiac vulnerability to the toxic effects of aerosol propellants.

Contrary to widely disseminated statements (13), fluoroalkane propellants are far from "inert." The present findings in monkeys raise anew the possibility of toxicity to the human heart. The popularity of medical, cosmetic, and household aerosols makes it important to measure the quantities, presently unknown, of propellant gas absorbed into the blood of frequent users and to explore further the possibility of deleterious effects.

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