Anesthesiology
58:314–321, 1983

Effects of Halothane, Enflurane, and Isoflurane on the SA Node

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The present experiments were carried out to study the influence of halothane, enflurane, and isoflurane on the electrophysiologic properties of single sinoatrial (SA) node cells of the guinea pig. The authors used the isolated, spontaneously beating guinea pig SA node superfused with modified Krebs' solution. These anesthetics were studied for their effects on spontaneous rate of discharge of the SA node cell, action potential amplitude, phase 4 dV/dt, phase 0 dV/dt, action potential duration, overshoot, maximum diastolic potential, and threshold potential. In addition, they have studied the interaction of increased extracellular calcium ion concentration with halothane, enflurane, and isoflurane (1 and 2 MAC). Anesthetic concentrations in the superfusing bath were measured using a gas chromatography procedure. Introduction of these anesthetics (1 and 2 MAC) for five minutes produced a significant decrease in the heart rate, decrease in the slope of the phase 4 and phase 0, and a decrease in the action potential duration. At concentrations of 2 MAC, these anesthetics produced a significant decrease in the action potential amplitude and its overshoot. There was no change in the threshold potential, and the maximum diastolic potential was decreased only with 2 MAC halothane. Increasing the extracellular calcium concentration counteracted the negative chronotropic effects of halothane, enflurane, and isoflurane. Addition of the calcium channel blocker, verapamil, potentiated the negative chronotropic effect of halothane. In the present study, a comparison of these anesthetics at equipotent anesthetic doses, indicated that their interaction with calcium does not appear to be competitive and calcium did not completely overcome the direct negative chronotropic effect of these potent anesthetics. (Key words: Anesthetics, volatile: halothane; enflurane; isoflurane. Heart: sinoatrial node. Membrane: cell, SA node.)

DURING THE ADMINISTRATION of inhalational anesthetics, alterations in heart rate and contractility have been reported by numerous investigators. Most of the data on chronotropic effects of inhalational anesthetics in the intact animal and human are difficult to interpret because of the many variables in these studies (surgical procedure, reflexes, different anesthetic concentrations, blood-gas changes, blood *p*H changes, drug interactions, species differences, different intrinsic heart rates, etc).

The rate of depolarization of SA node cells depends on the slope of phase 4 diastolic depolarization, the threshold potential, and the level of maximum diastolic potential. Contradictory reports have appeared in the literature dealing with the effects of inhalational anesthetics on the SA node. Hauswirth and Schaer[1] described the effect of halothane on the electrical activity of a single pacemaker fiber from the SA node of the rabbit and the spontaneously beating guinea pig atria. They found that the slope of phase 4 depolarization was decreased with a simultaneous decrease in the magnitude of the maximum diastolic potential. These opposing actions resulted in little change in mean atrial rate, since the threshold potential changed relatively little. Other studies have reported[2] a moderate slowing in the rate of phase 4 depolarization of the rabbit SA node after introduction of halothane. In these studies, halothane produced a marked decrease in the slope of phase 4 and maximum diastolic potential, overshoot, and action potential amplitude. The authors concluded that the negative chronotropic effects of both halothane and methoxyflurane were direct, since they could not be influenced by either atropine or propranolol. Krishna and Paradise[3] studied the effects of halothane, enflurane, and other anesthetics on isolated rat atrial preparations. They found that halothane in low concentrations depressed the frequency of contraction, whereas higher concentrations elicited a positive chronotropic effect. In their study, enflurane elicited a dose-dependent positive chronotropic effect.

In the present study the direct actions of halothane, enflurane, and isoflurane on the electrophysiologic properties of SA node cells were determined. In an attempt to clarify the mechanisms involved, we have compared the influence of these anesthetics on SA node cells in the presence of verapamil, epinephrine, atropine, increased calcium ion concentration, and electrical stimulation.

Materials and Methods

Thirty-one adult guinea pigs of either sex weighing 200–300 g were decapitated and their hearts immediately excised and placed in oxygenated Krebs' solution. The area of the sinus node was removed and mounted on the transparent Silastic® rubber floor (Sylgard-Dow Corning) of a tissue bath using fine (25 μm) tungsten wire pins. The tissue was superfused continuously at a rate of 15 ml/min with a modified Krebs' solution. The preparations were allowed to beat spontaneously with their endocardial surfaces uppermost. The Krebs' so-

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Received from the Departments of Anesthesiology and Physiology, The Medical College of Wisconsin, Milwaukee, Wisconsin. Accepted for publication August 26, 1982.

Supported by the National Institutes of Health (Grants HL 16511 and GM 29641) and the Medical Research Service of the Veteran Administration. Presented in part at the annual meeting of the American Society of Anesthesiologists, October 1981.

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0003-3022/83/0400/0314 $01.20

lution had the following composition (in mM): Na^+, 137; K^+, 5.9; Ca^{++}, 2.5; Mg^{++}, 1.2; Cl^-, 134; HCO_3^-, 15.5; $H_2PO_4^-$, 1.2; and glucose, 11.5. The fluid was equilibrated in a reservoir with a 97% O_2–3% CO_2 mixture and maintained at 37° C and *p*H 7.40 ± 0.05. Transmembrane potentials were measured by means of short tapered ultrafine tip glass microelectrodes. The microelectrodes were filled with 3 M KCl (50–80 MΩ resistance) and were placed on an electrode holder (WP Instruments, EH-1S) which was attached to a hydraulic microdrive and micromanipulator. Electrical activity was detected by means of an electrometer (WP Instruments M707) and a Tektronix® R5113 storage oscilloscope. Electrical activity was recorded simultaneously on an FM tape recorder (Tandberg Series 100), displayed on a digital oscilloscope (Nicolet Instrument Corp.), and either photographed or recorded on an X-Y plotter for permanent records. The resting membrane potential was measured as the potential change when the electrode was deliberately withdrawn from the cell into the bathing solution. Before administering the test solutions, the preparations were allowed to equilibrate in the bath for at least two hours.

Results are reported for experiments in which the same impalement was maintained without interruption throughout the determination of all control values and all changes were induced by the anesthetics and other drugs. Recordings were made for up to two hours in some SA node cells. Only those cells were selected for this study which satisfied the following criteria: a maximum diastolic potential of −55 to −65 mV, spontaneous phase 4 slow diastolic depolarization with slow transition to phase 0, action potential overshoot of less than 10 mV, and absence of phase 2 or plateau.[4] Thirty-one guinea pig hearts were studied with satisfactory recordings from three to six SA node cells in each preparation. Anesthetics were introduced by switching to superfusate equilibrated for 10 min with halothane (Draeger vaporizer) 0.75% and 1.5%, isoflurane (Ohio vaporizer) 1.4% and 2.8%, or enflurane (Ohio vaporizer) 1.7% and 3.4%. All anesthetics were administered with control periods (no anesthetics) interspersed between each anesthetic exposure. Electrophysiologic measurements were made before and five minutes after introduction of anesthetics. Analysis of anesthetic gases in the tissue bath were made during the control periods and during anesthetic exposure using a gas chromatograph (Perkin-Elmer) with a flame ionization detector. During the control periods, superfusion fluid contained no measurable amounts of anesthetic. During the anesthetic exposure concentrations in the bath were as follows: halothane: (0.4 and 0.9 mM), enflurane: (0.6 and 1.3 mM), and isoflurane: (0.9 and 1.57 mM).

Anesthetics were studied for their effects on the spontaneous rate of discharge of SA node cells; rate of rise of phase 4 and phase 0 in mV/s; APD_{50}—action potential duration at 50% amplitude in milliseconds; threshold potential; maximum diastolic potential, overshoot, and the total amplitude of the action potential. Since the action potential of the SA node has a characteristic smooth transition between the phase 4 and phase 0, the determination of threshold is arbitrary.[1] Therefore, threshold potential was taken as the point of intersection of two tangents, one along the slope of phase 4 and the other along the slope of phase 0 of the action potential.

The effect of atropine was studied in five preparations by addition to the stock solution of an amount sufficient to make a concentration of 1 μg/ml. Epinephrine hydrochloride (0.2 μg/ml) was administered in five preparations by continuous flow from the reservoir. In addition, we have electrically stimulated these preparations with bipolar tungsten electrodes connected to a stimulus isolation unit (2–8 mA, WP Instruments) at the control heart rates to overcome the negative chronotropic effect of these anesthetics. Verapamil was added to the superfusate to provide a concentration of 4×10^{-5} mM. Other concentrations of verapamil studied ranged from 10^{-4} mM to 10^{-6} mM. A verapamil concentration of 4×10^{-5} mM was chosen because it produced approximately the opposite effect on the heart rate as compared with an increase in the external calcium concentration from 2.5 to 5.0 mM. The effects of changes in calcium in the bathing medium were examined over the range of 0.5 mM to 5.0 mM, first without anesthetics, and then after equilibration with anesthetics.

Two-way analysis of variance was performed to detect differences among mean responses between control *vs.* 1 MAC and control *vs.* 2 MAC for each anesthetic. If this test was declared significant ($P < 0.05$), paired *t* tests were performed to test the sets of two means. Data analysis for calcium dose-effect curves were performed using the double reciprocal Lineweaver-Burk type of plot. A plot of 1/heart rate *vs.* 1/concentration of calcium yields a straight line that intersects the y-axis at 1/maximum heart rate.

Results

The effects of halothane, enflurane, and isoflurane on the electrophysiologic characteristics of guinea pig SA nodal cells from a typical preparation are shown in figure 1. The action potentials during the control and after a five-minute exposure to 2 MAC concentrations of anesthetics are superimposed at the slower and at the faster sweep velocity. The most prominent effect was a moderate slowing in spontaneous rate of discharge.

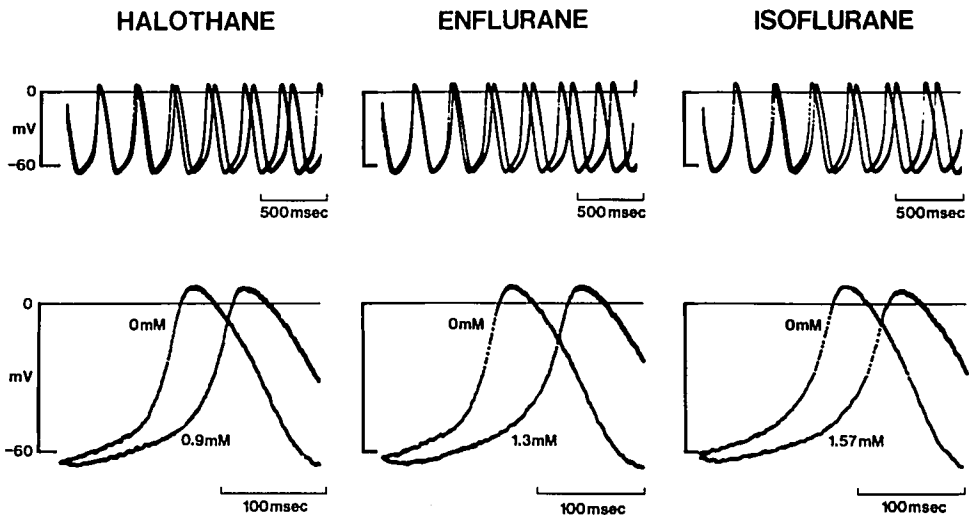

FIG. 1. The effects of halothane, enflurane, and isoflurane on the action potentials of spontaneously active fibers in the guinea pig SA nodal region. The action potential tracings of the control and after five minutes of the exposure to anesthetics (2 MAC) are superimposed at two different speeds and magnifications.

This was primarily the result of a reduced rate of rise of phase 4. The electrophysiologic properties of the SA node action potential in different concentrations of halothane, enflurane, and isoflurane are summarized from 31 experiments in table 1. With 1 and 2 MAC concentrations of anesthetic the heart rate, slope of phase 4, and slope of phase 0 showed significant decreases. The duration of the action potential (ADP_{50}) was increased at those concentrations of anesthetics. The action potential amplitude and the overshoot were significantly lower at 2 MAC for all anesthetics. There was no change in the threshold. A significant decrease of maximum diastolic potential occurred only with 2 MAC halothane. The effects of halothane, enflurane, and isoflurane on the sinus rate were identical in the presence of atropine (1 μg/ml) in five preparations for each anesthetic (table 2). Introduction of epinephrine hydrochloride (0.2 μg/ml), or electrical stimulation easily overcame the negative chronotropic effect in each preparation caused by 2 MAC halothane, enflurane, or isoflurane (five preparations for each anesthetic, table 2).

In six experiments we were able to record action potentials from the same SA node cell during the response to 1 and 2 MAC halothane, before and during superfusion with increased calcium, and before and during superfusion with verapamil. When the calcium concentration of the tissue bath was increased from 2.5 mM to 5.0 mM (typical effects are shown in figure 2), the following effects were observed: 1) a shortening of the beat-to-beat interval; 2) an increase in the rate of rise of phase 4 and phase 0; 3) an increase in the maximum diastolic potential (more negative); 4) an increase in overshoot; and 5) a decrease in the action potential duration. Introduction of verapamil (4×10^{-5} mM) to the control solution produced directly opposite effects on the above parameters (fig. 2). Figure 3 summarizes the effects of halothane (1 and 2 MAC) on the heart rate, dV/dt of phase 4 and phase 0 before and during ad-

TABLE 1. Effects of Halothane, Enflurane, and Isoflurane on the SA Node Action Potential

Treatment	HR (beats/min)	AAP (mV)	PH-4 (mV/s)	PH-0 (mV/s)	APD_{50} (ms)	OS (mV)	MDP (mV)	TP (mV)	N
Control	239 ± 5	66 ± 4	187 ± 16	2591 ± 213	81 ± 9	6 ± 1	60 ± 3	47 ± 4	9
1 MAC Halothane	225 ± 5†	64 ± 4	158 ± 15†	2260 ± 193†	86 ± 8†	5 ± 1	60 ± 3	47 ± 3	9
2 MAC Halothane	206 ± 6†	62 ± 4†	126 ± 13†	1952 ± 155†	89 ± 9†	3 ± 2*	59 ± 2†	46 ± 3	9
Control	228 ± 7	73 ± 3	180 ± 16	2509 ± 139	95 ± 4	9 ± 2	65 ± 2	52 ± 2	10
1 MAC Enflurane	216 ± 7†	72 ± 3	156 ± 14†	2275 ± 127†	100 ± 4†	8 ± 2	64 ± 2	52 ± 2	10
2 MAC Enflurane	204 ± 8†	70 ± 3*	135 ± 12†	1994 ± 115†	104 ± 4†	7 ± 1*	64 ± 2	51 ± 2	10
Control	246 ± 7	77 ± 3	189 ± 9	2923 ± 265	89 ± 2	10 ± 1	67 ± 3	52 ± 2	12
1 MAC Isoflurane	233 ± 8†	76 ± 3	154 ± 7†	2637 ± 243†	93 ± 2†	10 ± 1	67 ± 3	53 ± 2	12
2 MAC Isoflurane	222 ± 8†	73 ± 4†	142 ± 8†	2248 ± 224†	96 ± 3†	7 ± 2†	67 ± 3	52 ± 3	12

HR = heart rate; AAP = amplitude of the action potential; PH-4 = slope phase 4; PH-0 = slope phase 0; APD_{50} = action potential duration at 50% amplitude; OS = overshoot; MDP = maximum diastolic potential; TP = threshold potential; and N = number of successful experiments.

Values are means ± SEM.

* $P < 0.05$ *vs.* control value.

† $P < 0.01$ *vs.* control value.

TABLE 2. Heart Rate Changes

	Control	+ Anesthetic	Anesthetic + Atropine	Anesthetic + Epinephrine	Anesthetic + Electrical Stimulation	N
2 MAC Halothane	245 ± 10	224 ± 12*	223 ± 12*‡	297 ± 14†	245 ± 10	5
2 MAC Enflurane	232 ± 6	207 ± 7*	207 ± 7*‡	283 ± 8†	232 ± 6	5
2 MAC Isoflurane	254 ± 7	234 ± 7*	223 ± 7*‡	301 ± 8†	254 ± 7	5

N = number of experiments.
Values are means ± SEM.
* $P < 0.05$ *vs.* control.
† $P < 0.05$ *vs.* control and anesthetic alone.
‡ NS *vs.* anesthetic alone.

dition of calcium and verapamil. The introduction of calcium produced a parallel shift in the dose-response curve in an upward direction and blunted the overall depression of phase 4 and phase 0 as compared with the control. On the other hand, addition of verapamil produced a displacement of the dose-response curve downward and potentiated absolute depression of the heart rate and dV/dt of phase 0. All parameters measured in the presence of increased concentrations of calcium, and after addition of verapamil, were significantly different from the control values (calcium, 2.5 mM), before and during introduction of halothane (1 and 2 MAC).

From this part of the study it was apparent that the negative chronotropic action of halothane might be dependent on a calcium entry mechanism as indicated by a shift in the dose-response curve in the presence of excess calcium and the calcium entry blocker verapamil. Therefore, we decided to examine further the influence of external calcium ion concentration on the SA node in the presence of halothane, enflurane, and isoflurane. The calcium concentrations selected ranged from 0.5 to 5.0 mM. An example of typical dose-response curves for calcium alone and in the presence of halothane is shown in figure 4. Increasing calcium concentrations from 0.5 to 5.0 mM (in 0.5-mM increments) in the external bathing medium antagonized the depressant effect of 1 and 2 MAC halothane, enflurane, and isoflurane on the heart rate of pacemaker cells. This effect was analyzed by a Lineweaver-Burk type of plot (fig. 5). Interaction between the calcium and these inhalational anesthetics does not appear to be competitive because there is no common intercept of the extrapolated lines representing different anesthetic concentrations at the maximum heart rate on the y-axis.

Discussion

Any factor which changes the rate of phase 4 depolarization of pacemaker cells may produce alterations in heart rate and rhythm. A decrease in automaticity of primary pacemaker cells may permit the escape of a latent pacemaker, while an increase in automaticity of a latent pacemaker may permit it to assume the pace-

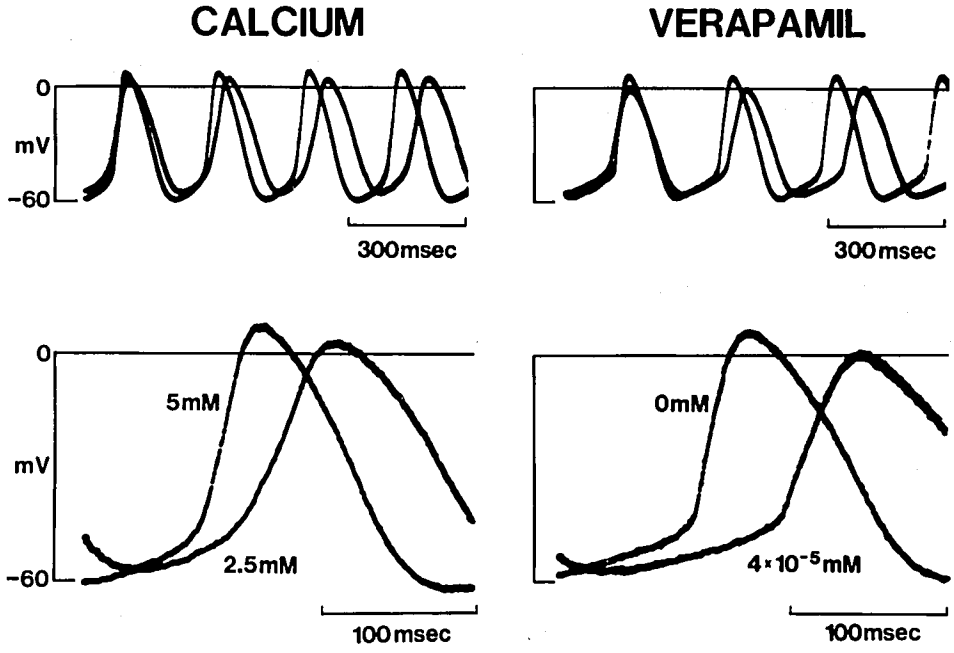

FIG. 2. The effects of increasing the calcium concentration in the superfusate medium from 2.5 to 5.0 mM are shown from a typical preparation at low and high speed and magnification. The effect of verapamil on the SA nodal cell also is shown with superimposed tracings.

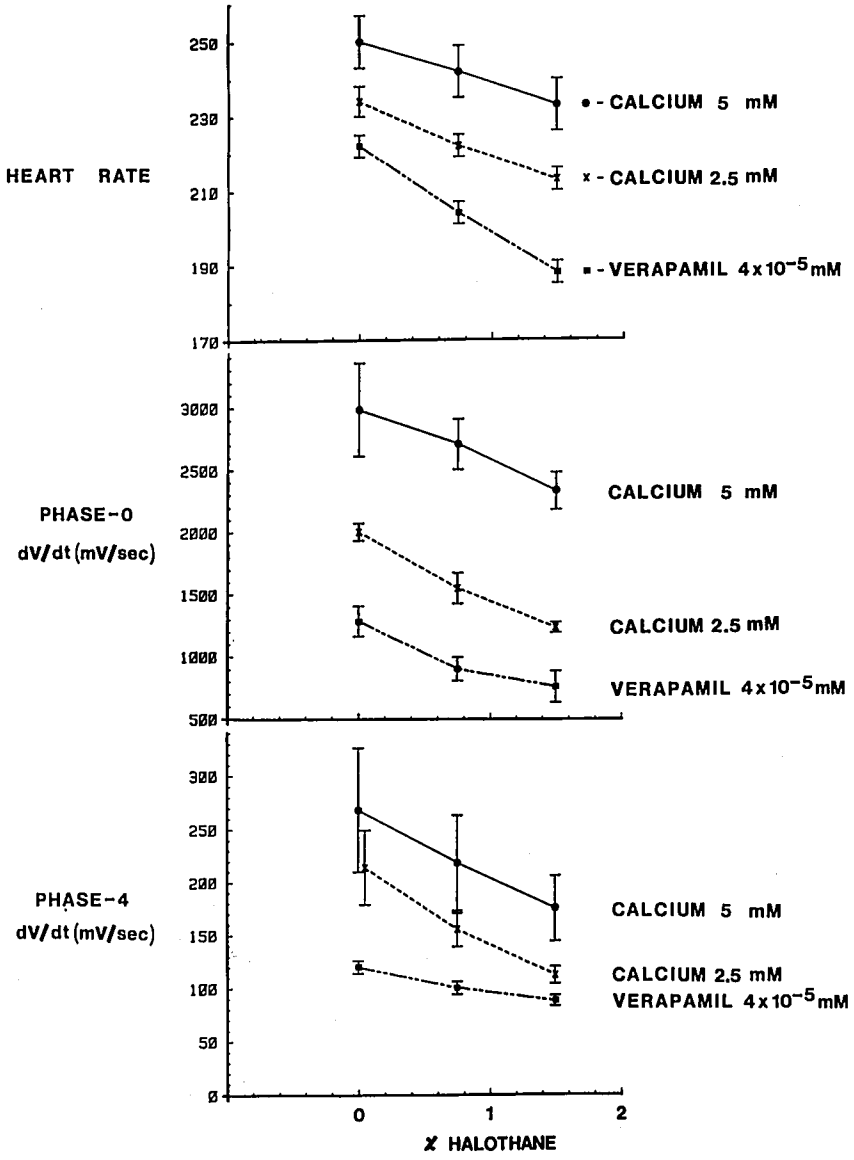

FIG. 3. The effects of 1 and 2 MAC halothane on spontaneously active fibers in the SA node before and during superfusion with increased calcium and before and during superfusion with verapamil. The heart rate, dV/dt (rate of rise in mV/s) of phase 4 and phase 0 were obtained from 6 SA nodal cells in six experiments. In these cells, single impalements were maintained throughout perfusion with calcium 2.5 mM, calcium 5.0 mM, and verapamil in that order.

maker role. In addition to their negative inotropic effects, effects on AV conduction and refractory period, the depressant effects of halothane, enflurane, and isoflurane on the action potentials of the SA node may result in sinus bradycardia, reentrant atrial rhythms, or sinus arrest.

The phase 4 depolarization in the sinus node is thought to be a result of a time-dependent fall in potassium conductance.[4-10] in the presence of an inward background current. The decay of the outward potassium current leads to diastolic depolarization.[8] The importance of calcium as a carrier of the inward current in the sinus node (along with sodium) is stressed by the fact that an increase in $[Ca^{++}]_0$ increases the sinus rate. Also, calcium antagonists suppress sinus node activity by decreasing the rate of phase 4 and phase 0 depolarization and the amplitude of the action potential.[11]

The rate of discharge of the sinus node is increased by a higher calcium concentration in the bathing medium through an increase in the slope of phase 4.[12] Thus, calcium may be carrying inward current not only during the action potential but also during the phase 4 depolarization of pacemaker cells. The process of diastolic depolarization and its control has been shown to differ in atrial and ventricular pacemakers.[8]

The inward current in the sinus node may be carried by both sodium and calcium ions, since sodium withdrawal diminishes upstroke velocity and overshoot in the isolated SA node of the rabbit.[13] It has been shown that halothane produces pronounced depression of the

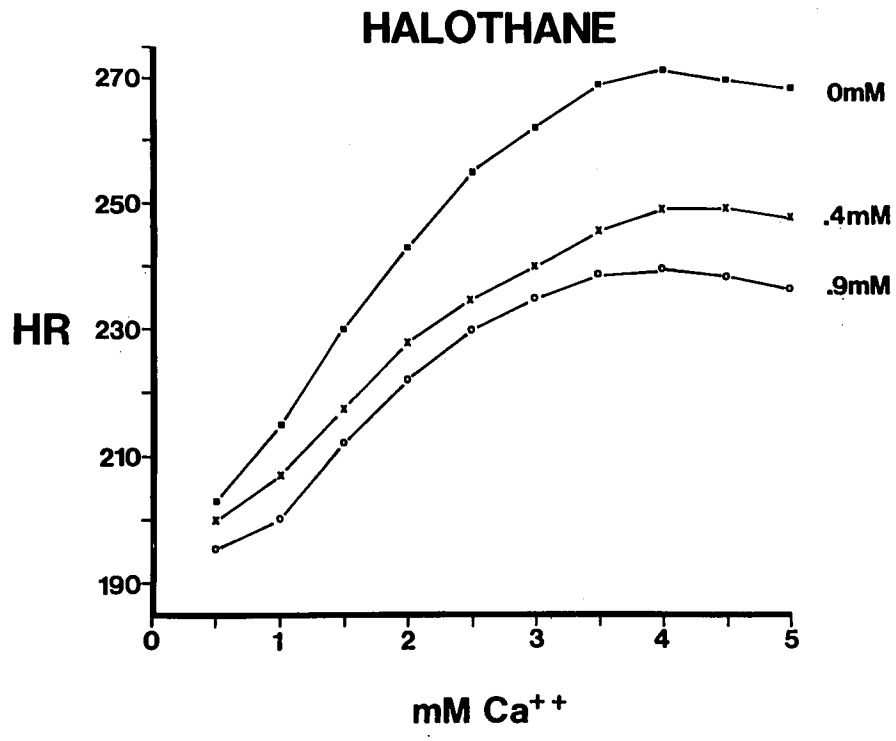

FIG. 4. Typical dose-response curves for calcium with 0, 0.4, and 0.9 mM halothane.

inward calcium current through voltage-dependent slow channels in partially depolarized papillary muscle cells.[14] It was postulated that halothane restricts the availability of calcium to the contractile proteins or inhibits the reaction between the calcium and these proteins.[15] Inhibition of myofibrillar ATPase (adenosine 5'-triphosphatase) by halothane and isoflurane also was suggested.[16] The depression of cardiac muscle function by halothane appears to be reversed by calcium.[15,17] Isoflurane also produces a dose-related depression of ventricular function in the intact dog, although the depression appears to be somewhat less than that seen with halothane and enflurane.[18] In addition, ventricular arrhythmias appear to be less common during maintenance of isoflurane anesthesia as compared with halothane anesthesia.[19] Although isoflurane, halothane, and enflurane decrease systemic arterial pressure, their mechanisms differ.[20] Isoflurane appears to depress systemic arterial pressure mainly by reducing the total peripheral resistance. In contrast, halothane and enflurane primarily affect the blood pressure by reducing the cardiac output.[20]

The effects of inhalational anesthetics on cardiovascular function and on electrical activity of cardiac cells

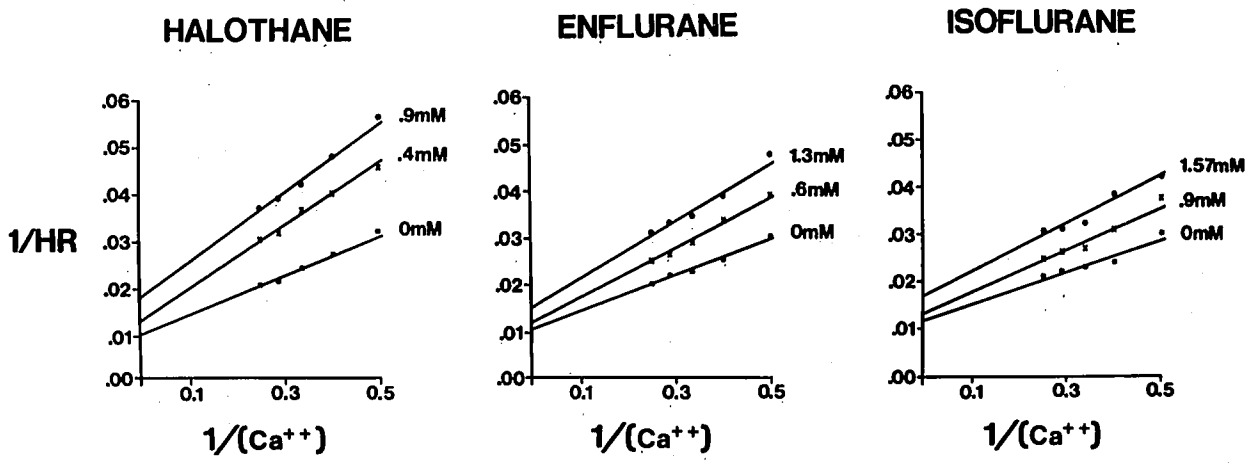

FIG. 5. Relation of maximal heart rate developed (1/HR) and calcium concentration ($1/Ca^{++}$) in the absence and in the presence of 1 and 2 MAC halothane, enflurane, and isoflurane.

have been reviewed.[20-23] The purpose of the present study was to focus upon the direct actions of halothane, enflurane, and isoflurane on the SA node.

We have found marked similarities in the effects of halothane, enflurane, and isoflurane on primary pacemaker cells of the guinea pig SA node. These anesthetic agents affected the rate of discharge of the SA node primarily by their effect on the rate of phase 4 depolarization. The threshold potential did not change while the maximum diastolic potential decreased slightly only with 2 MAC halothane. Decreasing the rate of phase 4 depolarization of SA node cells decreases heart rate and favors the emergence of pacemaker function in lower automatic cells unless they are similarly affected. These findings alone cannot account for the differences in clinical incidence of arrhythmias using the three agents studied. As noted, the incidence of ventricular arrhythmias following epinephrine injection is greater during halothane anesthesia as compared with isoflurane anesthesia.[19] In addition to direct effects of volatile agents on myocardial tissue, this group of anesthetics may in different degrees alter systemic blood pressure, respiration, acid-base balance, activity of the autonomic nervous system, myocardial sensitivity to catecholamines, A-V conduction, and other factors which may influence the incidence of arrhythmias in clinical situations. The mechanism of the direct negative chronotropic effects of these inhalational anesthetics is unclear, but appears to involve calcium influx across the cell membrane of the pacemaker cells. In addition, a decreased slope of phase 4 depolarization could be due to a relative decrease in the sodium influx or to a relative increase in potassium outflux. The factors underlying pacemaker activity and their importance in the pacemaker current has been a subject of numerous investigations.[1,2,4,6,8,-10,24-26] The slow inward current plays a major role in the phase 4 depolarization of the SA node. Other evidence in favor of such a hypothesis is that the amplitude of the slow inward current decreases when the extracellular calcium concentration is lowered.[26] The present investigation and other studies[11] show that verapamil decreases the spontaneous impulse initiation by the SA node. On the other hand, an increase in the extracellular calcium (up to 5–7 mM) leads to an increase in the rate of rise of phase 4 and an increase in the heart rate. Elevation of the extracellular calcium concentration above 8 mM, however, results in a decrease in heart rate,[12] and a decrease of the slow action potential overshoot.[27] This decrease is attributed to the accumulation of intracellular calcium. There are differences between these observations *in vitro* and those commonly noted in conscious intact animals and humans. In intact animals and humans, an increase in the extracellular calcium might not lead to an increase in heart rate, either due to individual or species differences, varying ionic concentrations of calcium associated with differences in buffer capacity, protein binding, and various extravascular labile pools. In addition, chronotropic effects at low calcium concentrations may be altered by changes in AV conduction and contractile force. Increases in calcium ion concentration in intact animals and in humans produce positive inotropic effects which may in turn result in increased left ventricular pressure and arterial blood pressure. Such increases in arterial blood pressure usually result in baroreflex-mediated decreases in heart rate. Indirect evidence for effects of altering calcium ion availability has been obtained from studies of the effects of calcium entry blockers.[28-31] Some of the calcium entry blockers may have widely varying effects on heart rate because of differences in their target organ affinity and differential effects on the SA node. Thus, verapamil which may be useful in controlling atrial rate and AV conduction in supraventricular tachycardia, differs from nifedipine which frequently results in reflex atrial tachycardia secondary to its hypotensive effects related to inhibition of calcium entry in vascular smooth muscle.

Our findings confirm the earlier halothane studies,[2,3] in that the effects of halothane, enflurane, and isoflurane on the isolated SA node are not due to an interaction with the intrinsically released autonomic mediator, acetylcholine. The slowing of phase 4 depolarization could be reversed easily with epinephrine. In addition, the effects of these anesthetics could be overcome with electrical pacing of the SA node.

In conclusion, there is a strong interaction between halothane, enflurane, and isoflurane and the slow ionic currents responsible for phase 4 and phase 0 in SA nodal tissue. The direct negative chronotropic effect of these agents appears to involve the slow calcium current but may not be explained solely on the basis of this membrane effect, since it was not completely reversed by excess calcium. The effects of these anesthetic agents on SA node pacemaker cells do not appear to be mediated by a competitive interaction with calcium entry mechanisms, and the results of our study indicate that these potent inhalational agents also may affect other ionic currents responsible for the SA node action potential. If is apparent that the interaction of calcium and anesthetics merits continued investigation.

The authors thank Ohio Medical Products for their generous supply of isoflurane.

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