Halothane and Methoxyflurane — A Comparison of Their Effects on Cardiac Pacemaker Fibers

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Halothane and methoxyflurane have some very similar and some very different effects on primary and latent pacemaker fibers. On fibers of the sinoatrial node, halothane has a negative chronotropic action which is not prevented by atropine. The effect of methoxyflurane is biphasic: an initial, brief acceleration precedes the negative chronotropic action. Both compounds can cause complete cessation of electrical activity of nodal fibers *"in vitro,"* and this may occur with relatively low concentrations of methoxyflurane. Arrest of activity is not preceded by progressive slowing. Rather, it is associated with loss of excitability of the fiber at a time when there is only a modest reduction in rate. The effect is reversible. Halothane antagonizes the positive chronotropic action of epinephrine, while methoxyflurane has little effect. There is one major difference between the effects of the two anesthetics on Purkinje fibers. Halothane depresses phase 4 depolarization and antagonizes the stimulant actions of epinephrine and ouabain—actions more characteristic of an antiarrhythmic agent. Methoxyflurane increases the rate of phase 4 depolarization and potentiates the action of epinephrine. In this respect, methoxyflurane resembles cyclopropane. (Key words: Halothane; Methoxyflurane; Sinus node; Purkinje fibers; Phase 4 depolarization; Arrhythmias.)

THE PROCLIVITY of adrenergic compounds such as epinephrine to evoke cardiac arrhythmias when used in conjunction with hydrocarbon anesthetics has been recognized for more than half a century. Because of the marked influences on the arrhythmias of such extracardiac effects as arterial pressure, hypercarbia and autonomic activity, even the primary locus of action has not been established conclusively. The basic mechanisms involved in the effects of the hydrocarbon–catecholamine combination are poorly understood. Recently, in a biochemical approach to the problem, Ngai and associates[1,2] and Naito and Gillis[3] concluded that the action of these anesthetics is not associated with changes in the biosynthesis, uptake or release of catecholamines. The action is believed to be distal to the adrenergic neuron.

Until recently, few studies of the problem had been conducted using intracellular recording techniques. The leading studies have been those of Davis *et al.*, who investigated the effects of cyclopropane on Purkinje fibers.[4-6] Perhaps most pertinent to the problem of hydrocarbon–epinephrine arrhythmias was the finding that cyclopropane enhanced the slope of phase 4 depolarization of Purkinje fibers and potentiated the increased slope and magnitude of phase 4 produced by epinephrine. Arrhythmias frequently intervened. Propranolol antagonized this potentiation by cyclopropane. The effects of cyclopropane were markedly influenced by the concentration of calcium in the medium. Recently, Hauswirth has reported studies of the effects of halothane on ventricular and Purkinje fibers of sheep.[7] The effects on ventricular fibers were much milder than those on Purkinje fibers. Excellent reviews of this subject have been prepared by Katz and Epstein[8] and by Alper and Flacke.[9]

Contradictory reports of the effects of these anesthetics on cardiac rate and rhythm have appeared in the literature. It is generally agreed that halothane in concentrations normally employed for clinical anesthesia produces bradycardia. There is some disagreement, however, regarding the ability of atropine to antagonize this effect.[10-13] In the case of methoxyflurane, cardiac slowing and car-

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diac acceleration both have been observed,[14-17] and wandering pacemaker has also been reported.[18, 19]

In the investigation reported here, we have compared the effects of halothane (Fluothane) and methoxyflurane (Penthrane) on single fibers of the sinoatrial nodes of the rabbit and the cat and on canine Purkinje fibers. In addition, in an attempt to clarify the mechanisms involved in arrhythmias associated with anesthetic–adrenergic interaction, we have compared their influences on the effects of epinephrine on these preparations.

Methods

The animals were anesthetized with sodium pentobarbital (Nembutal), 30 mg/kg i.v. Hearts were immediately excised and placed in oxygenated Tyrode's solution. Preparations of rabbit right atria or canine papillary muscles with attached false tendons composed of Purkinje fibers were lightly pinned to the wax floor of a 10-ml perspex bath, through which the Tyrode's solution at 37 C flowed continuously at a rate of 10 ml/min. The volume of the bath was kept constant by a suction device. The Tyrode's solution was equilibrated in a reservoir with a 95 per cent O_2–5 per cent CO_2 mixture. The composition of the Tyrode's solution in mmole/l was: NaCl 137; KCl 2.7; $CaCl_2$ 2.7; $MgCl_2$ 0.5; NaH_2PO_4 1.9; $NaHCO_3$ 24.0; dextrose 5.5.

Transmembrane potentials were recorded through conventional intracellular glass microelectrodes filled with 3 M KCl. These were connected to a negative-capacity electrometer through an agar–KCl bridge. This, in turn, was connected to the input of a Tektronix 556 oscilloscope and a Hewlett-Packard 3955 tape recorder. Records were made by photographing the scope face during the experiment, or later from the tape playback. Maximum rate of rise of the upstroke (phase 0) was determined by electronic differentiation.

Methoxyflurane and halothane were introduced into the reservoir of Tyrode's solution by passing the oxygen–carbon dioxide mixture through calibrated vaporizers (Pentec Mark II and Fluotec Mark II). Concentrations of methoxyflurane ranged from 0.5 to 2.5 per cent and concentrations of halothane, from 0.5 to 4.0 per cent. The effect of atropine was studied by addition to the stock solution of an amount sufficient to make a concentration of 1 μg/ml. Epinephrine hydrochloride was administered either by continuous flow from the reservoir of Tyrode's solution or by injection directly into the tissue bath according to the method of Dudel and Trautwein.[20] In studies involving propranolol, it was added to the reservoir of Tyrode's solution in amounts sufficient to make a final concentration of 3 μg/ml. In order to study the effects of halothane on an ectopic focus, aconitine in a concentration of 0.05 per cent was applied to the isolated atria by means of a small filter-paper disk. For studies of sinoatrial nodal fibers, preparations were allowed to beat spontaneously. In the studies on Purkinje fibers, three types of preparations were used, quiescent, spontaneously active, and electrically driven. The last were driven by suprathreshold rectangular pulses of 3-msec duration at a frequency of 60 or 90/min through bipolar platinum electrodes. The effect of halothane on the response of spontaneous fibers to ouabain, 0.2 μg/ml, was studied also.

Results

Effects on Sinoatrial Nodal Fibers and Their Response to Epinephrine

The most prominent effect was a moderate slowing in the rate of spontaneous beating (average in eight preparations, 16 per cent) (fig. 1). This was the result of a slightly reduced rate of slow diastolic depolarization (phase 4) and an increase in threshold potential. There was no change in maximum diastolic potential or overshoot, and no significant effect on the contour of the action potential. Figure 1, *C* and *D*, shows the effect of 2 per cent halothane, recorded at a faster sweep velocity. In addition to the marked change in the slope of phase 4, maximum diastolic potential, overshoot and amplitude decreased. The duration of the action potential was increased, but it must be remembered that changes in rate alone will modify the action potential.[21] The negative chronotropic action was not prevented by atropine, 1 μg/ml. A concentration of 4 per cent (maximum setting on the halothane vaporizer) produced progres-

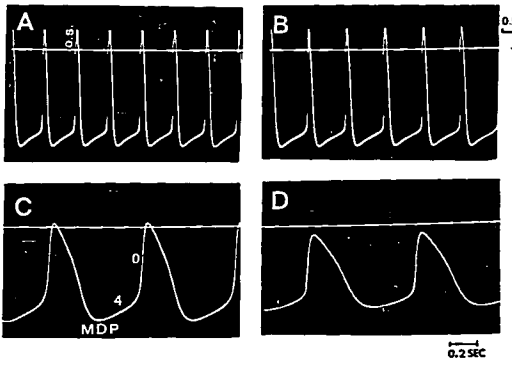

FIG. 1. The effect of halothane on the transmembrane potentials of spontaneously active fibers in the rabbit sinus nodal region. *A*, control; *B*, halothane, 1 per cent; *C*, control; *D*, halothane, 2 per cent. *A* and *B* were recorded at slow sweep velocity, *C* and *D* at faster sweep velocity, to show the effects on action potential contour. Records *A* and *C* are from different fibers. The sweep velocity in *C* and *D* is five times that in *A* and *B*. MDP = maximum diastolic potential; 4 = phase 4 of the action potential (slow diastolic depolarization); 0 = phase 0 or upstroke of action potential; OS = overshoot.

sive reductions in maximum diastolic potential, overshoot and amplitude. Complete arrest of the fiber occurred. The effect was completely reversed by washing (fig. 2).

Methoxyflurane in concentrations of 1 per cent or more consistently had a distinct but transient biphasic action. Slowing of the rate was always preceded by an initial positive chronotropic effect (average rate increase 10 per cent) (fig. 3*B*). The acceleration was due chiefly to a slight loss in maximum diastolic potential and was not prevented by propranolol, 3 μg/ml—a concentration which inhibited the stimulant action of epinephrine. The negative chronotropic action was associated with a further loss in maximum diastolic potential and a marked increase in the threshold potential. Overshoot was also reduced (fig. 3, *C* and *D*). Arrest of activity was observed consistently with this concentration (fig. 3*E*), and frequently with 0.5 per cent. The effect was completely reversible. When the rate was increased by the presence of epinephrine 10^{-6} in the Tyrode's solution, exposure to halothane once again caused a reduction in rate. Methoxyflurane, on the other hand, had little effect. In order to study this effect of halothane further, aconitine, 0.05 per cent, was applied focally to the atrial appendage. Aconitine creates an ectopic focus of impulse formation at the site of application. Following the development of the ectopic pacemaker, the preparations were exposed to 2 per cent halothane. Here again, a marked reduction in rate occurred, and it appeared that the depressant action of halothane on pacemaker tissue was nonspecific.

EFFECTS ON PURKINJE FIBERS AND THEIR RESPONSE TO EPINEPHRINE

Quiescent Fibers. Fibers were exposed to halothane, 1 per cent, and methoxyflurane, 1 per cent, for 20 minutes. The resting mem-

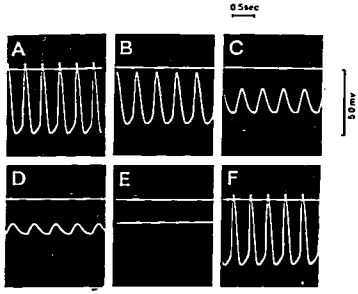

FIG. 2. The development of and recovery from arrest of activity induced by halothane, 4 per cent, in a spontaneously active fiber in the rabbit sinus nodal region. *A*, control in Tyrode's solution; *B–E*, records made at ten-minute intervals following the start of perfusion with halothane; *F*, record made after 15 minutes of washing with Tyrode's solution.

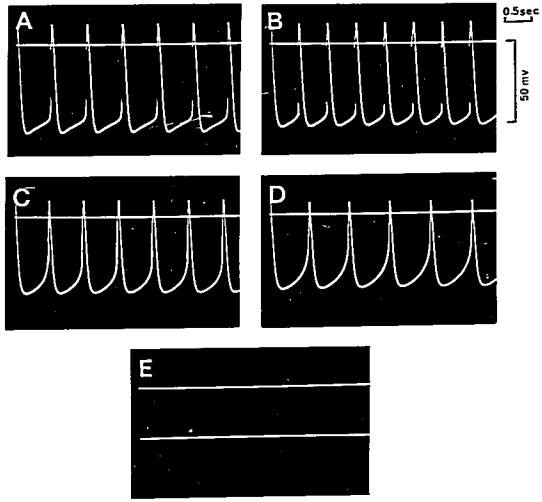

FIG. 3. The effect of methoxyflurane on the transmembrane potential of a spontaneously active fiber in the rabbit sinus nodal region. *A*, control; *B–E*, methoxyflurane, 1 per cent, recorded at five-minute intervals after commencement of exposure to methoxyflurane. The biphasic chronotropic action is clearly evident. Following arrest of the fiber (*E*) 20 minutes of washing restored the activity to the control pattern.

brane potentials, which in this group of preparations ranged from −75 mv to −92 mv, were unchanged by halothane. When methoxyflurane was present the resting potentials moved to values slightly less negative, but no automaticity developed.

Spontaneously Active Fibers. The effects of the two compounds on these fibers were strikingly different. With halothane in concentrations greater than 2 per cent, the most prominent effect was a slowing of the spontaneous rate due to an increase in threshold potential and a decrease in the slope of phase 4 depolarization (fig. 4, *A* and *B*). In addition to the decrease in rate, there was a characteristic steep increase in the slope of phase 2, resulting in almost complete disappearance of the plateau. Duration of the action potential was reduced. This effect on the plateau is more obvious in figure 6. Augmentation of phase 4 depolarization was not seen with any concentration. In contrast to the depressant action of halothane, methoxyflurane in concentrations of 0.5 and 1.0 per cent caused marked increases in rate, due largely to sharp increases in the rate of phase 4 depolarization (fig. 4, *C–F*).

The effects of the two compounds on the response of spontaneous fibers to epinephrine were strikingly different. Halothane decreased the slope of phase 4 depolarization augmented by epinephrine. Methoxyflurane increased the effect of epinephrine and caused acceleration of rate. The depressant effect of halothane on phase 4 depolarization and its suppression of the augmentation of slow diastolic depolarization by epinephrine are actions more characteristic of antiarrhythmic agents. Halothane has a similar depressant effect on phase 4 augmentation induced by ouabain, and counteracts ventricular arrhythmias evoked by this compound (fig. 5).

Effects on the Contour of the Action Potential of Driven Preparations. The effects of halothane and methoxyflurane on 22 electrically driven preparations from 16 hearts were studied. Usually, the effects of the two compounds were studied in different preparations. However, similar results were obtained when the same fiber was used for both agents, provided, of course, that an adequate recovery period was allowed between exposures. A typical record is shown in figure 6, *A–C*, for 1.0 per cent halothane and in *D–F* for 1.0 per

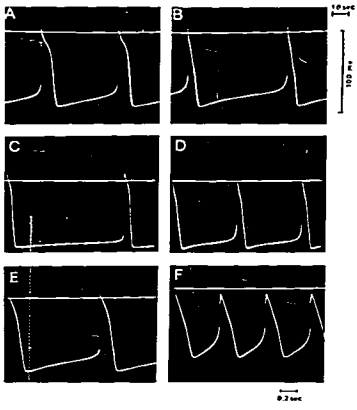

FIG. 4. The effects of halothane and methoxyflurane on spontaneously active canine Purkinje fibers. *A*, perfusion with control Tyrode's solution; *B*, perfusion with Tyrode's solution containing halothane, 2.5 per cent; *C*, perfusion with control Tyrode's solution; *D*, perfusion with Tyrode's solution containing methoxyflurane, 0.5 per cent; *E*, perfusion with control Tyrode's solution; *F*, perfusion with Tyrode's solution containing methoxyflurane, 1.0 per cent. The three sets of records are from different Purkinje fibers. Time calibration in *A–D* is as shown in *B*; in *F*, it is five times that in other records as shown.

cent methoxyflurane. There was a notable similarity in the general appearances of the action potentials following exposure to the two compounds. An important difference was the augmentation of phase 4 depolarization by methoxyflurane. By far the most prominent effect of both halothane and methoxyflurane on contour was that on phase 2 of repolarization. The slope of phase 2 was sharply increased in every preparation. Although the resulting reduction in the duration of the plateau was a consistent effect, it did not invariably lead to a decrease in the duration of the action potential. The reason for this was that, in many fibers, the rate of the terminal portion of repolarization, phase 3, was decreased. Thus, the opposite effects on phase 2 and phase 3 caused the duration of the action potential to remain almost unchanged. The rate of rise of the upstroke was not significantly affected by halothane (fig. 6, *A* and *C*). A consistent, but small, reduction was seen with methoxyflurane (fig. 6, *D* and *F*). This slight decrease in the velocity of phase 0 probably was associated with the increase in phase 4 depolarization. The effect of the combination of methoxyflurane and epinephrine on phase 4 depolarization is well illustrated in figure 7. This is a typical record and shows the effects of epinephrine alone, methoxyflurane alone, and the combination. The records have been superimposed to facilitate comparison. The pronounced effect of the combination of methoxyflurane and epinephrine was prevented by propranolol, 3 μg/ml (fig. 8, *A–E*). The maximum rate of rise of phase 0 was reduced by the methoxyflurane–epinephrine combination. It can be seen from figure 8 that it was reduced to below the recording capability of the differentiating circuit employed.

The maximum effects occurred after approximately 15 minutes of perfusion with halothane and 6 to 8 minutes with methoxyflurane. The effects of both compounds appeared to be completely reversible, but full recovery from methoxyflurane required a longer period of washing. This is in keeping with the well-known slow recovery from surgical anesthesia with methoxyflurane. However, the earlier de-

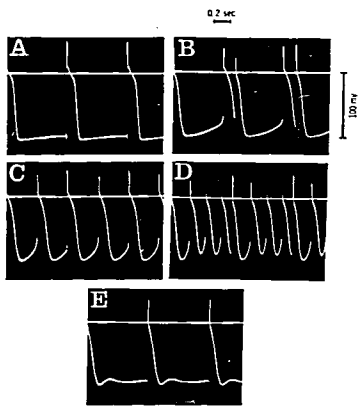

FIG. 5. The effect of halothane on ouabain-induced arrhythmias in canine Purkinje fibers. *A*, control; *B–D*, ouabain, 0.2 μg/ml. *B*, after 24 minutes of exposure; *C* and *D* at one-minute intervals after *B*. *E*, ouabain, 0.2 μg/ml, plus halothane, 2.0 per cent.

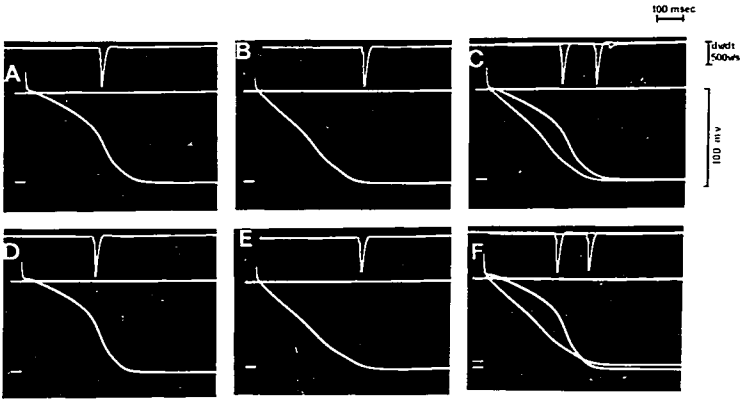

FIG. 6. The effects of halothane and methoxyflurane on the action potential of canine Purkinje fibers. *A*, perfusion with control Tyrode's solution; *B*, perfusion with Tyrode's solution containing halothane, 2 per cent; *C*; *A* and *B* superimposed; *D*, perfusion of same fiber with control Tyrode's solution; *E*, perfusion with Tyrode's solution containing methoxyflurane, 1 per cent; *F*, *D* and *E* superimposed. The downward spike in the top tracing, A–$F = dv/dt$ = rate of rise of upstroke of the action potential. The two records show striking similarities, but the difference between the effects of the two agents on phase 4 is apparent.

velopment of effects was not consistent with the notably slow onset of anesthesia with this agent. This may or may not mean that there is a difference between the rates of development of effects in the central nervous system and in cardiac tissue.

Discussion

There are marked similarities in the effects of halothane and methoxyflurane on primary and secondary pacemaker tissue and striking differences. The agents are notably different in their effects on the response of these tissues to epinephrine. Both halothane and methoxyflurane have depressant actions on nodal fibers of the sinoatrial region, and, in the case of the latter, cessation of spontaneous activity has been observed with a concentration of 0.5 per cent. With halothane, concentrations in excess of 3 per cent were necessary. The negative chronotropic effect of halothane was not prevented by atropine. This agrees with the findings of Morrow and co-workers in the dog *"in situ."*[13] Cessation of electrical activity does not follow progressive slowing to the point of arrest. Rather, it is associated with a marked loss of maximum diastolic potential, increase in threshold potential, and ultimate loss of excitability. Fibers which become inactive cannot be driven electrically. This effect of both compounds is completely reversible. Methoxyflurane has a biphasic action on this tissue, an action we have not observed with halothane. The initial acceleration which always preceded the negative chronotropic effect was not very great with concentrations below 1.0 per cent, and a concentration of 0.2 per cent had no observable effect on the action potential.

Perhaps the most striking difference between halothane and methoxyflurane was in their actions on Purkinje fibers. Although the effects of the two agents on action potential contour were very similar, they exerted directly opposite effects on phase 4 depolarization. Halothane in concentrations of 1 and 2 per cent had little or no effect on the rate of slow diastolic depolarization. Higher concentrations reduced the slope and antagonized the enhancement of phase 4 depolarization by epinephrine. These effects are more characteristic of an antiarrhythmic agent. Indeed, we have shown that halothane significantly reduces the cardiotoxicity of ouabain.[22] This is

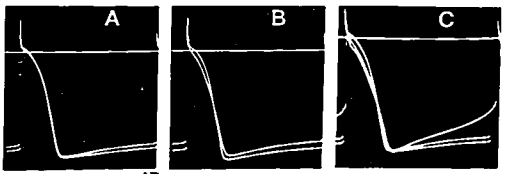

FIG. 7. The effect of methoxyflurane, 1 per cent, on phase 4 depolarization and its influence on the augmentation of phase 4 depolarization produced by epinephrine in the driven canine Purkinje preparation. *A*, the effect of epinephrine 10^{-6} (upper phase 4) superimposed on control (lower phase 4); *B*, the effect of methoxyflurane, 1 per cent (upper phase 4) superimposed on control; *C*, the effect of methoxyflurane, 1 per cent plus epinephrine 10^{-6} (upper phase 4) superimposed on the effect of epinephrine 10^{-6} (middle phase 4) and on control (lower phase 4). The very pronounced effect of the combination of methoxyflurane and epinephrine on phase 4 almost invariably resulted in arrhythmias.

in agreement with the findings of Morrow and Townley.[23] In addition, Morrow and his associates have recently pointed out the therapeutic effectiveness of halothane in ouabain-induced ventricular tachycardia.[24] Methoxyflurane, on the other hand, even in a concentration of 0.5 per cent, increased the rate of phase 4 depolarization and enhanced its augmentation by epinephrine. This action of methoxyflurane on Purkinje fibers shows a strong resemblance to that of cyclopropane, described by Davis and his associates.[5]

The peculiar combination of primary pacemaker depression and secondary pacemaker stimulation produced by methoxyflurane would favor a shift in the site of pacemaker activity in the ventricular conducting system. Indeed, this has been reported clinically by Arens [25] and Hudon [19] and Jacques and Hudon.[18] Moreover, the profound effect of the combination of methoxyflurane and epinephrine on phase 4 depolarization results in a marked decrease in the rising velocity of the action potential of Purkinje fibers. This re-

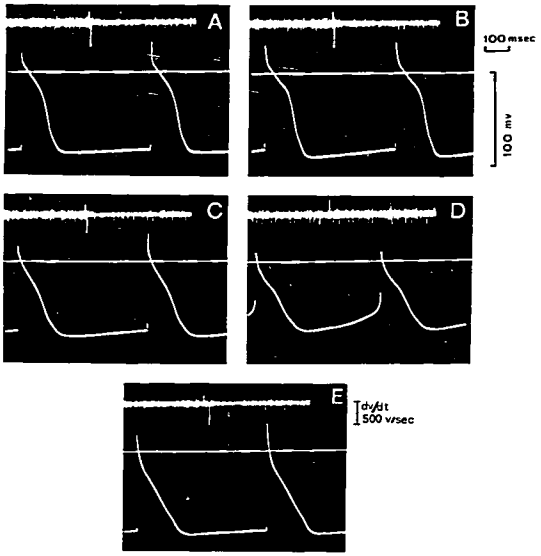

FIG. 8. The effects of the combination of methoxyflurane and epinephrine on the action potential of canine Purkinje fibers before and after propranolol. *A*, in control Tyrode's solution; *B*, in Tyrode's solution containing epinephrine 10^{-6}; *C*, in Tyrode's solution plus methoxyflurane, 1 per cent; *D*, in Tyrode's solution containing methoxyflurane, 1 per cent, plus epinephrine, 10^{-6}; *E*, in Tyrode's solution containing methoxyflurane and epinephrine and propranolol. 3 μg/ml. The top tracing in each figure = dv/dt (downward spike) = rate of rise of upstroke of the action potential.

sults from the reduction in take-off potential and contributes to decremental conduction and local block—conditions favoring re-entry of impulses. Halothane does not exert this effect on phase 4 depolarization. Studies of the effects of these compounds on refractory period and conduction velocity in ventricular and Purkinje fibers, currently in progress, indicate that the agents affect these variables differentially in the two types of fibers. This would greatly increase the electrical heterogeneity of the myocardium—a condition highly conducive to the development of disturbances in rhythm.

The depressant effect of halothane on pacemaker tissue suggests that it is highly unlikely that the arrhythmogenic action of this compound involves the development of ectopic foci. In contrast, the stimulant effect of methoxyflurane on phase 4 depolarization of Purkinje fibers, especially when combined with epinephrine, makes ectopic pacemaker development highly probable.

Our findings suggest that any tendency of halothane to induce cardiac arrhythmias is probably associated with its effects on conduction velocity and refractory period—not with ectopic pacemaker formation. On the other hand, the arrhythmogenic action of methoxyflurane could involve both mechanisms, because of the stimulant action on slow diastolic depolarization. This effect is particularly marked with the methoxyflurane–epinephrine combination. Phase 4 depolarization is believed to be associated with a slow decline in potassium current which allows the inward background currents to depolarize the membrane, and this process is accelerated by epinephrine.[26] Presumably, halothane and methoxyflurane influence this process in opposite directions. Cyclopropane,[4] halothane and methoxyflurane all have the same effect on the contour of the action potential, namely, acceleration of phase 2 and deceleration of phase 3. It is interesting that a similar effect is produced by ouabain.[27] The action of cardiac glycosides is believed to be intimately associated with calcium ions and, as pointed out by Alper and Flacke[9] and Temte and associates,[6] calcium ions also appear to be involved in the action of hydrocarbon anesthetics. Through action potential studies using voltage clamping techniques, we hope to be able to shed further light on this possible common denominator in the electrophysiologic actions of these compounds.

It should be emphasized that the conclusions drawn regarding the arrhythmia-inducing tendency of these compounds are based solely on studies conducted at the cell membrane level and on *in vitro* preparations. Moreover, there is evidence that the human heart is much less sensitive than the dog heart to the effects of the combination of methoxyflurane and epinephrine. For clinical anesthesia, methoxyflurane is used in lower concentrations than halothane. In some circumstances, however, a concentration of 2.5 per cent is used for induction. In isolated preparations of the sinoatrial node, we have observed arrest of electrical activity frequently with 0.5 per cent methoxyflurane and consistently with 1.0 per cent. In intact animals, we have observed loss of sinus dominance with 1.0 per cent; this also has been seen clinically with this concentration. In the light of these findings, and the stimulant action on secondary pacemakers that we have observed, we think the use of the higher concentrations of methoxyflurane is potentially hazardous. The risk would be even greater if epinephrine were used during anesthesia with methoxyflurane. It is now generally accepted practice to employ only minimum effective amounts of epinephrine and to avoid intravenous administration during anesthesia with these compounds. If this practice is followed, the profound effect of the combination of methoxyflurane and epinephrine probably would not develop. On the other hand, our studies indicate that the use of methoxyflurane in the presence of high levels of catecholamines would entail considerable risk. However, in man, Bain and Spoerel found no serious arrhythmias following the use of methoxyflurane in patients with pheochromocytoma.[28]

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Drugs

PENTAZOCINE METABOLISM Urinary excretion of pentazocine for 24 hours after oral and intramuscular administration of the drug was determined. Pentazocine is extensively metabolized. Less than 13 per cent of the dose appeared in the urine unchanged. From 12 to 13 per cent was excreted as a glucuronide conjugate. At least one other unidentified polar metabolite was detectable. Most of the drug was excreted within the first 12 hours. Prolonged side-effects in two subjects did not appear to correlate with the rate of excretion of pentazocine or its metabolites. (*Berkowitz, B., and Way, E. L.: Metabolism and Excretion of Pentazocine in Man, Clin. Pharmacol. Ther. 10: 681 (Sept.) 1969.*)