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Anesthetics and Automaticity in Latent Pacemaker Fibers: I. Effects of Halothane, Enflurane, and Isoflurane on Automaticity and Recovery of Automaticity from Overdrive Suppression in Purkinje Fibers Derived from Canine Hearts

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Knowledge of arrhythmic or antiarrhythmic actions of anesthetics on automaticity of latent pacemaker fibers has relevance to the intraoperative management of patients with bradyarrhythmia due to sinus node dysfunction or heart block. The authors determined the effects of halothane, enflurane, and isoflurane on automaticity and recovery of automaticity from overdrive suppression in canine Purkinje fibers derived from normal hearts. Purkinje fibers were superfused with a modified Krebs' solution (37° C) containing epinephrine (2 or 15 μM) and equilibrated with a 97% O_2–3% CO_2 gas mixture (control). Transmembrane action potentials (AP) were recorded using standard microelectrode techniques. Purkinje fibers were then exposed to anesthetics at vaporizer settings of 0.75 or 1.5% (halothane), 1.75 or 3.5% (enflurane), and 1 or 2% (isoflurane), which were equivalent to measured superfusate concentrations of 0.22 or 0.47 mM (halothane), 0.44 or 0.94 mM (enflurane), and 0.28 or 0.53 mM (isoflurane). Compared to control, there was no significant effect of either concentration of the anesthetics on upstroke (phase 0) depolarization, AP amplitude or duration (50% repolarization), or maximum diastolic potential. All three anesthetics increased spontaneous rate. The increase in rate with all three anesthetics was due to enhanced diastolic depolarization (rate dV/dt, phase-4 depolarization). Recovery times from overdrive suppression were determined after 30 or 60 s of pacing at drive cycle lengths of 800, 500, and 400 ms and only at higher anesthetic concentrations. Recovery of automaticity was shortened by halothane only in slowly paced fibers exposed to the lower concentration of epinephrine. Under all other conditions recovery times were not affected by halothane. Enflurane significantly shortened recovery times from overdrive suppression for most paced cycle lengths and durations at both concentrations of epinephrine, whereas isoflurane had little effect on shortening recovery of automaticity at either epinephrine concentration. The authors conclude that all three volatile anesthetics increase the rate of automaticity of normal Purkinje fibers exposed to epinephrine and that this increase is explained by enhanced phase 4 depolarization. Furthermore, recovery of automaticity from overdrive suppression is enhanced by enflurane but is little affected by halothane and isoflurane. (Key words: Anesthetics, volatile: halothane; enflurane; isoflurane. Animal: dog. Heart: arrhythmias; electrophysiology; automaticity. Purkinje fibers. Sympathetic nervous system, catecholamines: epinephrine.)

CARDIAC ARRHYTHMIAS are understood to be disorders of impulse initiation, propagation, or both. Among the mechanisms for impulse initiation are automaticity (spontaneous diastolic or phase-4 depolarization) and triggered activity or automaticity.[1,2] Automaticity may be normal or abnormal; the former occurs in primary or latent pacemaker cells with a normal diastolic membrane potential, and the latter in latent pacemaker or working myocardial fibers depolarized by the effects of disease or other interventions.[2] Knowledge of anesthetic drug effects on these mechanisms for impulse initiation is far from complete but is necessary for more complete understanding of mechanisms for intraoperative arrhythmias as well as anesthetic action.

As noted, normal automaticity is a property of primary (sinoatrial [SA] node) and latent pacemakers (atrial subsidiary pacemaker fibers, cells found in the AV junctional tissues, and Purkinje fibers). SA node pacemaker fibers, with the highest inherent automaticity, normally dominate latent pacemakers through the mechanism of overdrive suppression of automaticity.[3–6] Due to disease or other factors, the SA node may default with escape of the latent pacemakers, so that the latter control the rhythm of the heart for one or more beats (ectopic beats or rhythm). Alternatively, latent pacemakers may assume control of the heart's rhythm if their inherent discharge rate becomes greater than that of the SA node. Either of these postulated mechanisms for alterations in the normal relation between automaticity of primary and latent pacemakers (escape by default or usurpation) may be involved in the genesis of ectopic beats or rhythm disturbances in patients with sinus node dysfunction or atrioventricular (AV) heart block. However, the effect of anesthetic drugs

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on the relationships among pacemakers, and hence arrhythmia formation in patients with sinus node dysfunction or heart block, are incompletely understood. Particularly lacking are data for the effect of anesthetic drugs on normal mechanisms for automaticity in latent pacemaker fibers or for overdrive suppression of such automaticity by primary pacemakers.

Halothane, enflurane, and isoflurane are known to directly depress SA node automaticity.[7,8] Halothane in concentrations greater than 2% has been reported to slow automaticity of spontaneously active Purkinje fibers exposed to epinephrine,[9] but its effect on overdrive suppression of automaticity in such fibers has not been determined. Halothane also has been reported to increase ventricular escape time in dogs subjected to supramaximal right vagal stimulation.[10] In contrast to seemingly depressant effects of halothane on ventricular automaticity, enflurane has been reported to increase the spontaneous discharge rate of canine Purkinje fibers.[11] In addition, it reduced postoverdrive hyperpolarization in these same fibers,[11] suggesting that enflurane, by decreasing the time for diastolic (phase-4) depolarization to reach threshold, would facilitate recovery of automaticity from overdrive suppression if the SA node and AV node in some way defaulted. The effects of isoflurane on normal automaticity in Purkinje fibers, or on overdrive suppression of such automaticity, have not been reported.

Considerations such as these prompted us to assess the effects of clinically relevant concentrations of halothane, enflurane, and isoflurane on normal automaticity and overdrive suppression of automaticity in Purkinje fibers derived from normal canine hearts.

Materials and Methods

This research was approved by the Medical College of Wisconsin Animal Care Committee and conforms with standards set forth in the Guide for Care and Use of Laboratory Animals.¶ Adult mongrel dogs (10–22 kg) of either sex (n = 45) were anesthetized with pentobarbital sodium (30 mg/kg). The heart was quickly excised, and the anterior false tendon with attached papillary muscle from the left ventricle was removed and immersed in modified Krebs' solution (22° C) equilibrated with 97% O_2–3% CO_2. Small (less than 1 cm^2) preparations with free-running strands of Purkinje fibers were dissected from this tissue and pinned to the Silastic floor of a 2 ml chamber and superfused at a rate of 4 ml/min with modified Krebs' solution (37° C) containing epinephrine (2 or 15 μM in the superfusate reservoir) and equilibrated with a 97% O_2–3% CO_2 gas mixture. The millimolar composition of the Krebs' solution was: NaCl, 137; KCl, 3.8; $NaHCO_3$, 12; NaH_2PO_4, 1.8; $CaCl_2$, 2.5; $MgCl_2$, 0.5; glucose, 5.5; and EDTA, 0.05; the *p*H was 7.4.

Transmembrane action potentials (AP) were recorded using conventional microelectrode techniques. Glass microelectrodes (15–30 MΩ resistance) were coupled by Ag–AgCl wire to a preamplifier (World Precision Instruments, New Haven, CT). AP signals were recorded on frequency-modulated (FM) tape (AR Vetter Co., Rebersburg, PA) for later analysis of spontaneous rate, the rates (dV/dt) of phase-4 and phase-0 depolarization, AP duration at 50% repolarization, maximum diastolic potential, and AP amplitude measured electronically directly off the digital oscilloscope (Nicolet 310; fig. 1). Recovery from overdrive suppression was determined after 30 and 60 s of pacing (World Precision Instruments) at cycle lengths of 800, 500, and 400 ms. Recovery time was the time (in seconds) from the last paced to the first spontaneous beat after cessation of overdrive. Square-wave pulses were used for pacing and lasted 2 ms at 1.5 × threshold. Stimuli were provided by bipolar-Ag wire surface electrodes.

Anesthetics in the O_2–CO_2 mixture were introduced to the superfusate reservoir for at least 10 min *via* calibrated vaporizers at settings of 0.75 and 1.5% (halothane), 1.75 or 3.5% (enflurane), and 1 or 2% (isoflurane), equivalent approximately to 1.0 and 2.0 MAC for the dog.[12] Superfusate anesthetic concentrations equivalent to these settings were determined by gas chromatography from samples obtained from the tissue bath immediately after a 5-min washing period. Tissues were exposed to the desired concentration of anesthetic for at least 5 min prior to measurements. After measurements, there was a 10-min period for anesthetic wash-out.

Experiments lasted up to 330 min, during which time preparations were exposed to one or two concentrations of all three anesthetics at one or both epinephrine concentrations (2 or 15 μM). Changes in spontaneous rate

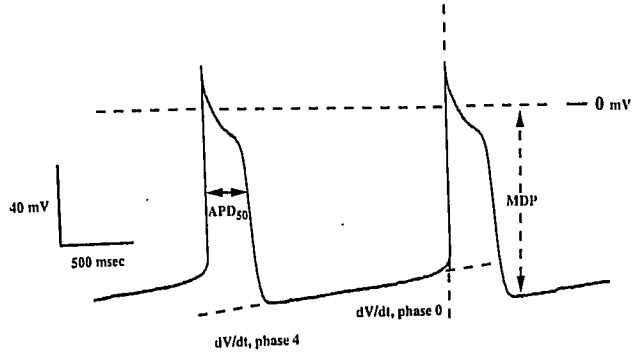

FIG. 1. Action potentials from spontaneously firing (exposed to 2 μM epinephrine) Purkinje fiber. An indication of the electronic measurements of action potential duration at 50% repolarization (APD_{50}), maximum diastolic potential (MDP), diastolic (dV/dt, phase 4), and upstroke depolarization (dV/dt, phase 0) is shown.

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of automaticity over time during exposure to either epinephrine concentration but in the absence of anesthetics are provided in table 1. Data are provided for experiments in which anesthetics were administered as well as for experiments in which no anesthetics were administered. Because there was a small reduction in rate (< 10%) over time in both groups of time controls, control data for each test condition were bracketed (average of values before and after exposure to anesthetic) for data tabulation and statistical analysis.

Data are provided as means ± standard errors of the means (SEM). Statistical analysis was performed by paired and unpaired *t* tests as well as by analysis of variance with the Duncan multiple-range test, as appropriate; $P < 0.05$ was considered statistically significant.

Results

Concentrations of halothane in the superfusate equivalent to vaporizer settings of 0.75 and 1.5% were 0.22 ± 0.03 and 0.47 ± 0.03 mM (n = 23), respectively. Concentrations of enflurane in the superfusate equivalent to vaporizer settings of 1.75 and 3.5% were 0.44 ± 0.03 and 0.94 ± 0.05 mM (n = 22), respectively. For isoflurane, vaporizer settings of 1 and 2% were equivalent to superfusate concentrations of 0.28 ± 0.01 and 0.53 ± 0.02 mM (n = 23), respectively. These anesthetic concentrations were converted into the partial pressures in the gas phase for the Krebs' solution at 37° C[13,14]: halothane was 0.71 and 1.52; enflurane 1.42 and 3.0; and isoflurane 1.22 and 2.3 vol %. These percentages compare reasonably well with the anesthetic potency ratio, based on MAC values in the dog, of 1:1.5:2.3 for halothane, enflurane, and isoflurane, respectively.[15]

There was no significant effect of the higher concentrations of the anesthetics on AP amplitude, AP duration at 50% repolarization, maximum diastolic potential, or rate (dV/dt) of phase-0 depolarization during exposure to epinephrine at either the 2 or the 15 μM concentration. Values for these AP parameters were not measured during exposure to the lower concentrations of the three anesthetics for either concentration of epinephrine.

TABLE 1. Changes in Spontaneous Rate Over Time

	EPI 2 μM		EPI 15 μM	
Anesthetics	(30 min)	(180 min)	(210 min)	(330 min)
With	38.7 ± 3.1 (31)	34.5 ± 2.6* (31)	46.6 ± 5.9 (12)	45.5 ± 5.6 (12)
Without	42.5 ± 2.1 (14)	40.1 ± 2.0 (14)	49.6 ± 3.0 (14)	47.4 ± 3.0† (14)

Spontaneous rate change over time (beats per minute) in experiments with and without administration of anesthetics. Values are listed as mean ± SEM, with the number of observations shown in parentheses.
* $P < 0.05$ *versus* value at 30 min; † $P < 0.05$ *versus* value at 210 min.

Spontaneous Rate and dV/dt, Phase 4

With epinephrine 2 μM, 0.75 and 1.5% halothane increased the rate from 32.9 ± 2.3 to 35.7 ± 2.4 and 36.7 ± 2.6 beats per min, respectively (mean ± SEM; n = 23; $P < 0.02$) and dV/dt, phase 4 from 5.53 ± 0.73 to 6.38 ± 0.87 (not significant) and 7.64 ± 1.17 mV/s (n = 11; $P < 0.02$). With epinephrine 15 μM, 1.5% halothane increased the rate from 43.2 ± 5.9 to 47.2 ± 6.0 beats per min (n = 11; $P < 0.001$) and dV/dt, phase 4 from 7.3 ± 1.28 to 10.02 ± 1.70 mV/s (n = 10; $P < 0.02$).

With epinephrine 2 μM, 1.75 and 3.5% enflurane increased the rate from 32.9 ± 2.9 to 39.1 ± 3.1 and 45.6 ± 3.4 beats per min, respectively (n = 22; $P < 0.001$) and dV/dt, phase 4 from 6.49 ± 1.39 to 9.51 ± 1.74 and 10.93 ± 1.84 mV/s (n = 10; $P < 0.001$). With epinephrine 15 μM, 3.5% enflurane increased the rate from 46.0 ± 5.7 to 55.8 ± 6.2 beats per min (n = 13; $P < 0.001$) and dV/dt, phase 4 from 10.10 ± 1.47 to 16.40 ± 2.56 mV/s (n = 12; $P < 0.001$).

With epinephrine 2 μM, 1 and 2% isoflurane increased the rate from 32.4 ± 2.8 to 34.0 ± 2.7 (not significant) and 35.1 ± 2.8 beats per min, respectively (n = 23; $P < 0.02$) and dV/dt, phase 4 from 4.54 ± 0.62 to 4.78 ± 0.44 (not significant) and 5.79 ± 0.81 mV/s (n = 10; $P < 0.02$). A typical tracing is shown in figure 2. With epinephrine 15 μM, 2% isoflurane increased the rate from 44.4 ± 7.0 to 47.3 ± 7.0 beats per min (n = 11; $P < 0.02$) and dV/dt, phase 4 from 7.58 ± 1.48 to 8.97 ± 1.34 mV/s (n = 10; not significant).

These data, compared in figures 3 and 4, indicate that all three anesthetics increased the rate of automaticity in Purkinje fibers. The increase in rate was due to enhanced phase-4 depolarization, since other AP parameters were not significantly altered.

Recovery of Automaticity from Overdrive Suppression

Data for recovery times in seconds during exposure to halothane, enflurane, and isoflurane (highest concentrations only) at either of the two epinephrine concentrations are shown in table 2. Although an obvious trend toward shortening of recovery time by halothane was seen, except for paced cycle lengths of 800 and 500 ms and epinephrine 2 μM, halothane did not significantly shorten recovery times. Enflurane shortened recovery times for all three paced cycle lengths and both durations of pacing (30 or 60 s) during exposure to the lower concentration of epinephrine. Except for paced cycle lengths of 500 ms (30 or 60 s) and 400 ms (30 s, only), this was also the case during exposure to the higher epinephrine concentration.

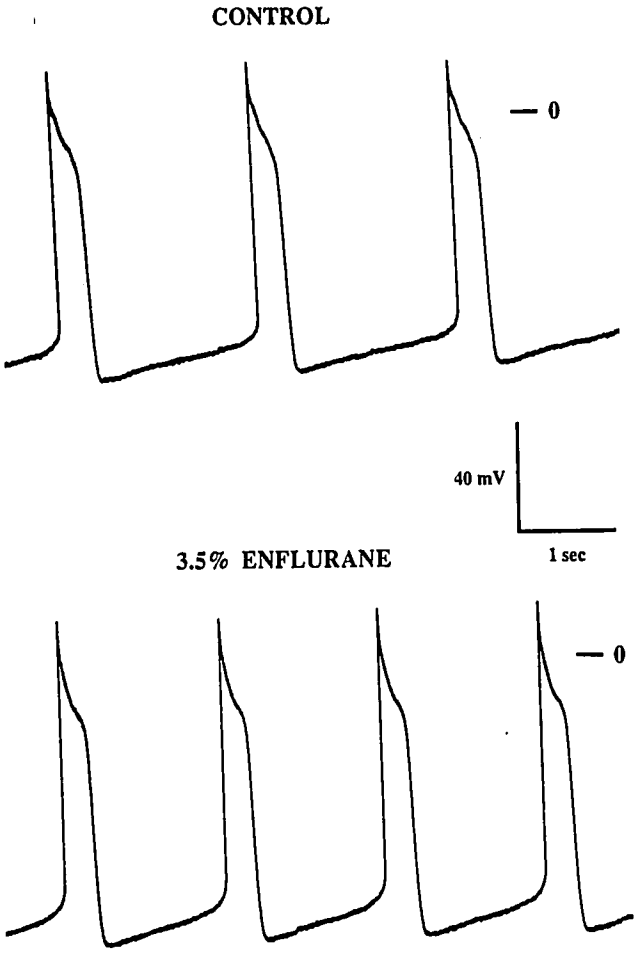

FIG. 2. Typical tracings from spontaneously firing (exposed to 2 μM epinephrine) Purkinje fiber (*top;* rate 25 beats per min) and the effect of 3.5% enflurane (*bottom;* rate 32 beats per min).

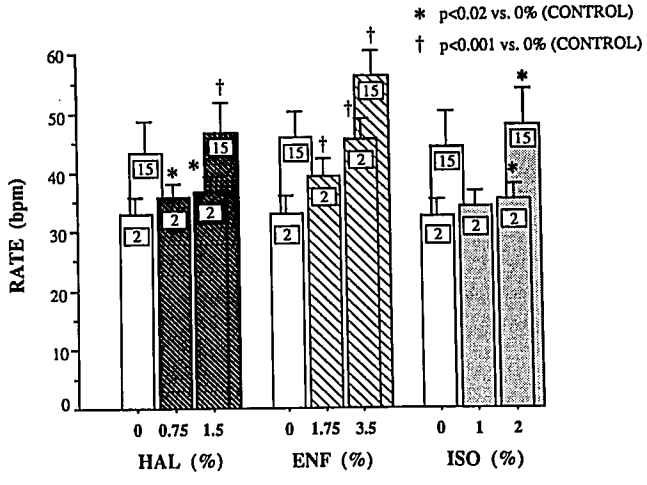

FIG. 3. Comparison of the effects of halothane (HAL), enflurane (ENF), and isoflurane (ISO) on the rate (beats per minute) of Purkinje fibers exposed to epinephrine 2 and 15 μM (shown in bars).

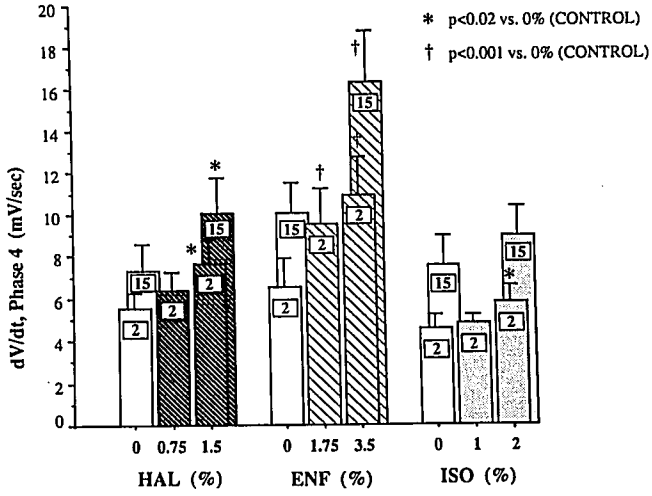

FIG. 4. Comparison of the effects of halothane (HAL), enflurane (ENF), and isoflurane (ISO) on phase 4 depolarization (millivolts per second) of Purkinje fibers exposed to epinephrine 2 and 15 μM (shown in bars).

A typical tracing is shown in figure 5. Isoflurane, in contrast to halothane or enflurane, had no significant effects on recovery times during exposure to either epinephrine concentration; nevertheless, there was an obvious trend toward shortened recovery times with isoflurane. Effects of the three volatile anesthetics on recovery of automaticity from overdrive suppression are compared in figures 6 and 7.

Discussion

Our data indicate that clinically relevant concentrations of enflurane moderately accelerate the spontaneous discharge rate of Purkinje fibers exposed to epinephrine. This increase in normal automaticity, as compared to abnormal or depolarization-induced automaticity,[2] appears to be due to enhanced diastolic (phase-4) depolarization since maximum diastolic potential was not affected by enflurane. We cannot exclude an effect of enflurane to reduce threshold potential. However, this parameter was not estimated,** since even small beat-to-beat changes in spontaneous rate are likely to affect the calculation of this value. Isoflurane, in contrast to enflurane but comparable to halothane, produced only a small increase in the spontaneous rate of Purkinje fibers exposed to epinephrine. This effect also appears to be due to enhanced phase-4

** Threshold potential can be estimated from the intersection of two lines, the first drawn tangent to the maximum slope of phase-4 (diastolic) depolarization and the second to the maximum slope of phase-0 (upstroke) depolarization.

TABLE 2. Effect of Halothane, Enflurane, and Isoflurane on Recovery Times of Automaticity from Overdrive Suppression

EPI	Condition	CL 800		CL 500		CL 400	
		30 s	60 s	30 s	60 s	30 s	60 s
2 μM	Control	3.09 ± 0.29	5.80 ± 0.98	7.94 ± 1.78	12.78 ± 2.76	9.51 ± 1.97	17.03 ± 3.47
	1.5% HAL	2.01 ± 0.27*	2.62 ± 0.43*	3.27 ± 0.47*	7.37 ± 1.42	4.37 ± 0.79	11.42 ± 2.04
	3.5% ENF	1.36 ± 0.06†	1.66 ± 0.21†	2.15 ± 0.45*	4.52 ± 0.94*	3.03 ± 0.72*	7.60 ± 1.85*
	2% ISO	2.73 ± 0.36	3.99 ± 0.60	4.42 ± 0.64	7.33 ± 0.89	5.90 ± 0.97	11.56 ± 2.05
15 μM	Control	1.99 ± 0.26	2.71 ± 0.60	4.04 ± 1.29	6.86 ± 2.23	5.56 ± 1.62	10.73 ± 2.27
	1.5% HAL	1.39 ± 0.15	1.56 ± 0.20	1.85 ± 0.23	4.44 ± 1.13	2.65 ± 0.54	9.31 ± 3.62
	3.5% ENF	1.09 ± 0.06†	1.29 ± 0.15*	1.70 ± 0.45	3.13 ± 1.03	2.54 ± 0.67	6.78 ± 1.56*
	2% ISO	1.48 ± 0.15*	1.58 ± 0.15	2.27 ± 0.53	3.55 ± 0.89	2.47 ± 0.53	6.46 ± 1.51

Values (seconds) are shown as mean ± SEM (N = 8). *$P < 0.05$ or †$P < 0.005$ *versus* control.

EPI = epinephrine; CL = cycle length; HAL = halothane; ENF = enflurane; ISO = isoflurane.

depolarization, since maximum diastolic potential was not affected. Bar graphs comparing the effects of halothane, enflurane, and isoflurane on spontaneous rate and diastolic depolarization (dV/dt, phase 4) in Purkinje fibers exposed to epinephrine (2 and 15 μM) are provided in figures 3 and 4.

Spontaneous diastolic (phase-4) depolarization must result from a gradual, net reduction in the movement of outward positive charges.[2,16,17] This could be due to an increase in inward (Na^+ and Ca^{2+}) current or to a decrease in outward (K^+) repolarizing currents, or to both. In Purkinje fibers, the pacemaker current (i_f) is believed to be an inward current carried by Na^+ and Ca^{2+}, one that is inactivated at levels of transmembrane potential equal to −50 mV and is slowly activated by hyperpolarization.[17] The pacemaker current is not the same as the fast-inward current (i_{Na}), the current responsible for the upstroke (phase 0) of the AP in cardiac Purkinje and muscle fibers. In addition to i_f, K^+ currents responsible for repolarization may also be involved in the pacemaker process.[17] Our current findings indicating that certain anesthetics increase the rate of phase 4 depolarization suggest that these

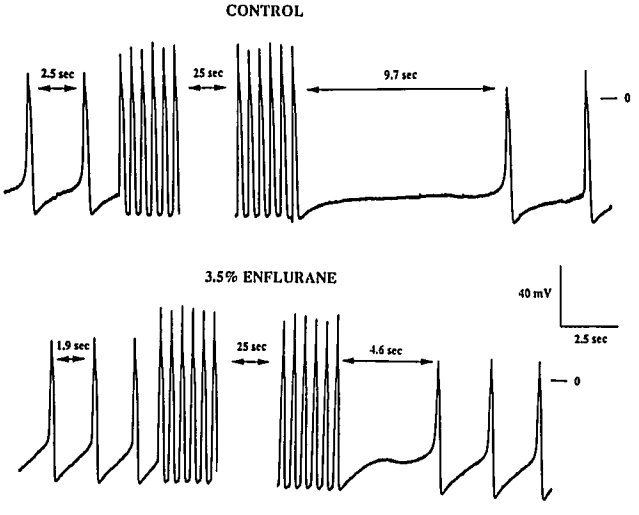

FIG. 5. Typical tracings showing the effect of overdrive suppression (following 30 s of pacing at drive cycle length of 500 ms) on spontaneously firing (exposed to 2 μM epinephrine) Purkinje fiber (*top;* rate is 24 beats per min, and recovery time is 9.7 s) and the effect of 3.5% enflurane (*bottom;* rate is 32 beats per min, and recovery time is 4.6 s).

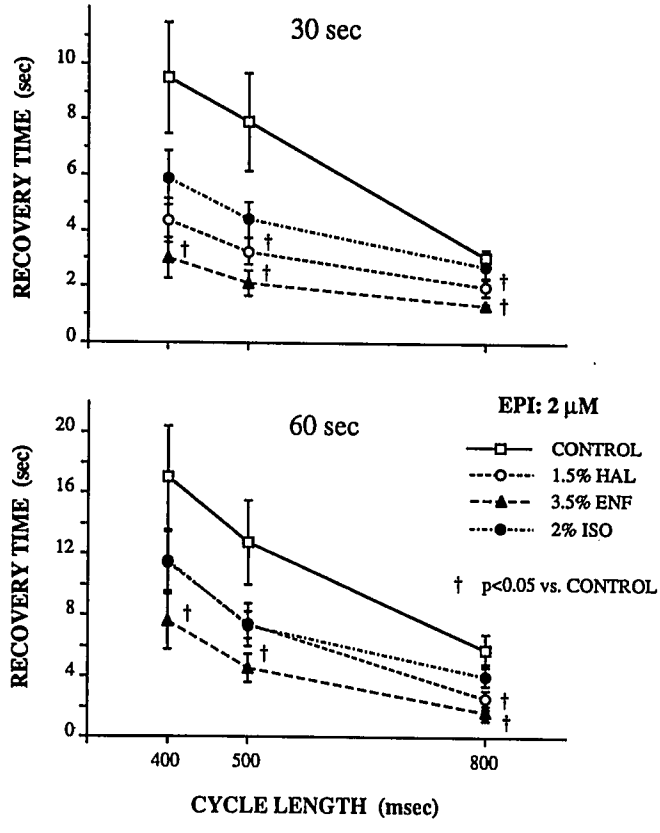

FIG. 6. Comparison of the effects of the higher concentrations of halothane (HAL), enflurane (ENF), and isoflurane (ISO) on recovery of automaticity from overdrive suppression (recovery time) during exposure to 2 μM epinephrine (EPI) and pacing durations of 30 s (*top*) and 60 s (*bottom*).

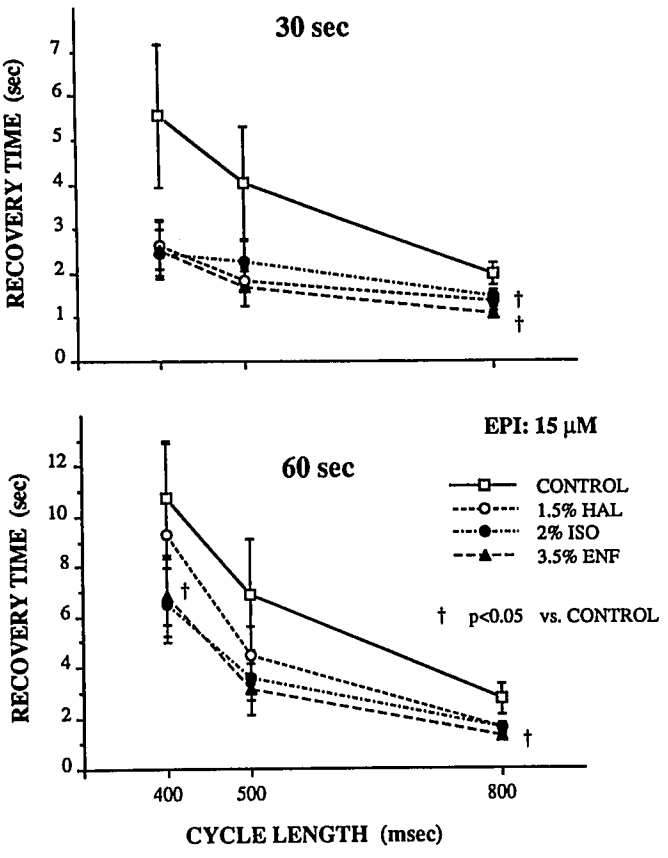

FIG. 7. Comparison of the effects of the higher concentrations of halothane (HAL), enflurane (ENF), and isoflurane (ISO) on recovery of automaticity from overdrive suppression (recovery time) during exposure to 15 μM epinephrine (EPI) and pacing durations of 30 s (*top*) and 60 s (*bottom*). *Top:* For a pacing cycle length of 800 ms, significant differences from control were for ISO and ENF only. *Bottom:* Significant effects noted at paced cycle lengths of 800 and 400 ms were with ENF only.

agents enhance normal automaticity of Purkinje fibers by decreasing i_f or by depressing K^+ repolarization currents or resting conductance or by doing both. The identity of the current(s) affected remains to be determined in voltage clamp experiments.

Our results are different than those of Reynolds *et al.*, who reported that concentrations of halothane in excess of 2% slowed spontaneous rate in canine Purkinje fibers exposed to epinephrine.[9] This effect was due to a decrease in the rate of phase-4 depolarization and to an increase in threshold potential, with little apparent effect on maximum diastolic potential.[9] Differences between our data and those of Reynolds *et al.* may be related to the higher concentrations of epinephrine and halothane or the different buffers and lower potassium concentration used by Reynolds *et al.*

Generally, impaled Purkinje fibers in our experiments did not beat spontaneously unless exposed to the lower concentration of epinephrine (2 μM). In addition, in preliminary experiments, exposure to concentrations of epinephrine greater than 15 μM did not further increase the discharge rate of spontaneously beating Purkinje fibers; from these results we selected epinephrine concentrations to determine dose-related effects of anesthetics and epinephrine on normal automaticity in Purkinje fibers.

Logic and Morrow reported that halothane (1–2% in O_2) prolonged ventricular escape time and decreased idioventricular escape rate during supramaximal right vagal stimulation in pentobarbital-anesthetized dogs.[10] Additionally, halothane restored sinus rhythm in dogs with ectopic ventricular tachycardia due to toxic amounts of ouabain.[10] These results suggest that halothane opposes automaticity in ventricular pacemakers. However, the results of Logic and Morrow should not be directly compared with ours. *First,* vagal stimulation or acetylcholine (ACh) is expected to slow the discharge rate of ventricular foci exhibiting normal automaticity.[18] Halothane, as suggested by the findings of Logic and Morrow,[10] augments this effect of vagal stimulation. *Second,* in Logic and Morrow's experiments, slow ventricular escape rhythms and ectopic ventricular tachycardia probably were accompanied by significant reductions in arterial pressure.[10] Increased sympathetic discharge in response to significant reductions in arterial pressure should augment the effects of the vagus or ACh on ventricular automaticity, a phenomenon termed "accentuated antagonism."[19] The effect of halothane on the phenomenon of accentuated antagonism is not known, although halothane does attenuate the baroreceptor reflex.[20] Experiments in which the effect of halothane on automaticity of Purkinje fibers exposed to ACh with and without epinephrine would further our understanding of the effect of combined vagal and sympathetic discharge on automaticity of ventricular pacemakers. *Third,* the focus or mechanism of automatic discharge in Logic and Morrow's experiments cannot be determined. In this regard, ectopic ventricular tachycardia due to toxic digitalis is due probably to delayed afterdepolarizations and triggered activity.[21,22] Gallagher *et al.* have recently reported that halothane antagonizes ouabain-induced delayed afterdepolarizations and triggered activity in canine Purkinje fibers.[23] Thus, the circumstances of our and Logic and Morrow's experiments were such that direct comparisons between the two studies are not possible.

Increased paced or spontaneous rates slow the discharge rate of latent pacemakers, an effect called overdrive suppression of automaticity.[3,4] Overdrive suppression of automaticity results from the intracellular accumulation of Na^+ and K^+ accumulation immediately outside the membrane during prolonged periods of rapid overdrive.[24] Because increased intracellular Na^+ increases

the turnover rate of the Na^+-K^+ exchange pump, which exchanges three intracellular Na^+ ions for two extracellular K^+ ions, there is a net increase in intracellular negative charges.[5,6] As a direct result, the maximum diastolic membrane potential becomes more negative, and a longer time is required for phase-4 depolarization to bring the fiber to threshold potential. Thus, spontaneous discharge rate is slowed temporarily following a period of overdrive suppression, at least until intracellular Na^+ can be restored to its former level. Pacemaker fibers whose AP upstrokes are more dependent on the influx of Na^+ (as compared to SA node or AV node fibers, which are more dependent on Ca^{2+} influx) are suppressed most after overdrive stimulation.[24]

The effect of the volatile anesthetics on overdrive suppression of automaticity was determined in our experiments by calculating recovery times in Purkinje fibers after 30 or 60 s of pacing at paced cycle lengths of 800, 500, and 400 ms. Under control conditions, increased duration and rate of pacing prolonged recovery times in Purkinje fibers, whereas increased epinephrine shortened recovery times. Data for the effects of the three volatile anesthetics on recovery of automaticity from overdrive suppression are provided in table 2 and are compared in figures 6 and 7. Shortened recovery times with enflurane are consistent with its reported effect of inhibiting post-overdrive hyperpolarization,[11] which, similar to overdrive suppression of automaticity (above), results from increased turnover of the Na^+-K^+ exchange pump.[5,6,11,24] Thus, our data suggest that enflurane may act to inhibit the Na^+-K^+ exchange pump. In contrast, our observations that halothane and isoflurane exerted little effect on recovery times suggest that inhibition of this pump by halothane should be smaller and inhibition by isoflurane rather minimal. However, even if it did not reach the level of statistical significance, an obvious trend toward shortening of recovery time by halothane and isoflurane was also observed.

Our current findings for the effects of halothane, enflurane, and isoflurane on automaticity or recovery of automaticity from overdrive suppression in Purkinje fibers derived from normal canine hearts must be extrapolated with caution to intact animals or to humans, where the effects of nervous and other intrinsic or extrinsic regulatory mechanisms are largely unknown. If applicable to clinical settings, our findings suggest that the increase in Purkinje fiber automaticity produced by halothane, enflurane, or isoflurane during exposure to epinephrine is insufficient to account for ventricular arrhythmias during the course of anesthetic sensitization.[25] However, in intact animals or in humans, the increase in blood pressure produced by epinephrine would evoke increased vagal efferent discharge, which might alter the direct effects of halothane or epinephrine on normal automaticity of ventricular pacemakers. Other possible mechanisms for ventricular arrhythmias during sensitization include abnormal forms of automaticity, reentry of excitation, and triggered activity or automaticity.[1]

Finally, our results suggest that halothane, enflurane, and isoflurane should be expected to have little effect on the occurrence of ventricular escape beats or on the rate of idioventricular rhythm in patients with SA node dysfunction, advanced degrees of AV heart block, or permanent pacemaker failure with either of these two conditions.

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