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Effects of Halothane With and Without Histamine and/or Epinephrine on Automaticity, Intracardiac Conduction Times, and Development of Dysrhythmias in the Isolated Guinea Pig Heart

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Histamine is released during allergic reactions, and is known to produce cardiac dysrhythmias. The authors compared the cardiac effects of histamine and epinephrine during exposure to halothane in the isolated perfused guinea pig heart. Responses studied were spontaneous sinus rate, intra-atrial conduction time, atrial-septal conduction time (ASCT), intraventricular conduction time (IVCT), and left ventricular pressure (LVP). The incidence and type of dysrhythmias with histamine and halothane and with epinephrine and halothane were analyzed from electrograms. The authors found that halothane alone (0.7 to 2.1 vol%) causes dose-dependent depressions of sinus rate and LVP, prolongs ASCT and IVCT, and produces atrioventricular (AV) block with junctional bradycardia. Histamine alone (.01–10 μM) increases sinus rate and LVP but, like halothane, prolongs ASCT. Halothane antagonizes the inotropic and chronotropic effects of histamine, but enhances ASCT compared with histamine alone. Histamine with halothane greatly increases the incidence of junctional tachycardia with AV dissociation from 0% with histamine alone up to 48%. Epinephrine alone (0.1–5 μM), like histamine, increases sinus rate and LVP, but does not cause a relative increase in ASCT. Halothane antagonizes the inotropic and chronotropic effects of epinephrine, but increases the incidence of ventricular tachycardia from 6% to 28%, and the incidence of premature ventricular excitations from 0% to 40%, compared with epinephrine alone. The authors' *in vitro* findings show that histamine and halothane, like epinephrine and halothane, can cause dysrhythmias, but that the genesis and type of dysrhythmias induced by these agents are dissimilar. Consequently, the release of histamine with an anaphylactoid reaction during halothane anesthesia, and the treatment of the reaction with epinephrine, could result in dangerous ventricular tachydysrhythmias. (Key words: Anesthetics, volatile: halothane. Animal: guinea pig. Drugs: epinephrine; histamine. Heart: atrioventricular conduction time; contractility; dysrhythmias; intraventricular conduction time; isolated.)

ALLERGIC REACTIONS to drugs and blood products are not uncommon during anesthesia.[1] Histamine is the most important chemical mediator released by mast cell degranulation upon stimulation by an allergen. Although histamine produces peripheral vasodilatation, it is a potent direct stimulator of cardiac rate and contractile force.[2] Histamine increases sinoatrial (SA) nodal and atrioventricular (AV) nodal automaticity, and enhances ventricular cell contractility in all species studied, including humans.[3] The positive chronotropic and inotropic effects are produced by histamine-type 2 (H_2) receptor agonists, and are blocked by H_2 receptor antagonists.[3] Histamine also slows conduction at the AV node in the many species studied.[3] In the guinea pig, this effect has been shown to be mediated by H_1 receptor agonists and inhibited by H_1 receptor antagonists.[4] Histamine itself can produce dysrhythmias. In the ventricle, histamine enhances normal automaticity of Purkinje fibers and induces abnormal automaticity of Purkinje fibers and working myocytes.[3] Ventricular tachydysrhythmias produced by histamine in hearts with AV block have been shown to result from enhanced ventricular automaticity and changes in ventricular pacemaker sites.[5] In the isolated guinea pig atrium, as little as 0.1 μM histamine has been shown to decrease the fibrillation threshold by 50%.[6]

Halothane, unlike histamine, is a potent direct inhibitor of automaticity and contractility in denervated and isolated hearts, and in the intact human heart.[7] However, like histamine, halothane slows conduction at the AV node.[8] Halothane is well known to sensitize the heart to dysrhythmias produced by catecholamines, an effect which appears to be mediated by both alpha and beta receptors.[9] Histamine is itself released in response to sympathetic stimulation, and may blunt the effects of catecholamines.[10] Cardiac release of histamine, like catecholamine stimulation, may produce serious dysrhythmias during halothane anesthesia; these may worsen if epinephrine is used for the treatment of an allergic reaction.[11]

There are no known reports on the direct effects of halothane and histamine, nor of halothane with epinephrine and histamine, on cardiac function and on the development of dysrhythmias. Such a comparative study might furnish useful information on the genesis and severity of dysrhythmias induced with these agents. The aims of this study were: 1) to examine the individ-

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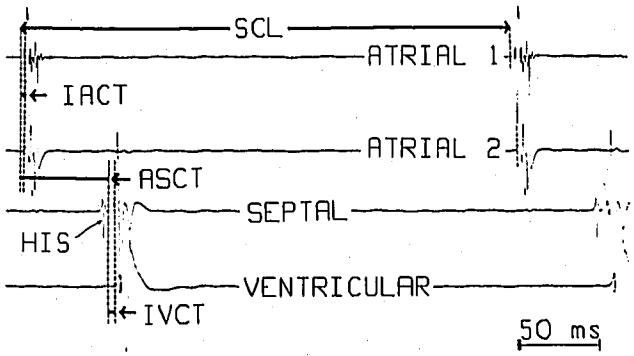

FIG. 1. Sample control tracings of electrograms obtained from the isolated heart showing intervals for determination of intracardiac conduction times. HIS = apparent His bundle deflection appearing before septal deflection; SCL = sinus cycle length; IACT = intra-atrial (superior = 1, inferior = 2) conduction time; ASCT = atrial septal conduction time; IVCT = intraventricular conduction time.

ual and combined direct cardiac effects of histamine and halothane, and of epinephrine with halothane and/or histamine, on cardiac automaticity, ventricular pressure development, and intracardiac conduction times; and 2) to systematically identify and characterize any dysrhythmias which might arise during treatment with these agents.

Materials and Methods

Thirty-two albino English short-haired guinea pigs (400–600 g females) were injected intraperitoneally with 10 mg of ketamine and 500 units of heparin, and were killed 10 min later when unresponsive to noxious stimulation. In each animal, the inferior and superior vena cavae were cut, and the aorta was cannulated distal to the aortic valve. The heart was removed within 1 min after perfusing the heart retrograde through the aorta with a modified Krebs-Ringer solution (in mM: Na^+ 137, K^+ 5.9, Mg^{++} 1.2, Ca^{++} 2.5, Cl^- 134, HCO_3^- 15.5, $H_2PO_4^-$ 1.2, glucose 12, mannitol 16.4) equilibrated with a 97% O_2 and 3% CO_2 mixture (pH 7.41 ± .02). EDTA (ethylenediaminetetraacetic acid 99%) was added to the perfusate to a concentration of 50 μM to inhibit oxidation of epinephrine. Each heart (average 2.8 ± 0.1 g) was submerged in a bath of perfusate solution; perfusate and bath temperatures were maintained at 37 ± 0.1° C (SEM) using a thermostatically controlled water circulating system (Haake® E52). The vasculature of the isolated heart was perfused by a pump (Masterflex® 7520) at 8–10 ml/min to maintain a stable aortic root pressure (mean 52 ± 4 mmHg). Left ventricular pressure (LVP) was measured with a transducer (Gould-Statham® P23) connected to a thin, saline-filled latex balloon inserted into the left ventricle through the mitral valve from a cut in the left atrium; balloon volume was adjusted to maintain a diastolic pressure of zero.

Four pairs of bipolar plunge electrodes (teflon coated silver, diameter 125 μm, Cooner Wire Company, Chatsworth, CA) were placed selectively in the heart to monitor intracardiac electrograms from which spontaneous sinoatrial rate and conduction times were measured (fig. 1). Electrodes placed in the superior right atrium and in the inferior right atrial appendage were used to measure intra-atrial conduction time (IACT); those placed in the superior left ventricular septum and in the anterior right ventricular wall were used to measure intraventricular conduction time (IVCT). Sinus cycle length (SCL) was measured from the superior right atrial beat-to-beat interval; atrial-septal conduction time (ASCT) was determined from the superior right atrial beat to left ventricular septal beat interval. A His bundle electrogram deflection, as shown in figure 1, was often recorded by the high septal electrode. In some studies, the superior right atrial electrode was alternatively used to selectively pace the heart (5 ms pulse, 0.1–1 V) over 20 min at 0.5 Hz intervals from 3 to 6 Hz. The four electrode signals were amplified 100–1000-fold, were filtered at frequencies below 1 Hz and above 10 K Hz, and were displayed continuously on a polygraph and on an image storage oscilloscope (Tektronix® 5A26, 5113). One atrial and one ventricular electrogram were audibly amplified. Electrograms, LVP, perfusion pressure, and a calibrated 50-ms square wave pulse signal were intermittently tape recorded (Vetter® D1) at 38 cm/s for playback later at 2.4 cm/s. Electrogram intervals were measured from polygraph tracings recorded at paper speeds of 50 or 100 mm/s by an observer blinded to the treatments.

After a stabilization period of 30 min, group I hearts (N = 16) were exposed stepwise to logarithmically increasing concentrations of histamine (0.01–10 μM) by adding known aliquot concentrations of stock histamine dihydrochloride USP (Sigma®) to a known volume of the perfusate. Group II hearts (N = 16) were similarly stabilized and exposed to logarithmically increasing concentrations of epinephrine hydrochloride USP (Bristol®). Minimal exposure time at each increasing concentration of either histamine or epinephrine was 10 min. Five-minute, drug-free control periods were interposed between each period of increasing drug perfusion. Each heart of group I was exposed randomly to 0.7 and 1.4 volume % halothane for a minimum of 15 min before, during, and after perfusion with an increasing dose of histamine. Each heart of group II was exposed randomly to 0.7% halothane and/or 0.5 μM histamine before, during, and after perfusion with an increasing dose of epinephrine. Twelve of the group I and group II hearts were exposed additionally to 2.1

volume % halothane. Halothane USP (Halocarbon Labs,® Hackensack, NY) was vaporized (Ohio Medical Products, Madison, WI), and was introduced into the perfusate with the O_2, CO_2 gas mixture. Halothane was measured in the perfusate at the aorta from sealed, air-free 1 ml samples by gas chromatography, as described previously.[12] Measured mean concentrations of halothane (N = 20) were 179 ± 11 μM (0.7%), 409 ± 36 μM (1.4%), and 607 ± 31 μM (2.1%). Exposure to the three levels of halothane was randomized and was separated by halothane-free control periods of 20 min. Halothane concentration was less than 10 μM during control periods. Data were tape recorded when sinus rate and LVP had stabilized with any given treatment.

Hearts were monitored continuously for dysrhythmias with and without AV dyssynchrony by listening to the cadence of atrial and ventricular rhythms, and by observing changes in electrogram intervals on the storage oscilloscope. Only hearts in which there were no more than two singlet, uniform premature atrial or ventricular excitations/min during control periods were used in this study. If dysrhythmias occurred during exposure to a drug treatment, drug perfusion was continued an additional 3 min to determine if the altered electrogram pattern was stable or changing. The coronary vasculature was perfused continuously during dysrhythmias.

For these experiments, AV dissociation was defined by an asynchrony of the atrial and septal electrograms. Tachycardia was defined arbitrarily by an atrial, septal, or ventricular pacemaker rate exceeding 220 beats/min. Junctional tachycardia (JT) was defined by the presence of AV dissociation, and by the absence of any morphologic or temporal changes in septal and ventricular electrogram waveforms from those observed with sinus tachycardia. Sustained (>30 s) ventricular tachycardia (VT) was defined by the presence of uniform or multiform, septal or ventricular electrogram waveforms, and by an unstable and varying IVCT. Ventricular fibrillation (VF) was defined by a marked and widely varying IVCT interval and by a minimal or absent development of LVP.

Each heart served as its own control for treatment effects. All data are expressed as means ± standard errors of the mean. Pre- and post-control values for each variable were not significantly different ($P > .05$) by the paired t test, and, therefore, were averaged. Histamine dose effects *versus* the histamine-free control (horizontal data), at each of the two levels of halothane (group I), and the epinephrine dose effects *versus* the epinephrine-free control (horizontal data), at each of the levels of histamine and halothane, alone or together (group II), were evaluated by analysis of variance and subsequent comparison of means by least significant difference (LSD) testing using the Hewlett-Packard® (98820A) Statistical Library. The effects of halothane doses alone (group I controls), and of single concentrations of halothane and histamine alone or together (group II controls), *i.e.*, without exposure to increasing concentration of histamine or epinephrine, were similarly evaluated and compared (vertical data). Only comparisons with the averaged pre- and post-controls are shown. Because of dysrhythmias at higher concentrations of histamine or epinephrine, the decreasing number of data points for rates and LVP resulted in larger standard errors. The incidences of specific types of abnormal conduction patterns were summarized beginning with the threshold concentration of histamine (group I) or of epinephrine (group II), with or without halothane, at which there was a significant total incidence of conduction or rhythm abnormalities. Differences in the total incidences (% frequencies) of all types of conduction abnormalities and in the frequencies of identified specific types of dysrhythmias were analyzed by the Chi-square test. The dependence of ASCT on sinus rate during atrial pacing and drug treatments was analyzed by linear regression; differences in regression lines were determined by comparison of slopes.

Results

Halothane Alone

The effects of halothane alone on the isolated heart are shown in figure 2. Sinus rate and isovolumetric LVP (control 38 ± 3 mmHg) were greatly depressed as a function of halothane. ASCT and IVCT (control 8.3 ± 0.7 ms) increased with halothane as the spontaneous sinus rate decreased. IACT (control 11.8 ± 1.9 ms), not shown, did not change significantly with halothane. Junctional bradycardia with AV dissociation occurred in 18% of hearts exposed to 2.1% halothane.

Histamine Plus Halothane (Group I)

The log dose-cardiac effects of histamine alone and with halothane are shown in figure 3. Histamine alone decreased SCL from 313 ± 10 to 218 ± 5 ms, which reflects a sinus rate increase from 192 ± 7 to 276 ± 4 b/min. The effect of halothane, which alone increased SCL, plus histamine paralleled the effect of histamine which alone decreased SCL. A rise in LVP (control 36 ± 3 mmHg) accompanied the increase in sinus rate with histamine alone. Similarly, the combined effects of halothane, which alone depressed LVP, and histamine paralleled the effect of histamine which alone increased LVP. At histamine concentrations of 5 and 10 μM, the opposing chronotropic and inotropic effects of halothane and histamine became statistically indistinguishable. In contrast to its positive chronotropic and inotro-

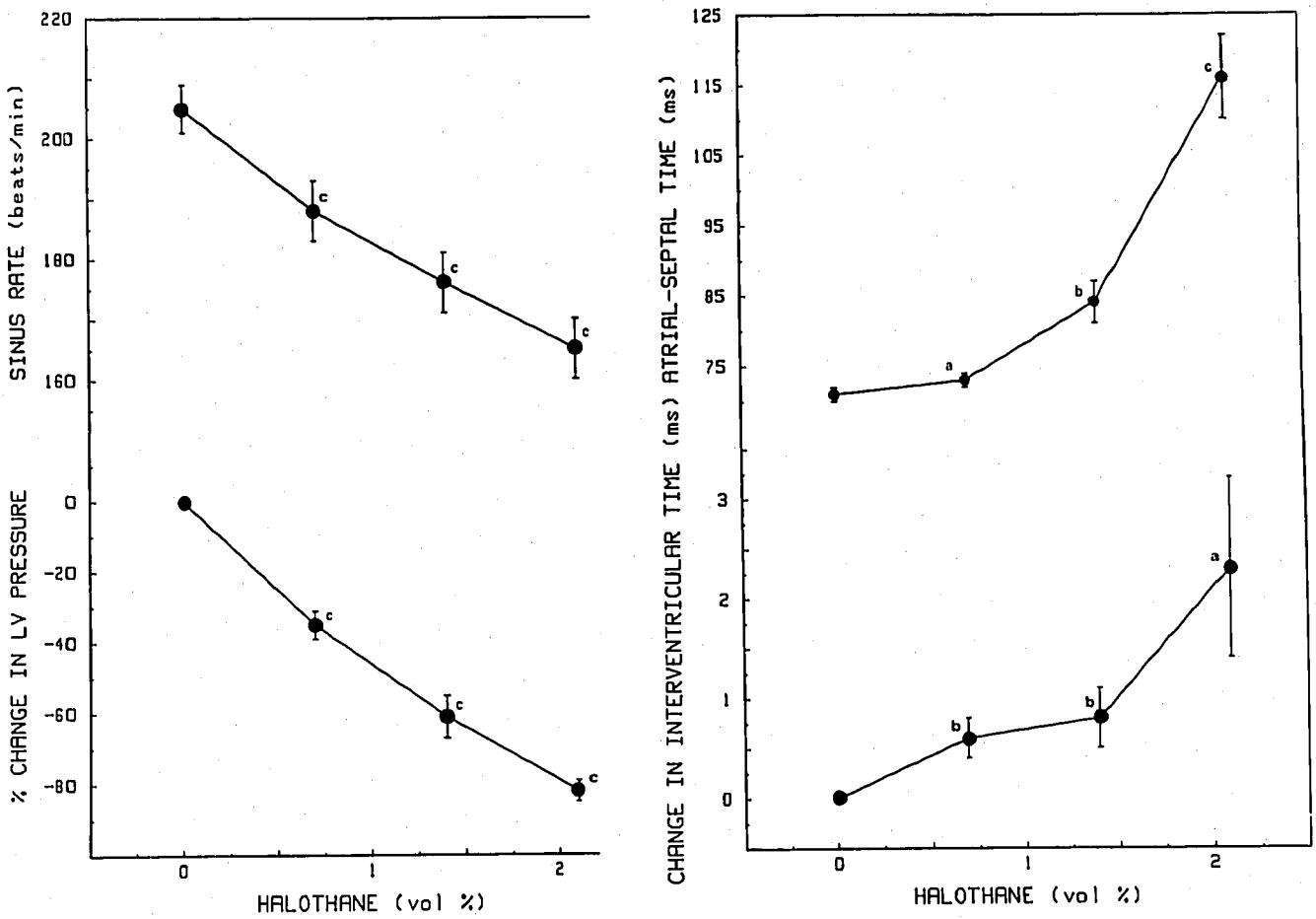

FIG. 2. Halothane effects on 12 isolated, perfused hearts beating spontaneously. Halothane was delivered by vaporizer and the administered dose was randomized. Halothane-free controls are averages of pre- and post-treatment effects. Halothane concentrations were: 179 ± 11 μM (0.7%); 409 ± 36 μM (1.4%); 607 ± 31 μM (2.1%). a = $P < .05$, b = $P < .01$, c = $P < .001$ *versus* halothane-free control.

pic effects, histamine alone produced a negative dromotropic effect, as shown by the increase in ASCT. The delay of conduction by histamine was little altered at 0.7% halothane, but was markedly accentuated by 1.4% halothane. Histamine did not alter significantly IACT (control 7.4 ± 1.2 ms) or IVCT (control 9.5 ± 0.9 ms).

Figure 4 summarizes the incidence of dysrhythmias of all types with AV dissociation observed with histamine alone and with halothane. Up to 1 μM histamine alone and with 0.7% or 1.4% halothane was not associated with any dysrhythmia other than sinus tachycardia. The threshold for developing dysrhythmias with histamine did not change with exposure to halothane; the incidence of dysrhythmias with AV dyssynchrony, however, increased from 13% at 5 μM histamine alone to 65% with 1.4% halothane ($P < .01$), and increased from 38% at 10 μM histamine alone to 91% with 0.7% and with 1.4% halothane ($P < .005$). In the presence of halothane, one-fifth as much histamine produced about the same incidence of dysrhythmias as did histamine alone.

Figure 5 details the frequencies of the final types of dysrhythmias produced by histamine and halothane. Since only 5 and 10 μM histamine produced any significant dysrhythmias, the incidences of the final type of dysrhythmias occurring at these concentrations were pooled. Histamine, 5 and 10 μM, produced neither JT nor VT with AV dissociation, but did cause a significant incidence of VF ($P < .05$). With either level of halothane plus histamine, there was a high incidence ($P < .01$) of JT with AV dissociation. The small increases in the incidence of VT and VF with halothane plus histamine were not significantly different from those of histamine alone. A maximal increase in ASCT always preceded the onset of JT with AV dissociation. Of those studies in which VT or VF occurred, JT preceded VT (100%) and VF (63%), and VT preceded VF (50%). The rate of junctional tachycardia was about 90% of the

rate of atrial tachycardia during AV dissociation. In all studies, including those below, washout of these agents and bolus infusion of 50 μg lidocaine completely converted JT or VT with AV dissociation to a sinus rhythm. In those hearts with VF, electrical defibrillation (1 Joule) was additionally required to successfully convert this dysrhythmia to a sinus rhythm. Dysrhythmias could be reproduced with these agents after washout of lidocaine.

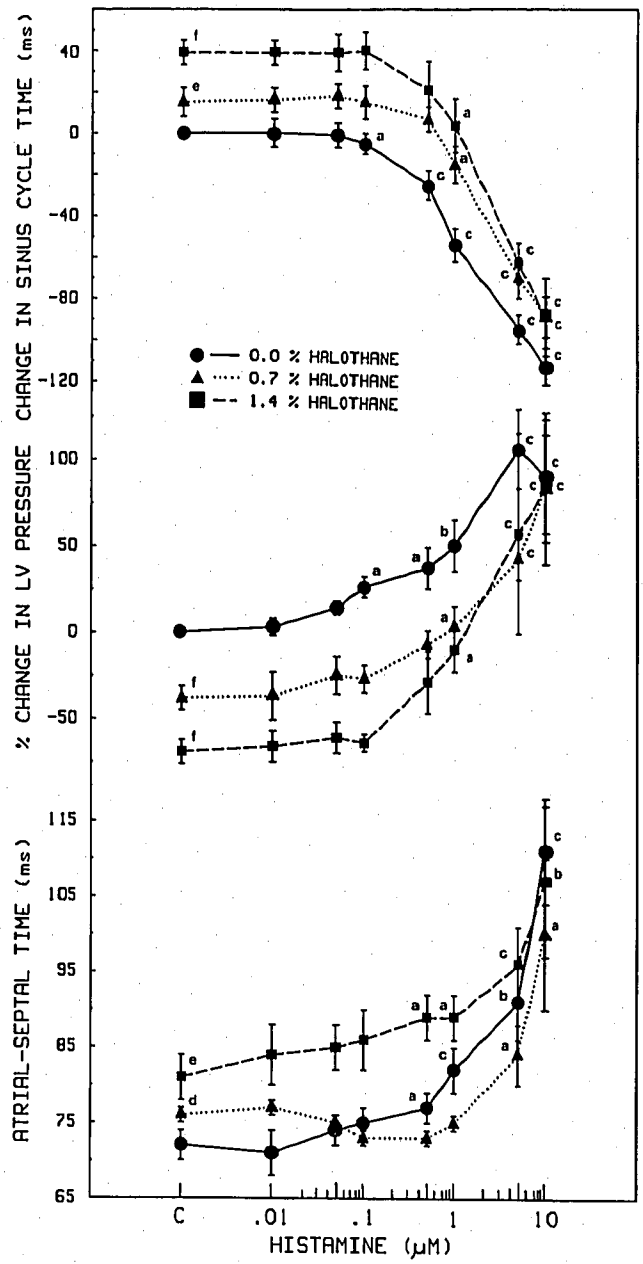

FIG. 3. Log dose-response effects of histamine alone and with halothane on isolated hearts (group I). Controls (C) are averages of pre- and post-treatment effects. a = $P < .05$, b = $P < .01$, c = $P < .001$ refer to histamine dose effects *versus* histamine-free controls at each of two levels of halothane (horizontal effects); d = $P < .05$, e = $P < .01$, f = $P < .001$ refer to halothane dose effects *versus* halothane, histamine-free controls (vertical effects). N = 16, 12, and 12 for control, 0.7% and 1.4% halothane treatments, respectively. Dysrhythmias with higher histamine levels account for increased variability of means.

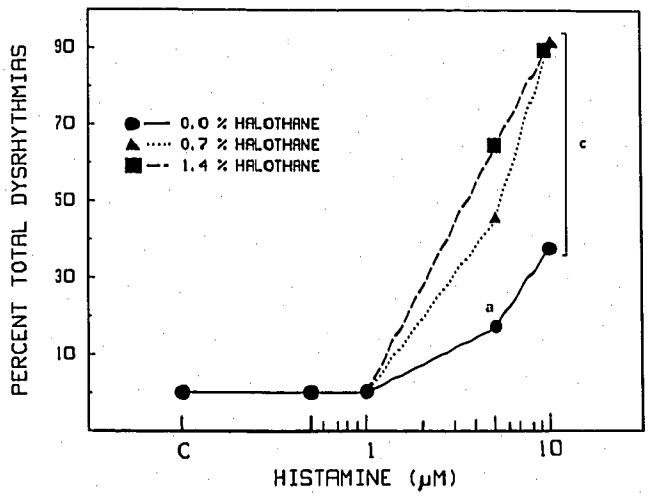

FIG. 4. Percentage of group I hearts exhibiting dysrhythmias of all types 3 min after the onset of a dysrhythmia during perfusion with a constant concentration of histamine alone or with exposure to halothane. a = $P < .05$ and c = $P < .001$ refer to significance of incidences.

EPINEPHRINE PLUS HISTAMINE AND HALOTHANE (GROUP II)

In the second group of experiments, the concentrations of histamine (0.5 μM) and halothane (0.7%), which produced, respectively, a 40% increase ($P < .05$) and a

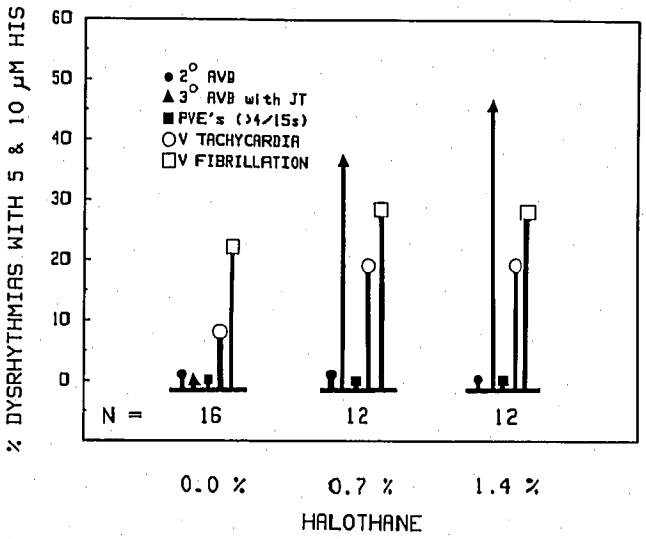

FIG. 5. Percentage of group I hearts exhibiting a defined, final type of dysrhythmia under conditions described as in figure 4. AVB = atrioventricular block; JT = junctional tachycardia; PVEs = preventricular excitations; V = ventricular. See text for significance of incidences with treatments.

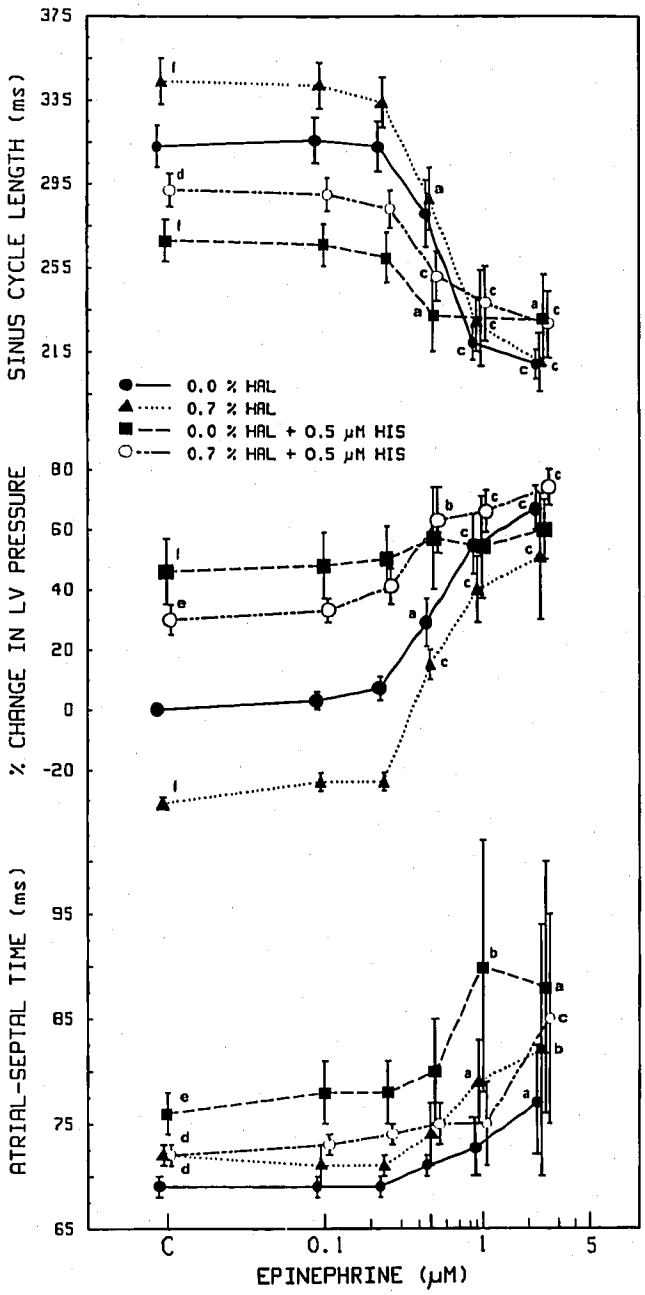

FIG. 6. Log dose-response effects of epinephrine alone and with histamine and/or halothane on group II hearts. Controls (C) are averages of pre- and post-treatment effects. a = $P < .05$, b = $P < .01$, and c = $P < .001$ refer to epinephrine dose effects *versus* epinephrine-free controls at each of the four halothane, histamine groups (horizontal effects). d = $P < .05$, e = $P < .01$, and f = $P < .001$ refer to halothane and histamine effects alone or together *versus* halothane-free, histamine-free controls (vertical effects). N = 14, 16, 12, and 14 for 0% halothane, 0.7% halothane, 0.5 μM histamine, and 0.7% halothane plus 0.5 μM histamine, respectively. Dysrhythmias with higher epinephrine levels account for increasing variability of means.

40% decrease ($P < .01$) of LVP in group I, were administered before, during, and after increasing steady-state concentrations of epinephrine. Chronotropic, inotropic, and dromotropic effects of epinephrine alone and with 0.5 μM histamine and/or 0.7% halothane are shown in figure 6. Like histamine, epinephrine increased both sinus rate, as shown by the decrease in SCL, and isovolumetric LVP. ASCT increased significantly only with doses of 2.5 μM epinephrine and larger. The effects of 0.7% halothane and 0.5 μM histamine alone or in combination to alter SCL and LVP generally paralleled the effects of increasing concentrations of epinephrine to 0.5 μM. With higher concentrations of epinephrine, the effects of halothane and histamine approached those of epinephrine alone. The increases in ASCT due to histamine and to halothane also paralleled the lesser effect of epinephrine alone to increase ASCT. IACT (control 6.9 ± 1.8 ms) and IVCT (control 9.3 ± 0.9 ms) were not altered by epinephrine as sinus rate increased.

Since hearts were not normally paced, sinus rate and ASCT changed simultaneously during drug treatments. Figure 7 compares the effects of pacing and drugs on the rate-dependence of atrial-septal conduction. ASCT was increasingly prolonged as sinus rate increased with either histamine, atrial pacing, or epinephrine. Linear regression slopes (m) and coefficients (r) were: histamine, m = 0.39, r = 0.85; pacing, m = 0.17, r = 0.95; and epinephrine, m = 0.08, r = 0.87. Comparison of linear regression slopes showed that, relative to pacing, ASCT was significantly prolonged ($P < .001$) with histamine and shortened ($P < .05$) with epinephrine as a function of sinus rate.

Figure 8 summarizes the incidence of dysrhythmias of all types with AV dissociation observed with epinephrine alone and in combination with halothane and/or

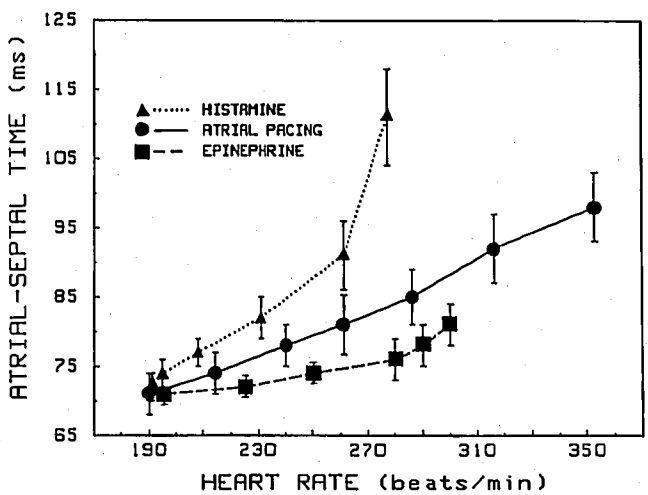

FIG. 7. Differences in atrial-septal conduction time as a function of sinus heart rate during perfusion with histamine alone, epinephrine alone, or with atrial pacing. Relative to atrial pacing, histamine greatly accentuated and epinephrine moderately attenuated the increase in atrial-septal conduction time with increased sinus rate.

histamine. No significant dysrhythmias, except sinus tachycardia, occurred with less than 5 μM epinephrine alone. The epinephrine log dose-response curve was shifted greatly to the left with the addition of halothane and/or histamine; in effect, similar incidences of dysrhythmia occurred with doses of epinephrine which were 10–20-fold less than with epinephrine alone. At 0.5 μM epinephrine and above, there were significant increases in the percentage of all dysrhythmias in the presence of halothane and/or histamine; there were no significant differences among the halothane, histamine, or halothane plus histamine data groups, but these groups differed significantly from the epinephrine group between 0.5 and 10 μM epinephrine.

Figure 9 details the frequencies of the final types of dysrhythmias with AV dyssynchrony produced by 0.5–10 μM epinephrine alone and with halothane and/or histamine. Since doses of 0.5 μM epinephrine and greater caused a significant total incidence of dysrhythmias, the incidences of the final types of dysrhythmias between 0.5 and 10 μM epinephrine were pooled. With epinephrine alone, the only dysrhythmia of significant incidence was JT with AV dissociation ($P < .05$); the combinations of epinephrine plus halothane, and of epinephrine plus halothane and histamine, also produced similar significant incidences of JT with AV dissociation ($P < .05$). The significant incidences of PVEs with 0.5–10 μM epinephrine and halothane ($P < .001$), with histamine ($P < .001$), and with both halothane and histamine ($P < .001$) were significantly greater ($P < .05$) than the incidences of PVEs with epinephrine alone. The significant incidences of VT with epinephrine and halothne ($P < .01$), and with halothane plus histamine ($P < .01$) were significantly greater ($P < .05$) than the incidence of VT with epinephrine alone. Compared with the response to epinephrine alone, the incidence of VF was unaltered by epinephrine in combination with halothane or histamine or with halothane plus histamine. In those studies in which VT or VF occurred, JT preceded VT (89%) and VF (75%), and VT preceded VF (25%). Of those studies in which PVEs were observed, 48% of the PVEs occurred during JT with AV dissociation.

Discussion

We used the isolated, perfused guinea pig heart to examine direct cardiac effects of halothane with histamine and epinephrine; 1) because we wished to extend to the intact guinea pig heart our electrophysiologic studies on the effects of volatile anesthetics and sympathomimetic agents,[12–15] and 2) because the guinea pig heart has a similar histamine dose-response curve to that of isolated human cardiac tissue.[3,6] Although ketamine has indirect sympathomimetic effects, it has a direct but small negative inotropic effect.[16] We observed that ketamine given prior to euthanasia did not alter the spontaneous *in vitro* rate compared to the rate obtained when halothane was given prior to euthanasia.

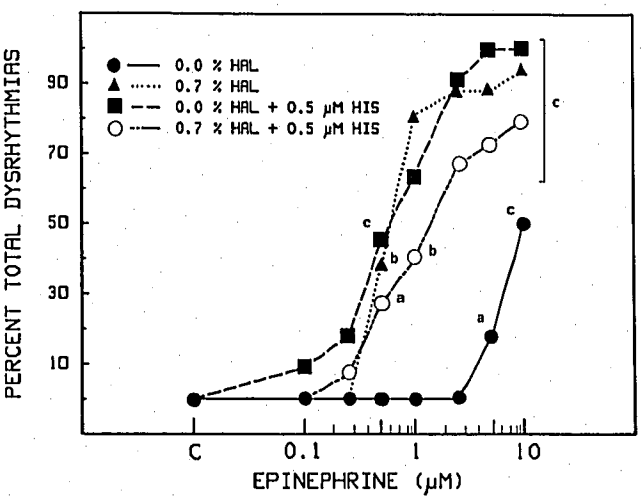

FIG. 8. Percentage of group II hearts exhibiting dysrhythmias of all types 3 min after the onset of a dysrhythmia during perfusion with a constant concentration of epinephrine alone or with exposure to halothane and/or histamine. a = $P < .05$, b = $P < .01$, and c = $P < .001$ refer to significance of incidence.

In summary, our findings are as follows.

First, halothane causes dose-dependent decreases in sinus automaticity (increases SCL), left ventricular pressure (LVP), ASCT, and IVCT while IACT is not altered. Dysrhythmic effects of halothane alone are sinus bradycardia with a progressive slowing of AV conduction and, at 2.1% halothane, junctional bradycardia with AV dissociation (18% of hearts).

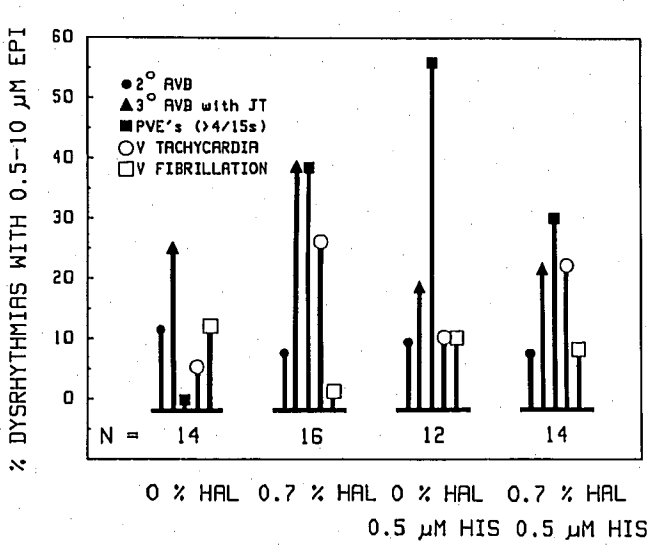

FIG. 9. Percentage of group II hearts exhibiting a defined, final type of dysrhythmia under conditions described as in figure 8. Legend as in figure 5. See text for significance of effects.

Second, histamine causes progressive increases in sinus automaticity, pressure development, and ASCT, but produces no changes in IACT or IVCT. Histamine slows AV conduction independently of its effect to increase sinus rate, as demonstrated by the much greater increase in AV conduction time compared with pacing alone. Dysrhythmic effects of higher steady-state doses of histamine alone are sinus tachycardia with a progressive slowing of AV conduction and, at higher doses, induction of VF (23% of hearts).

Third, halothane antagonizes the chronotropic and inotropic effects of histamine, but enhances the negative dromotropic effect of histamine; at the higher concentrations of histamine and halothane, the effects of halothane and histamine approach those of histamine alone. Dysrhythmic effects of halothane plus histamine are similar to those of histamine alone, with the added effect of a marked increase in junctional tachycardia with AV dissociation. This effect is consistent with the augmented increase in ASCT produced by the combination of the two negative dromotropic agents. In the presence of halothane, the dose of histamine necessary to produce a 50% incidence of AV block and any type of dysrhythmia is reduced to one-fifth of the amount required with histamine alone.

Fourth, epinephrine, like histamine, maximally increases sinus rate and LVP. But, unlike histamine, epinephrine does not enhance the rate dependence of AV nodal conduction time as seen by comparing the ASCT, sinus relationship of epinephrine with pacing and with histamine. Epinephrine, like histamine, does not alter IACT or IVCT as sinus rate increases. The dose of epinephrine necessary to produce a 50% incidence of dysrhythmias is reduced about 20-fold in the presence of halothane, histamine, or the combination of halothane and histamine. The incidence of junctional tachycardia due to epinephrine is not enhanced by halothane, but halothane significantly increases the incidences of PVEs and VT.

Fifth, importantly, the frequency of dysrhythmias with AV block produced by histamine plus halothane are dissimilar to those produced by epinephrine and halothane with or without histamine. Halothane with histamine increases the incidence of JT with AV dissociation, while halothane with epinephrine increases the incidences of PVEs and VT.

Halothane Alone

Our finding of dose-dependent depressions of isovolumetric LVP and sinus rate by halothane in the isolated perfused heart confirms the many other *in vitro* studies, *e.g.*, those on contractility[17,18] and sinus automaticity.[13,14,19] Depression of AV conduction time by halothane has been also reported in intact dogs,[8,20,21] and in isolated perfused rabbit[22] and cat[23,24] hearts. Halothane decreases the rate of rise of the phase 0 depolarization of SA nodal fibers.[13,14,19] AV nodal fibers, however, are relatively resistant to halothane because AV nodal activity is observed to continue even after maximal suppression of SA nodal activity by halothane.[24]

Although we did not directly measure conduction through the AV node, other studies in which His-Purkinje-ventricular muscle recordings were employed[8,20,21] show that the increasing delay of conduction between the atrial and ventricular conduction systems with halothane occurs primarily within the AV node. Although not quantitated in our study, recordings in which the His bundle deflection was evident show that the atrial-to-His interval changed more than the His-to-septal interval. In our study, IACT was not affected by halothane as sinus automaticity decreased. This supports our assumption that the increase in ASCT with halothane results from enhanced delay of conduction within the AV node, and not through delay in nonspecialized atrial tissue. Along with our observation of enhanced AV conduction delay with halothane, we found that halothane slightly increased IVCT, an effect reported by others.[8,20-22] We observed additionally that 2.1% halothane itself caused sinus bradycardia with AV block and a slow junctional rhythm in many hearts.

Although halothane has reflex, as well as direct cardiac effects in the intact animal and in humans, which makes results more difficult to interpret, many of the direct effects of halothane observed in our isolated animal heart model have also been reported in humans.[7] The mechanisms of the negative chronotropic and dromotropic effects of halothane are not well understood, but induced alterations in pacemaker currents, particularly the current carried by calcium,[14,15,25] are probably involved. Multiple effector sites of action have been implicated to account for the negative inotropic effects of halothane.[15,26] Several studies support the hypothesis that halothane slows conduction through specialized conduction tissue, as shown in canine Purkinje fibers[24] by the increase in refractory period, and in SA nodal cells[13,14,19] by the decrease in the slope of phase 4 depolarization.

Histamine Alone

Direct cardiac effects of histamine have been examined intensively by Levi *et al.*[2-6] Using the isolated guinea pig heart model, their studies showed that both exogenous and endogenous histamine induced positive inotropic and chronotropic effects, prolonged AV conduction, and caused AV dissociation at higher doses of histamine; they showed that the negative dromotropic effect was not a result of the increase in sinus rate.[2] The

positive inotropic and chronotropic effects of histamine were found to be completely blocked by H_2 receptor antagonists, whereas the negative dromotropic effect was inhibited by H_1 receptor antagonists.[4] They suggested that H_2 receptors are located in the SA node, while H_1 receptors are located in the AV node. Moreover, the histamine effects were not mediated through adrenergic or cholinergic receptors.[27] By varying extracellular K^+ and Ca^{2+} concentrations of solutions bathing SA nodal tissue and examining the action potential depolarization rates, they observed that norepinephrine, acting on beta$_1$ receptors, exerted very similar dose-response effects as did histamine on H_2 receptors.[28] The final common pathway for both H_2 and beta$_1$ receptor stimulation appears to be through an increase in cyclic 3'5' adenosine monophosphate,[29] which mediates an increase in the slow inward Ca^{2+} current.[30]

Histamine can produce dysrhythmias. In guinea pig hearts with surgically produced complete AV block, H_2 agonists enhance and H_2 antagonists attenuate the idioventricular rate at original and altered pacemaker sites.[5] The authors suggested that H_2 agonists, and, similarly, norepinephrine, enhance automaticity of idioventricular pacemakers and induce faster rhythms *via* re-entry circuits; re-entry could lead to triggered activity in normally quiescent fibers because of depolarizing afterpotentials. Even low concentrations of histamine (.01 μM) have been shown to reduce the ventricular fibrillation threshold in isolated guinea pig hearts,[6] an effect believed to be mediated by both H_1 and H_2 receptors.[31] In human atrial tissue,[32] histamine induces automaticity in quiescent preparations, increases automaticity of spontaneously beating fibers, and induces delayed afterpotentials and triggered activity at concentrations (1–10 μM) equivalent to those producing dysrhythmias in guinea pig hearts. Thus, stimulation of H_1 receptors, which slows AV conduction and which can result in complete AV block, and stimulation of H_2 receptors, and perhaps H_1 receptors, which enhances ventricular automaticity, together might facilitate development of ectopic ventricular pacemakers and lead to VT and VF.

The inotropic, chronotropic, dromotropic, and dysrhythmic effects of exogenous histamine which we observed in our study are very similar to those observed by Levi *et al.*[2–6] Moreover, we found that histamine had no significant effect on changing IACT or IVCT. We also examined in detail the progression of dysrhythmias with steady-state levels of histamine by carefully analyzing intracardiac electrograms. With increasing histamine, we observed a marked increase in ASCT which invariably preceded JT with AV dissociation, and which often preceded VT and VF. The effect of histamine to prolong ASCT appeared to be independent of the histamine-associated increase in sinus rate because the increase in conduction time with histamine was greater than that seen with pacing alone at any given sinus rate. Concurrent with the increase in ASCT, we saw a significant increase in VF and a small, nonsignificant increase in the occurrence of VT.

Histamine is contained in human cardiac tissue and can be released by appropriate chemicals and drugs.[3] The concentration of histamine is greatest in the right atrium, a location abundant in mast cells.[6] Agents which can induce significant histamine release include many anesthetic drugs, *e.g.*, d-tubocurarine, succinylcholine, morphine, ketamine, thiobarbiturates, trimethaphan, and foreign products, such as protamine and blood.[1] The dose and rate of administration of these agents is directly related to the release of histamine by mast cells and the resulting concentration of histamine in the plasma. In humans, for example, intravenous bolus doses of 0.5 mg/kg of curare and 1 mg/kg morphine have been shown to produce peak plasma histamine concentrations of about 4 μM and 10 μM histamine,[33,34] respectively. Moreover, reduction of systemic vascular resistance with 1 mg/kg morphine in man can be completely prevented by prior H_1 and H_2 blockade.[35] Even plasma histamine levels as low as 1.6 μM have produced tachycardia in 30% of human volunteers.[36] Hemodynamic monitoring during anaphylactic reactions in humans demonstrates increases in heart rate and stroke volume, along with decreases in blood pressure and systemic vascular resistance;[11,37] the inotropic and chronotropic effects probably result from the direct stimulatory effect of histamine on the heart and from an indirect autonomic effect triggered by hypotension.[11,37] Many kinds of tachydysrhythmias have been reported during anaphylactic or anaphylactoid reactions in humans.[3,11]

Halothane Plus Histamine

We know of no other reports on the direct cardiac effects of histamine during exposure to halothane. We found that halothane was effective in attenuating the positive inotropic and chronotropic effects of histamine. However, halothane accentuated the negative dromotropic effect of histamine. Although 0.7% halothane unexplicably blunted the effect of intermediate doses of histamine on conduction time, the marked additive increase in AV conduction time with histamine and 2.1% halothane was most likely responsible for the increased incidence of AV block and JT. This effect may be clinically significant because junctional rhythms, occasionally observed during general anesthesia, may also reflect a drug-induced increase in plasma histamine. With halothane exposure, we found small but insignificant increases in VT and VF as compared with histamine alone. Perhaps the concomitant attenuation

of sinus automaticity and of contractility by halothane protects the heart from dysrhythmias associated with, or induced by, the increase in AV conduction delay and eventual AV block. Further studies using selective H_1 and H_2 agonists and antagonists during halothane exposure may unmask the AV nodal effects of histamine from the inotropic, chronotropic effects, and may aid in determining the role of histamine in producing AV block and dysrhythmias with halothane.

Epinephrine Plus Halothane and Histamine

The cardiostimulatory effects of epinephrine are well known. Epinephrine has both beta- and alpha-adrenergic properties. The $beta_1$ agonist effects on sinus rate and contractility are similar to those effects of H_2 agonists.[10,28,38] Other beta effects include decreases in AV nodal refractory period and AV conduction time and increases in ventricular automaticity and vulnerability to dysrhythmias.[38] Cardiac alpha agonist effects include depression of automaticity of Purkinje and atrial conduction fibers.[38]

The incidence of ventricular dysrhythmias with epinephrine is markedly increased in the presence of halothane.[39] The arrhythmic dose of epinephrine (ADE) is defined as that dose of epinephrine that produces four or more PVEs within 15 s during 3 min of infusion.[9] The threshold for ventricular dysrhythmias for epinephrine is reduced several-fold in the presence of halothane in dogs.[9,40–43] The mechanisms underlying the increase in ventricular dysrhythmias generated in the presence of halothane are not known. Recent evidence[9,40,41] suggests that both alpha and beta effects are responsible, since alpha and beta blockade greatly reduces the ADE, and because concurrent administration of alpha- and beta-selective agonists increases the ADE.[41]

Our study shows that the isolated guinea pig heart can also be used to model the direct sensitization of the heart to epinephrine by halothane. We found that 0.7% halothane with and without 0.5 μM histamine caused a high incidence of PVEs as defined by the ADE in dogs. Epinephrine alone caused no significant individual incidences of second degree heart block, VT, or VF, but did produce a significant incidence (27%) of JT with AV dissociation. Histamine (group I) or epinephrine (group II) with 0.7% halothane caused about 40% incidences of JT with AV dissociation. In our study, the histamine- and halothane-induced increases in ASCT always preceded junctional tachycardia, and JT most often preceded the more serious ventricular dysrhythmias. Reynolds[24] has reported that exposure of the isolated, perfused cat heart to halothane and epinephrine causes a pacemaker shift from the SA to AV node, and suggested that this shift may be a major factor contributing to development of ventricular dysrhythmias. Our study shows that equimolar concentrations of histamine and epinephrine produce quantitatively similar positive inotropic and positive SA and AV chronotropic effects. The negative dromotropic effect of halothane coupled with its effect on alpha and beta sensitization may underlie the increased frequency of PVEs and of VT compared with epinephrine alone. Is it possible that histamine and halothane produce ventricular dysrhythmias, at least in part, through a mechanism different from that of epinephrine and halothane?

Our comparative study on histamine and epinephrine suggests that the genesis and progression of dysrhythmias induced with histamine and halothane and with epinephrine and halothane may be dissimilar. We observed a major difference in the effect of histamine and epinephrine on AV conduction, and similarities in the effects of histamine and epinephrine on sinus and AV nodal automaticity and of halothane and histamine on AV conduction. Halothane may promote ventricular tachydysrhythmias with histamine by progressively enhancing the delay in AV conduction caused by histamine alone. An increase in AV nodal automaticity with histamine, which may not be attenuated adequately by halothane,[24] coupled with complete AV block may allow escape ventricular dysrhythmias to develop *via* re-entrant excitation; this could appear as VT and rapidly progress to VF if the ventricular ectopy compromises cardiac perfusion. Histamine could reduce indirectly the incidences of VT and VF induced by epinephrine and halothane by attenuating the stimulatory effects of catecholamines.[10] However, histamine directly enhances development of VT and VF by increasing both AV nodal delay and AV automaticity. The above studies suggest that dysrhythmias produced with halothane and epinephrine develop through enhanced sensitization of ventricular tissue, leading to formation of ectopic foci (PVEs) with triggered activity leading to VT and VF. Dysrhythmias produced with halothane and histamine may develop, in part, through enhanced AV automaticity and decreased refractoriness of the conduction system. Coupled with a delay of AV conduction caused by histamine, these conditions could lead to re-entry and ventricular dysrhythmias. Halothane, however, could also indirectly attenuate the tendency to the development of cardiac dysrhythmias by reducing the positive inotropic and chronotropic effects of histamine as shown for catecholamines.[13,15,24] Halothane has also been shown to decrease the release of norepinephrine at adrenergic nerve endings.[44]

We cannot directly extend our *in vitro* results to humans. In the intact heart, baroreceptor reflexes and cardiotonic hormones may blunt the responses to these agents;[7] coronary perfusion *in vivo* may be compromised during dysrhythmias. Our findings, however, do

suggest that direct exposure of the heart to combinations of these agents at significant concentrations during anesthesia may predispose the heart to development of serious, life-threatening ventricular dysrhythmias. The concentrations of histamine and halothane used in our model are equivalent to those found in human plasma during studies in volunteers and during anesthesia. Indeed, a recent clinical study showed that supraventricular tachycardia (SVT) was the most common ECG finding during severe anaphylactic circulatory collapse;[11] moreover, in 2% of these patients, all of whom had received boluses of epinephrine and had undergone anesthesia with halothane, VF followed the onset of SVT. The study also showed that, during an allergic reaction in patients with pre-existing cardiac disease, the incidence of dysrhythmias other than SVT was 92%, compared to only 6% in patients without cardiac disease.

To avoid a histaminergic reaction, histamine-releasing agents, such as d-tubocurarine, morphine, and protamine, should not be administered rapidly. If a severe anaphylactoid reaction occurs during general anesthesia, as assessed by an abrupt onset of tachycardia, hypotension, wheezing, and erythema, halothane is best discontinued. H_1 and H_2 blockers may be given to retard the effects of histamine.[1] Subcutaneous or intravenous administration of epinephrine to retard mast cell release of histamine ($beta_2$ effect) and to counteract the peripheral vasodilatory effect of histamine (alpha effect) may be warranted, but exogenous epinephrine may contribute to the elevation of endogenous catecholamines resulting from hypotension. The $beta_1$ and $alpha_1$ effects of catecholamines may sensitize the heart and cause ventricular dysrhythmias in the presence of remaining significant cardiac levels of halothane and histamine. If circulatory function is not compromised, terbutaline, a relatively pure $beta_2$ agonist, is an alternative agent for treatment of bronchospasm and for inhibition of release of histamine by mast cells.

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